Clinical Development Protocol

An Open-Label Phase I/IIa Study of the Safety and Efficacy of Melphalan-flufenamide (Melflufen) and Dexamethasone Combination for Patients with Relapsed and/or Relapsed-Refractory Multiple Myeloma

Investigational Product	Melflufen (L-melphalanyl-p-L-fluorophenylalanine ethyl ester HCl)
Study Sponsor	Oncopeptides AB Västra Trädgårdsgatan 15 SE-111 53 Stockholm, Sweden
Protocol Number	O-12-M1
EUDRACT Number	2012-004315-31
Investigational New Drug Number	116362
Clinical Research Organization	CCI [redacted]
Development phase	Phase I/IIa
Document status	Version 1.2FINAL: February 8, 2013 Amendment 1: October 2, 2013 Amendment 2: May 7, 2014 Amendment 3: January 27, 2015 Amendment 4: June 20, 2015 Amendment 5: July 6, 2016 – Version 6 Amendment 6, Version 7: November 2, 2018

CONFIDENTIAL

This document contains confidential information belonging to Oncopeptides AB. Except as may be otherwise agreed to in writing, by accepting or reviewing these materials, you agree to hold such information in confidence and not to disclose it to others (except where required by applicable law) nor use it for unauthorized purposes. In the event of actual or suspected breach of this obligation, Oncopeptides AB should be promptly notified.

Signature Page

Protocol Number: O-12-M1

Protocol Title: An Open-Label Phase I/IIa Study of the Safety and Efficacy of Melphalan-flufenamide (Melflufen) and Dexamethasone Combination for Patients with Relapsed and/or Relapsed-Refractory Multiple Myeloma.

Date of Original Protocol: December 4th, 2012
Date of version 1.1: January 28, 2013
Date of Version 1.2: February 8, 2013
Date of Version 2.0: October 2, 2013
Date of Version 3.0: May 7, 2014
Date of Version 4.0: January 27, 2015
Date of Version 5.0: June 20, 2015
Date of Version 6.0: July 6, 2016
Date of Version 7.0: November 2, 2018

Approved By:

PPD

Chief Medical Officer

5 Nov 2018
Date

PPD

Sponsor's Medical Expert

5 Nov 2018
Date

PPD

VP, Head of Clinical Development

2 November 2018
Date

Protocol Acceptance Page

Protocol Number: O-12-M1

Protocol Title: An Open-Label Phase I/IIa Study of the Safety and Efficacy of Melphalan-flufenamide (Melflufen) and Dexamethasone Combination for Patients with Relapsed and/or Relapsed-Refractory Multiple Myeloma.

Protocol Date: Date of Version 1.2: February 8, 2013
Date of Version 2.0: October 2, 2013
Date of Version 3.0: May 7, 2014
Date of Version 4.0: January 27, 2015
Date of Version 5.0: June 20, 2015
Date of Version 6.0: July 6, 2016
Date of Version 7.0: November 2, 2018

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

_____
Principal Investigator Name (Printed)

_____ _____
Principal Investigator Signature Date

This study is to be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, Title 21 of the Code of Federal Regulations §§ 50, 56, and 312, the International Conference on Harmonization E6, and any applicable regulatory requirements.

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

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

Table of contents

List of Appendices

List of Figures

List of Tables

Protocol Synopsis:

Compound Name	Melflufen (J1)
Molecular Formula	$C_{24}H_{31}CL_3F\ N_3O_3$
Chemical Name	L-melphalanyl-p-L-fluorophenylalanine ethyl ester HCl
Study Protocol Title	An Open-Label Phase I/IIa Study of the Safety and Efficacy of Melflufen (Melphalan-flufenamide) and Dexamethasone Combination for Patients with Relapsed and Relapsed-Refractory Multiple Myeloma
Study Sponsor	Oncopeptides AB
Sponsor's Medical Expert	PPD
Site(s)	Approximately 6 - 8 international sites located in the United States and Europe.
Study Period and Phase of Development	Phase I/IIa FPFV – 3Q 2013 LPFV – 1Q 2016 LPLV – 1Q 2017
Background and Rational	Melflufen (L-melphalanyl-p-L-fluorophenylalanine ethyl ester hydrochloride) is an optimized derivative of the classical alkylating agent melphalan that has been in clinical use as an anti-tumor agent for nearly fifty years. Chemically melflufen may be described as the ethyl ester of a dipeptide with melphalan and para-fluoro-L-phenylalanine. The transport of melflufen into cells is rapid. Once inside the cytoplasm melflufen will rapidly be subjected to enzymatic activation by cleavage of the dipeptide and ester bonds, thereby releasing free melphalan. Aminopeptideases like Aminopeptidase N (APN), (for which melflufen is a substrate) is frequently over-expressed in tumors. Because of the differential rate of transport of melflufen into cells (rapid) and free melphalan out of cells (slow), a high intracellular concentration of melphalan is achieved as a result of the intracellular cleavage. Thus, treatment with melflufen efficiently results in the intracellular trapping of melphalan. It has been demonstrated that treatment with melflufen results in a 10-20 fold higher intracellular concentration of melphalan in tumor cells compared with direct treatment with equal doses of melphalan.[1,2] When studied in cell cultures of human tumors representing approximately 20 different diagnoses of human cancers including myeloma, melflufen showed 50 to 100 fold higher potency compared with that of melphalan. After the targeted delivery of melphalan to the tumor cells, the detailed mechanism of action is naturally expected to be that of melphalan, i.e. alkylation of tumor cell DNA.

Compound Name	Melflufen (J1)
Molecular Formula	$C_{24}H_{31}CL_3F\ N_3O_3$
Chemical Name	L-melphalanyl-p-L-fluorophenylalanine ethyl ester HCl
	Collaborative work performed at CCI [redacted],[3] has shown that melflufen has substantial activity in various myeloma cell lines both in vitro and in vivo. In vivo studies show that melflufen is well-tolerated and inhibits tumor growth in mice and rats.[4] Preclinical safety studies conducted with melflufen showed it to have a comparable toxicity to that of melphalan with no suggestion of any additional or qualitatively different toxicity. The primary adverse effects were on the hematopoietic system. In groups of animals treated with high doses of melflufen, microscopic evaluation revealed changes in the histopathological appearance in the lymphoid organs, testis and lungs. No pulmonary changes were however observed in the human subjects treated with melflufen (clinical and radiological examination, see Oncopeptides AB Investigators Brochure). Results from animal studies also showed increased anti-tumor activity by melflufen compared with that of melphalan thus supporting the cell culture observation of targeted delivery of melphalan to the tumor cells by melflufen. It is therefore considered that melflufen has the potential for delivering enhanced therapeutic efficacy at no greater toxicity compared to standard melphalan anticancer regimens and thus increasing the therapeutic window. A phase I/II dose finding human clinical study has been conducted with melflufen, where seven patients with advanced solid tumor disease were administered melflufen (25-130 mg) as a 30-min intravenous (IV) infusion every 3rd week in a total of 25 treatment cycles. Dose limiting toxicity was found to be bone marrow related, i.e. neutropenia and thrombocytopenia, mainly occurring at doses of 75 mg or above. The dose recommended for phase II was established at 50 mg. In the subsequent phase IIA parts conducted in Sweden and Russia a total of 38 patients (22 in Sweden, 16 in Russia) were treated with a total of 116 infusions (SWE:65 cycles) at doses 25-75 mg + RU:51 cycles at doses 30-50 mg). Early efficacy data based on radiology after three treatment cycles (n = 27) show that there is one patient with a partial response (ovarian cancer), 18 patients (67 %) with stable disease and 8 patients (30 %) with progressive disease. Eighteen patients were not evaluated after three cycles due to discontinuation from the study. Melflufen side effects seen in more than 10% of subjects were leucopenia, neutropenia (including febrile

Compound Name	Melflufen (J1)
Molecular Formula	$C_{24}H_{31}CL_3F\ N_3O_3$
Chemical Name	L-melphalanyl-p-L-fluorophenylalanine ethyl ester HCl
	neutropenia) and thrombocytopenia, which appeared dose-related and reversible, and appeared more pronounced in heavily pretreated patients. Fatigue, nausea, occasional vomiting, diarrhea and anemia were also observed (see Oncopeptides AB Investigator Brochure). In summary, the cell culture studies demonstrated that melflufen provides targeted delivery of melphalan to the cancer cells and therefore higher concentrations are achieved in tumors. In preclinical animal studies, melflufen shows equimolar bone marrow toxicity profile to melphalan with better tumor growth suppression. The phase I-II trial conducted in advanced cancer patients has established the recommended phase II dose (RPTD) of melflufen to be 50 mg every 3 weeks, at least in previously treated patients with an acceptable safety profile. Melphalan is currently used clinically in multiple myeloma (MM). Cell culture studies demonstrate a greater cytotoxic potency of melflufen versus melphalan against MM cells without significant toxicity in normal cells. Overall, these preclinical and clinical studies provide the rationale for clinical protocols evaluating melflufen in MM.
Study Design	This is an open-label, phase I/IIa, multicenter study which will enroll patients with relapsed and or relapsed-refractory MM. Phase I will follow the standard 3 + 3 modified Fibonacci design with 3 to 6 patients, depending on dose limiting toxicity (DLT) observed, at each dose level to be tested. Up to 5 dose levels will be tested; IV melflufen at 15 mg, 25 mg, 40 mg, 55 mg and 70 mg, given on Day 1, in combination with a fixed dose of dexamethasone 40 mg PO or IV on Days 1, 8 and 15 of each 21-day cycle. Once the maximum tolerated dose (MTD) has been determined in Phase I, an additional 49 patients will be enrolled and treated at the MTD in the Phase IIa part of the study. Patients will be assessed for response after each cycle according to the IMWG response criteria. Patients may receive up to 8 cycles of therapy. However, patients who have benefit from the therapy may continue treatment at the discretion of the investigator and after approval by the study sponsor for each individual case. Doses of melflufen or dexamethasone may be interrupted or reduced in an attempt to manage toxicity according to the protocol guidelines. Amendment 4 aims to establish the single agent activity of melflufen, and hence the dexamethasone dose will be reduced to a

Compound Name	Melflufen (J1)
Molecular Formula	$C_{24}H_{31}CL_3F\ N_3O_3$
Chemical Name	L-melphalanyl-p-L-fluorophenylalanine ethyl ester HCl
	maximum of 24 mg per cycle for anti-emetic purpose. As dexamethasone alone is not regarded as an effective treatment in RRMM, it is important to explore if the main activity of the promising effect seen with the combination of melflufen and dexamethasone arise from the melflufen component. If so, future patients may be treated with melflufen with lower dose of dexamethasone, thus avoiding many of the well-known dexamethasone side effects. 8 mg dexamethasone will be administered on Days 1 and 2 of each cycle, and in addition 4 mg is allowed on Days 3 and 4 if needed for delayed emesis. Amendment 4 will also increase the standard cycle length of melflufen from 21 to 28 days. This was decided by the DSMC 18 May 2015 after review of the available dosing and safety data. As this was regarded a safety precaution, this change has already been implemented. Amendment 5 described that in the event that the DSMC, at any time, determines that the risk-benefit balance of single agent melflufen is sub optimal, they will have the possibility to recommend that subsequent patients be treated with the combination of melflufen with weekly 40 mg dexamethasone in order to optimize efficacy, without any further amendment. In this case, patients will follow the same dexamethasone dose, schedule and dose modification guidelines as the combination cohort previously described in accordance with protocol version 4.0 Amendment 3 dated 27 January 2015. A total of 40 patients have to date been treated with this combination. Patients ongoing in the single agent cohort may then have weekly dexamethasone added at the investigator's discretion. Amendment 5 also includes an additional melflufen vial strength, 20 mg. Amendment 6 includes an additional final OS follow-up for those approx. 40% of patients who were still alive 24 months after their last melflufen dose or progression. This is done to better understand the long-term benefit of melflufen treatment, where median OS is 20.7 months. After this, the study will be closed for all patients and results will be reported.
Objectives	**Primary Objective(s)** **Phase I (Phase 1 is complete)**

Compound Name	Melflufen (J1)
Molecular Formula	$C_{24}H_{31}CL_3F\ N_3O_3$
Chemical Name	L-melphalanyl-p-L-fluorophenylalanine ethyl ester HCl
	The primary objective of the Phase I portion of the study is to determine the MTD of the combination of melflufen and dexamethasone in patients with relapsed and relapsed-refractory multiple myeloma (MM). **Phase IIa** To evaluate the objective response rate ≥ PR and the clinical benefit (including minimal response [MR]) to the combination of melflufen and dexamethasone and to melflufen as single agent at the MTD determined in Phase I. **Secondary Objective(s)** To evaluate the overall response including the complete response/stringent complete response (CR/sCR), very good partial response (VGPR), PR and clinical benefit (≥ MR), time to progression, duration of response, progression free survival and overall survival in all evaluable patients. To further explore the safety and tolerability of the combination and single agent melflufen at the MTD. **Exploratory Objective(s)** To identify mechanisms of response and or resistance to melflufen. Pharmacokinetics will be evaluated in patients enrolled at a select site with the training and expertise to collect and process the required samples. ECG assessments to screen for major effects on the QTc interval will be conducted at select sites. Should a signal be detected further evaluations will be conducted in future studies.
Inclusion Criteria	Eligible patients will be considered for inclusion in this study if they meet all of the following criteria: 1. Male or female, age 18 years or older. 2. Patient has a diagnosis of multiple myeloma with documented relapsed and/or relapsed-refractory disease. 3. Patient has measurable disease defined as any of the following: • Serum monoclonal protein ≥ 0.5 g/dL by protein electrophoresis. • ≥ 200 mg of monoclonal protein in the urine on 24-hour

Compound Name	Melflufen (J1)
Molecular Formula	$C_{24}H_{31}CL_3F\ N_3O_3$
Chemical Name	L-melphalanyl-p-L-fluorophenylalanine ethyl ester HCl
	electrophoresis • Serum immunoglobulin free light chain ≥ 10 mg/dL AND abnormal serum immunoglobulin kappa to lambda free light chain ratio. • If no monoclonal protein is detected (non-secretory disease), then ≥ 30% monoclonal bone marrow plasma cells. 4. Patient has had at least 2 or more prior lines of therapy including lenalidomide and bortezomib and has demonstrated disease progression on or within 60 days of completion of the last therapy. (see appendix D for the definition of lines of therapy); 5. Life expectancy of ≥ 6 months; 6. Patient has an ECOG performance status ≤ 2. (Patients with lower performance status based solely on bone pain secondary to multiple myeloma will be eligible); 7. Females of childbearing potential (FCBP)† must have a negative serum or urine pregnancy test prior to initiation of therapy; 8. Female patients of child bearing potential and non-vasectomized male patients agree to practice appropriate methods of birth control; 9. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information; 10. The patient has or, accepts to have, an acceptable infusion device for infusion of melflufen (Port A Cath, PICC line or central venous catheter); 11. 12 lead ECG with QTcF interval of ≤ 470 msec; (see Appendix G) 12. The following laboratory results must be met within 21 days, or as specified in the table of assessments, prior to initiation of therapy: • Absolute neutrophil count (ANC) ≥ 1,000 cells/mm^3 (1.0 x 10^9/L) (Growth factors cannot be used within 14 days prior to initiation of therapy).

Compound Name	Melflufen (J1)
Molecular Formula	$C_{24}H_{31}CL_3F\ N_3O_3$
Chemical Name	L-melphalanyl-p-L-fluorophenylalanine ethyl ester HCl
	• Platelet count ≥ 75,000 cells/ mm^3 (75 x 10^9/L) (platelet count ≥ 50,000 cells/ mm^3 for patients in whom ≥ 50% of bone marrow nucleated cells are plasma cells (without transfusion during the previous 7 days to initiation of therapy). • Hemoglobin ≥ 8.0 g/dL (RBC transfusions are permitted) • Total Bilirubin ≤ 1.5 X upper limit of normal (ULN); • Renal function: Estimated creatinine clearance ≥ 45 ml/min and serum creatinine ≤ 2.0 mg/dL; • AST (SGOT) and ALT (SGPT) ≤ 3.0 x ULN. † (FCBP) is any sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally postmenopausal (not having menstrual cycles due to cancer therapy does not rule out childbearing potential) for at least 24 consecutive months.
Exclusion Criteria	Patients will be ineligible for this study if they meet any one of the following criteria: 1. Patient has evidence of mucosal or internal bleeding and/or is platelet transfusion refractory (i.e., unable to maintain a platelet count ≥ 50,000 cells/mm^3); 2. Any medical conditions that, in the Investigator's opinion, would impose excessive risk to the patient or would adversely affect his/her participating in this study. Examples of such conditions are: a significant history of cardiovascular disease (e.g., myocardial infarction, significant conduction system abnormalities, uncontrolled hypertension, ≥ grade 3 thromboembolic event in the last 6 months), renal insufficiency (unless felt to be secondary to MM); 3. Known active infection requiring parenteral or oral anti-infective treatment; 4. Other malignancy within the past 3 years with the exception of adequately treated basal cell carcinoma, squamous cell skin cancer, carcinoma in-situ of the cervix; 5. Other ongoing anti-myeloma therapy. Patients may be receiving concomitant therapy with bisphosphonates and

Compound Name	Melflufen (J1)
Molecular Formula	$C_{24}H_{31}CL_3F\ N_3O_3$
Chemical Name	L-melphalanyl-p-L-fluorophenylalanine ethyl ester HCl
	low dose corticosteroids (e.g., prednisone up to but no more than 10 mg PO q.d. or its equivalent) for symptom management and comorbid conditions. Doses of corticosteroid should be stable for at least 7 days prior to initiation of therapy; 6. Pregnant or breast-feeding females; 7. Serious psychiatric illness, active alcoholism, or drug addiction that may hinder or confuse compliance or follow-up evaluation; 8. Known HIV or hepatitis B or C viral infection; 9. Patient has concurrent symptomatic amyloidosis or plasma cell leukemia; 10. POEMS syndrome (plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein and skin changes); 11. Previous cytotoxic therapies, including cytotoxic investigational agents, for multiple myeloma within 3 weeks (6 weeks for nitrosoureas) prior to initiation of therapy. Biologic, novel therapy (including investigational agents in this class) or corticosteroids within 2 weeks prior to initiation of therapy. Patient has side effects of the previous therapy > grade 1 or previous baseline. 12. Prior peripheral stem cell transplant within 12 weeks of initiation of therapy; 13. Radiotherapy within 21 days prior to initiation of therapy. However, if the radiation portal covered ≤ 5% of the bone marrow reserve, the patient may be enrolled irrespective of the end date of radiotherapy; 14. Known intolerance to steroid therapy.
Study Treatment(s)	Treatment will be given in an outpatient treatment setting in cycles. Each cycle is 28 days. Melflufen concentrate for solution for infusion is to be diluted in 250 ml of 5% glucose solution. The study treatment will be administered as a 30 minute IV infusion every 4 weeks via central line. (See protocol for complete guidelines on drug preparation and administration). Safety precautions regarding preparation and handling of alkylating agents should be followed in

Compound Name	Melflufen (J1)
Molecular Formula	$C_{24}H_{31}CL_3F\ N_3O_3$
Chemical Name	L-melphalanyl-p-L-fluorophenylalanine ethyl ester HCl

accordance with institutional guidelines. Prophylactic treatment with antiemetics is recommended.

Dexamethasone oral tablets or IV solution is available either from commercial supplies or otherwise oral tablets will be supplied by Oncopeptides AB where required by local regulations.

Phase I (Phase I is completed)
Phase I Dose Levels to be tested:

Dose Level	Melflufen Dose (IV)	Dexamethasone dose (PO or IV)
Cycle = 21 days	Day 1	Day 1, 8, 15
Level 1	15 mg	40 mg
Level 2	25 mg	40 mg
Level 3	40 mg	40 mg
Level 4	55 mg	40 mg
Level 5	70 mg	40 mg

The first cohort of patients enrolled in the Phase I portion of the study will receive dose level 1. A full safety evaluation will be conducted when these patients have completed one cycle (21 days) of combination therapy. Dose escalation for subsequent patients will proceed as follows:

- If no DLT is reported in the first three patients at a dose level, that dose level will be considered safe and three patients will be enrolled at the next dose level.

- If 1/3 patients in a cohort at a dose level has a DLT, the dose level will be expanded to obtain six evaluable patients.

- If 2/3 patients in a cohort at a dose level has a DLT, that dose level will not be considered safe, no further dose escalation will take place, and the MTD will have been exceeded*.

- If there are < 2 patients with a DLT among the expanded cohort of six evaluable patients a cohort of three patients will be enrolled in the next higher dose level.

Compound Name	Melflufen (J1)
Molecular Formula	$C_{24}H_{31}CL_3F\ N_3O_3$
Chemical Name	L-melphalanyl-p-L-fluorophenylalanine ethyl ester HCl
	• If there are 2 or more patients with a DLT among the expanded cohort of six evaluable patients, that dose level will not be considered safe, no further dose escalation will take place, and the MTD will have been exceeded*. * When the MTD has been exceeded: If less than 6 patients have been treated in the next lower dose level (the possible MTD level), additional patients will be entered into this dose level until there are 6 patients treated. If ≤ 1 of these 6 patients encountered DLT, then this dose level will be declared to be the MTD. If 2 or more of the 6 patients encounter DLT, then the MTD has been exceeded. NOTE: If a patient discontinues treatment for reasons unrelated to adverse events such that safety in cycle one cannot be fully evaluated, an additional patient may be enrolled; these will be reviewed on a case by case basis in conjunction with the sponsor. Intra-Patient Dose Escalation: In consultation with Oncopeptides AB medical monitor, intra-patient dose escalation may be considered at the discretion of the investigator if the patient has not had a DLT in cycle 1, has not required a dose modification in cycle 2+ and has achieved only SD or MR as best response. In addition, the higher dose with which the patient is to be treated must be a dose that has completed evaluation and has not exceeded the MTD. The 6 patients treated at MTD will be the first 6 patients of the phase IIa component of the study. **Definition of Maximum Tolerated Dose (Phase I only. Phase I is completed):** The MTD of the combination of melflufen and dexamethasone in multiple myeloma patients shall be defined as the highest dose level resulting in ≤ 1 out of 6 patients experiences DLT. The dose will be escalated either until an MTD is identified or the maximum planned dose is achieved. **Definition of DLT (Phase I only. Phase I is completed):**

Compound Name	Melflufen (J1)
Molecular Formula	$C_{24}H_{31}CL_3F\ N_3O_3$
Chemical Name	L-melphalanyl-p-L-fluorophenylalanine ethyl ester HCl
	• Grade 3 or greater non-hematologic toxicity possible/probable/definite related to treatment with melflufen or the combination of melflufen and dexamethasone. (*If a patient experiences a grade 3 or greater non-hematologic toxicity (see table 7-5 for the list of toxicities) that is clearly and solely related to dexamethasone during cycle one of therapy – this will not necessarily be counted as a DLT. The event will be considered by the Data Monitoring Safety Committee (DSMC) upon review of all other toxicities noted for the given cohort and the DSMC will determine if dose escalation should continue or if a reduced dose of dexamthasone (20 mg) will be implemented for subsequent cohorts).* • Grade 3-4 thrombocytopenia (platelet count < 50,000/ mm^3) with clinically significant bleeding. • Platelet transfusions in the absence of bleeding will not be considered a DLT because thrombocytopenia is an anticipated effect of the disease as well as a side effect of treatment, particularly in a heavily pretreated patient population and patients can enter the study with pre-existing thrombocytopenia. • Grade 4 neutropenia must occur for more than 5 days to be considered dose limiting. A grade 4 neutropenia with duration of less than 5 days or grade 3 neutropenia must result in neutropenic fever with elevated temperature (defined as ANC < 1000/mm3 with a single temperature of > 38.3°C or sustained temperature of ≥ 38°C for more than one hour) to be considered dose-limiting. Other grade 4 hematological toxicity (other than thrombocytopenia, neutropenia and lymphopenia) • Inability to receive Day 1 dose for Cycle 2 within 14 days from planned Day 1 Cycle 2,-due to continued drug related toxicity from cycle one or drug related toxicity newly encountered on Day 1 of Cycle 2. Patients must meet the criteria as outlined in the protocol (see section 7.9.7); Initiation of A New Cycle of Therapy (including platelet count ≥ 50,000/ mm^3 and Neutrophils ≥ 1,000 cells/ mm^3 (1.0 x 10^9/L); to begin cycle 2 or subsequent cycles. The DLT criteria will not change the adverse event reporting which will be done according to National Cancer Institute – Common

Compound Name	Melflufen (J1)
Molecular Formula	$C_{24}H_{31}CL_3F\ N_3O_3$
Chemical Name	L-melphalanyl-p-L-fluorophenylalanine ethyl ester HCl
	Terminology Criteria for Adverse Events Version 4.03 (CTCAE 4.03). The prophylactic use of growth factors and platelet transfusions in cycle one of the dose escalation cohorts in Phase 1 is not permitted. However, at the discretion of the investigator, the use of growth factors and platelet transfusions to facilitate retreatment is permitted.
	Phase II Patients will be treated at the MTD as determined in Phase I with the same schedule. All patients will follow the same procedures for drug administration and observation as Phase I. Amendment 4 introduced a 28-day cycle based on the May 18, 2015 DSMC recommendation. Ongoing patients may increase to 28-day schedule at investigator discretion; new patients will start therapy with 28-day cycles. Amendment 4 also aim to explore the effect of melflufen alone, and hence dexamethasone will be given as 8 mg on Days 1 and 2 of each cycle, and an additional 4 mg may be given on Days 3 and 4 at investigator discretion, if needed, for a total maximum of 24 mg per cycle as anti-emetic prophylaxis.
Duration of Treatment	Phase I and Phase II: Treatment will be administered in cycles of 21 days (Amended to 28 days for all new patients enrolled after May 18, 2015). Up to 8 cycles will be administered. However, patients who have benefit from the therapy may continue treatment at the discretion of the investigator after approval by the study sponsor for each individual case. Response will be evaluated every cycle starting with cycle 2 according to the IMWG response criteria.
Concomitant Drug/Therapy	All blood products and concomitant medications received from screening until the end of study visit treatment should be recorded. • Prophylactic treatment with anti-emetic(s) just prior to study treatment administration is recommended. • Patients should receive full supportive care while on this study at the investigators discretion including transfusions, anti-emetics, anti-diarrheals, analgesics etc., and treatment of other concurrent medical conditions. • IV or PO Bisphosphonate therapy, if indicated, is permitted. • Colony-stimulating factors may be used if neutropenia occurs but should not be used prophylactically during Cycle 1 of Phase I.

Compound Name	Melflufen (J1)
Molecular Formula	$C_{24}H_{31}CL_3F\ N_3O_3$
Chemical Name	L-melphalanyl-p-L-fluorophenylalanine ethyl ester HCl
	• No anticancer agents other than the study medications administered as part of this study protocol are permitted.
Number of Patients	A maximum of 6 patients per dose level will be enrolled in 5 planned dose levels. An additional 6 patients may be required should dexamethasone toxicity require switching to the alternate dose levels regardless of the level at which the change is made. A maximum of 36 patients can be enrolled in the Phase I part of the study. The 6 patients treated at the MTD in Phase I, will be included in the Phase IIa assessment. An additional 49 patients will be enrolled in the Phase IIa portion of the study for a total of 55 at the MTD. Amendment 4 will include a cohort of ≥20 efficacy-evaluable patients treated with single agent melflufen. All patients following approval of the amendment 4 will be treated with single agent melflufen. The aim is to have at least 20 patients treated with single agent melflufen. The overall objective is to treat 55 efficacy-evaluable patients with 40 mg of melflufen. The 55 efficacy-evaluable patients will therefore also include the cohort of ≥20 single agent patients. When 55 evaluable patients have been obtained, further recruitment will be stopped but all patients that have signed informed consent will be allowed to continue. If the ≥ 20 efficacy-evaluable single-agent cohort has NOT been fulfilled within the total of 55 patients, recruitment will continue until this cohort is complete.
Assessments	Safety Assessments: • Serial physical examinations with vital signs and assessment of performance status; • Routine safety laboratory tests (CBC with differential and platelets; clinical chemistry, coagulation tests) with calculation of creatinine clearance (either estimated by Cockcroft-Gault formula [Appendix F] or measured through 24-hour urine collection); • Chest X-ray; • Pregnancy testing; • Electrocardiogram; • Neurological assessments; • Assessment and grading of adverse events.

Compound Name	Melflufen (J1)
Molecular Formula	$C_{24}H_{31}CL_3F\ N_3O_3$
Chemical Name	L-melphalanyl-p-L-fluorophenylalanine ethyl ester HCl
	Adverse experiences, including clinical laboratory and vital sign abnormalities, will be graded using the NCI's CTCAE 4.03 (Appendix B). Patients are evaluable for toxicity if they receive one dose of study treatment.

	Efficacy Assessments
	• M-protein determination using both of the following procedures:
	  o Serum protein electrophoresis (SPEP) and serum protein immunofixation with quantitative immunoglobulins; and
	  o Urine protein electrophoresis (UPEP) and urine protein immunofixation (all using the same 24-hour urine collection);
	• Serum free light chains (SFLC);
	• Plasmacytoma evaluation;
	• Bone marrow aspirate to quantify percent myeloma cell involvement;
	• 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. (CT/PET scan may be utilized to support conventional X-ray of spine, ribs and pelvis with the same technique to be used with each evaluation or as clinically indicated).
	• Beta2 microglobulin.
	
	Disease status will be assessed at screening and C1, Day 1 and starting with Cycle 2, response to treatment will be assessed every cycle by M protein quantitation and immunofixation from serum, a 24-hour urine collection and SFLC. Full disease response assessment, including assessment of plasmacytomas and skeletal survey and/or CT/PET scan will be performed if indicated according to the IMWG response criteria for all patients or at the end of treatment for any reason. Bone marrow aspirate will be performed to confirm CR in patients who have achieved a CR by immunofixation. Additional skeletal survey and or CT/PET scan may be performed if the patient has bone symptoms suggested by pain and/or progression of lesions documented at baseline. If soft tissue plasmacytomas are present and measurable on physical examination they will be assessed at every cycle. Those extramedullary plasmacytomas

Compound Name	Melflufen (J1)
Molecular Formula	$C_{24}H_{31}CL_3F\ N_3O_3$
Chemical Name	L-melphalanyl-p-L-fluorophenylalanine ethyl ester HCl
	documented and measurable only by MRI and/or CT/PET scans will be assessed by the relevant modality to confirm response according the IMWG response criteria and the end of treatment evaluation.
	Correlative Sample Assessments Peripheral blood and bone marrow aspirate samples will be collected at pre-therapy, Cycle 1 Day 2, to confirm CR and at end of study. (Cycle 1 Day 2 and end of study samples are optional for consenting patients). Cells will be subjected to proteomics, microarray analysis, enzymatic assays, and Tissue Microarray Analysis (TMA). The studies will be oriented on biomarkers relevant to efficacy of melflufen. **Correlative samples will only be collected at US sites.**
	Pharmacokinetic Assessments Plasma samples for determination of melflufen and melphalan concentrations will be drawn in connection to the first treatment cycle, prior to start of infusion (baseline), at 15 and 25 minutes post start of infusion, immediately before end of infusion, and at 5, 10 15, 30, 60, 120 and 210 minutes post end of infusion. The PK samples **will only be collected at one to two dedicated sites** trained in the procedures for sample processing.
Statistical Methods	**Study Endpoints** **Primary Endpoint** **Phase I** The primary end point of Phase I is to determine the MTD by monitoring and analyzing the frequency and grade of adverse events occurring at each dose level of melflufen and dexamethasone to be tested. **Phase IIa** The primary end point of Phase IIa is the objective response rate (CR, sCR, VGPR, PR) and clinical benefit (≥ MR) and the rate of SD and PD observed in patients treated at the MTD. **Secondary Endpoint(s)** The overall response rate (CR/sCR, VGPR, PR) and clinical benefit (≥ MR), time to progression, duration of response, progression free and overall survival in all evaluable patients. To further evaluate the frequency and grade of all adverse events of the combination of melflufen and dexamethasone and of melflufen alone, including the rate and type of second primary malignancies.

Compound Name	Melflufen (J1)
Molecular Formula	$C_{24}H_{31}CL_3F\ N_3O_3$
Chemical Name	L-melphalanyl-p-L-fluorophenylalanine ethyl ester HCl
	Exploratory Endpoint(s) To identify mechanisms of response and or resistance to melflufen. Pharmacokinetics of melflufen and melphalan will be collected at the following time points: start of infusion (baseline), at 15 and 25 minutes post start of infusion, immediately before end of infusion, and at 5, 10 15, 30, 60, 120 and 210 minutes post end of infusion, at one to two centers. Assessment of QTc interval will be conducted at select sites. **Analysis Sets** **Safety Analysis:** All patients that have initiated treatment (at least one dose) will be considered evaluable for safety analysis(s). The maximum grade for each type of adverse event will be recorded for each patient, and frequency tables will be reviewed to determine patterns. Additionally, the relationship of the adverse event(s) to the study treatment will be taken into consideration. **Efficacy Analyses:** All patients who have baseline evaluation, receive at least 2 cycles of therapy and have at least one post dose efficacy measurement will be considered evaluable for response. The Phase IIa portion of the study was originally designed using a one-stage design to enter 20 eligible patients for a total of 26 including the 6 patients treated at the MTD. It was calculated that if 4 or more (≥ 15%) responses were reported among 26 evaluable patients, the treatment would be regarded as effective. However, based on initial promising response data in the first 10 patients treated at the MTD the patient number was amended to 55 patients treated at the MTD in order to demonstrate an ORR (≥ PR), better than previously reported for competitive compounds in similar patient populations. Assuming an ORR for melflufen of 50% and including 55 patients, the study will have 80% power to show that the lower limit of a 95 % confidence interval is above 32%. Amendment 4: At least 20 efficacy-evaluable patients will be treated with single agent melflufen to explore if the main activity in the promising effect seen with the combination of melflufen and dexamethasone is coming from melflufen alone**.** These patients will

Compound Name	Melflufen (J1)
Molecular Formula	$C_{24}H_{31}CL_3F\ N_3O_3$
Chemical Name	L-melphalanyl-p-L-fluorophenylalanine ethyl ester HCl
	be included in the main efficacy analysis set, as well as be assessed separately. As described above, an ORR of ≥15% would suggest that melflufen has single agent activity.
Ethics	The study will be conducted in accordance with the International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) and the appropriate regulatory requirement(s).

List of Abbreviations

AE	Adverse Event
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/SGPT
ANC	Absolute neutrophil count
AML	Acute Myelocytic Leukemia
APN	Aminopeptidase N
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/SGOT
AUC	Area under the curve
BLQ	Below the level of quantification
CBC	Complete blood count
CDP	Clinical Development Plan
Cmax	Maximum plasma concentration
CRF(e)	Case Report Form(electronic)
CRO	Contract Research Organization
CR	Complete response
CT	Computerized tomography
CTCAE	Common terminology criteria for adverse events
CXR	Chest X-Ray
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic acid
DOR	Duration of response
DSMC	Data Safety Monitoring Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOT	End of therapy
FCBP	Female of child bearing potential
GCP	Good Clinical Practice
G-CSF	Granulocyte colony stimulating factor
IMWG	International Myeloma Working Group
HIV	Human immunodeficiency virus
IV	intravenous(ly)
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
JNK	c-Jun N-terminal kinases
MM	Multiple Myeloma
MR	Minor response
MRI	Magnetic resonance imaging
mRNA	Messenger RNA
MTD	Maximum tolerated dose
NSCLC	Non-small cell lung cancer
OS	Overall survival
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression free survival

PHI	Protected Health Information
PK	Pharmakokinetics
PO	Per os/by mouth/orally
POEMS	Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein, Skin changes
PR	Partial response
PTC	Peptichemio
q.d.	quaque die/one a day
RBC	Red blood count
REB	Research Ethics Board
RPTD	Recommended phase two dose
TMA	Tissue microarray analysis
TTP	Time to progression
SAE	Serious Adverse Event
SD	Stable disease
SFLC	Serum free light chain
siRNA	Small interfering RNA
SPEP	Serum protein electrophoresis
ULN	Upper limit of normal
UPEP	Urine protein electrophoresis
VGPR	Very good partial response

1 Background

1.1 Overview of Multiple Myeloma

Multiple myeloma (MM) is a heterogeneous clonal B-cell malignancy characterized by the accumulation of abnormal antibody producing plasma cells in the bone marrow. The disease is associated with a variety of clinical manifestations including lytic bone lesions, hypercalcemia, renal impairment and anemia. MM is the second most common hematologic malignancy and accounts for approximately 11,000 deaths per year in the United States and 19,000 in Europe.[5,6]

Current treatment strategies include the use of immunomodulatory drugs such as thalidomide and its derivatives, proteasome inhibitors such as bortezomib, synthetic steroids, alkylating agents such as melphalan, anthracyclines and autologous stem cell transplant. Despite recent therapeutic advances and the use of "novel agents", MM remains an incurable disease with a median survival of approximately 5 - 7 years. [7]

Melphalan has wide spread use in the treatment of MM, both as a low dose agent in elderly patients and in myeloablative treatment supported by autologous stem cell transplantation. However, melphalan treatment is associated with significant toxicities and the development of drug-resistance. Since the introduction of melphalan, nearly 50 years ago, attempts have been made to improve the therapeutic index and thus provide a greater margin of clinical safety during treatment with the drug.

1.2 Overview of Melflufen

During the 1960's six peptide derivatives of m-L-sarcolysin (the meta-isomer of melphalan) were tested in the clinic and marketed as a cocktail under the name Peptichemio (PTC). PTC demonstrated clinical activity in a number of tumor types.[8,9] However, production was stopped in the 1980's. Researchers at Oncopeptides AB subsequently synthesized similar analogues of peptide derivatives of melphalan that showed higher anti-tumor activity in nonclinical studies.

From a large group of synthesized compounds with different amino acid additions, 2 were selected by Oncopeptides AB to enter into extensive assays against primary human tumors and tumor cell lines in vitro and in vivo, and eventually melflufen was selected as a candidate drug.

1.2.1 Melflufen Description

Melflufen (L-melphalanyl-p-L-fluorophenylalanine ethyl ester hydrochloride) is a derivative of the classical alkylating agent melphalan that has been in clinical use as an anti-tumor agent for nearly fifty years. The chemical name for Melflufen is L-melphalanyl-p-L-fluorophenylalanine ethyl ester hydrochloride and the chemical structure is provided in Figure 1.2-1. The molecular weight is 498 (free base).

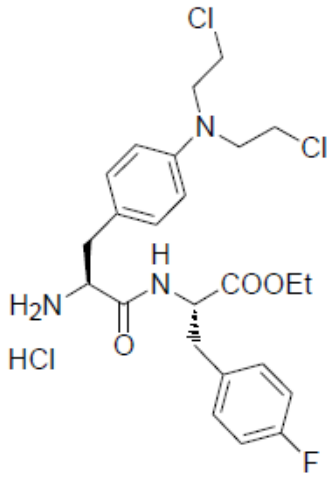

Figure 1.2-1: Structure of Melflufen

1.2.2 Non-clinical experience

1.2.2.1 Mechanism of Action and In Vitro Studies

Chemically melflufen may be described as the ethyl ester of a dipeptide consisting of melphalan and para-fluoro-L-phenylalanine. The dipeptide is hydrolyzed by the action of peptidases (for example aminopeptidase N), inside or in the vicinity of tumor cells, thereby releasing free melphalan, which has a better ability to interact with cellular DNA. Melphalan and melflufen, which can be classified as nitrogen mustard derivatives, exert their cytotoxic action through covalent interaction with intracellular nucleophiles, especially DNA, as a result of the spontaneous formation of reactive cyclic aziridinium ion intermediates. Difunctional agents, able to crosslink a DNA strand within a double helix (intrastrand), between two strands (interstrand) or between DNA and proteins, are more active than monofunctional agents. Cross-linking of DNA is probably the most important factor for the cytotoxic effect, resulting in inhibitory effects on DNA replication and transcription, which subsequently leads to cell death. The reactivity of the nucleophilic sites in DNA relates to electronic and steric properties, as well as to the involvement in hydrogen bonds within the DNA double helix. Detailed studies have suggested that the N-7 position of guanine is the most susceptible site for alkylation.[10]

When evaluated on different human cancer cell lines in vitro melflufen is, on a molar level, 10 to 139 times more potent than melphalan despite equal alkylating capacity i.e. one bis(2-chloroethyl)amino group per molecule.[11] For the RPMI8226 MM cell lines the difference in potency is approximately ten times, regardless of resistance mechanism in the sublines (i.e. Glutathione mediated or Pgp-mediated).[2] Based on correlation analysis of melflufen and melphalan in a panel of different cell lines it is concluded that the two drugs share the same main mechanism of action, i.e. alkylation of cancer cell DNA (Pearson´s correlation coefficient = 0.8).[2] This similarity in mechanism, but discrepancy in potency favoring melflufen, has also been confirmed with direct measurements of DNA syntheses[12], the alkaline single cell gel electrophoresis (Comet assay), TUNEL assay (Terminal deoxynucleotidyl transferase (dUTP)

nick end labeling) and direct comparisons of mRNA response to treatment (cMAP assay). An increased DNA damage after melflufen treatment has also been observed in MM cells where an increased level of γ-H2AX, a marker of DNA double strand break, has been observed after melflufen treatment with a concomitant activation of the DNA-damage signaling component p53.[19]

Combination studies in vitro suggest synergistic antitumoral activity of melflufen with e.g. etoposide in various human cancers[13], or with lenalidomide and bortezomib in MM cells.[19]

The potency difference between melflufen and melphalan is dependent on hydrolysis of the peptide bond in melflufen. If this bond is chemically modified to be non-hydrolysable (e.g. by using a D-amino acid, or adding a methyl group to the peptide bond) the activity is significantly impaired and the targeted superiority eliminated.[14] In searching for possible peptidases involved in this activation various human tumor cell lines were pre-treated with the enzyme inhibitors bestatin (inhibitor of several aminopeptidases) and ebelactone A (inhibitor of esterases), both which significantly decreased the cytotoxic activity of melflufen, but not melphalan.[15]

Hydrolysis of melflufen in the cytoplasm of the tumor cells appears to be a rapid event. In vitro studies in different human cancer cell lines have shown that the maximum intracellular melphalan concentration (following melflufen exposure) was reached after 15 minutes, thereafter declining with a half-life of approximately 1 hour, closely to what is expected for melphalan in aqueous solution.[15,16,16,17] Following equimolar exposure of melphalan to the same tumor cells, the levels of intracellular melphalan was below the limit of quantification. Based on the assay's limit of quantification, it was estimated that the intracellular concentration of melphalan was at least 10 times higher after exposure to melflufen than after melphalan itself, consistent with the difference in potency regarding cell death. Preincubation with bestatin, an aminopeptidase inhibitor, 60 minutes before melflufen exposure, resulted in lower intracellular concentration of melphalan and somewhat higher concentrations of melflufen.[15-16]

Aminopeptidases are widely distributed enzymes catalyzing the cleavage of amino acids from the amino terminus of protein or peptide substrates, and may localize as subcellular organelles in the cytoplasm or as membrane components. Some are monomeric and others are assemblies of relatively high mass (50 kDa) subunits. Many, but not all, of these peptidases are zinc metalloenzymes and are inhibited by the transition-state analog bestatin. Aminopeptidase N (APN, also known as CD13) is probably the most studied aminopeptidase with respect to cancer, and its expression has been associated with a number of characteristics of the malignant phenotype (e.g. cell proliferation, secretion, invasion and most often angiogenesis). A specific role of APN in hydrolyzing melflufen releasing free melphalan has been demonstrated in vitro with: i) pure APN enzyme, ii) plasmid-based overexpression of APN, or iii) down regulation of endogenous APN with siRNA.[17]

(See Oncopeptides AB Investigators Brochure).

1.2.3 In Vivo Studies

In vivo studies show that melflufen is well-tolerated and inhibits tumor growth in mice and rats.[4] Preclinical safety studies conducted with melflufen showed it to have a comparable

toxicity to that of melphalan with no suggestion of any additional or qualitatively different toxicity.

Single and repeated dose toxicity studies have been performed in mice and rats, and the resulting toxicology profile matches the expectations for an alkylating agent with significant effects on hematopoesis, particularly the white blood cell lineage is the primary target organ. In groups of animals treated with high doses of melflufen, microscopic evaluation revealed changes in the histopathological appearance in the lymphoid organs, testis and lungs. However, no pulmonary changes were observed in the human patients treated with melflufen (clinical and radiological examination).

Furthermore, the calculated lethal dose for melflufen in mice correlated to previously reported determinations for melphalan, thus confirming equi-toxicity. The single dose LD_{50} of melflufen was determined to be 132 and 66 mg/m^2 in mice and rats respectively.

Necrosis of the injection site were readily seen in mice at relatively low dose levels when dosed via the tail vein but was only seen upon histological examinations at high dose levels in rats. In order to minimize the potential for local toxic effects of melflufen, as is the case with melphalan, an acceptable infusion device will be used in the planned clinical study.

Results from animal studies also showed increased anti-tumor activity by melflufen compared with that of melphalan thus supporting the cell culture observation of targeted delivery of melphalan to the tumor cells by melflufen. It is therefore considered that melflufen has the potential for delivering enhanced therapeutic efficacy at no greater toxicity compared to standard melphalan anticancer regimens and thus increasing the therapeutic window.

1.2.4 Preclinical Multiple Myeloma Studies

Pre-clinical studies have been performed in collaboration with CCI [redacted].[18] The anti-myeloma activity of melflufen was investigated in a series of assays to determine in vitro activity in melphalan and bortezomib sensitive and resistant MM cell lines. It was shown that melflufen is more potent than melphalan, and induces apoptosis even in melphalan-, and bortezomib-resistant myeloma cells. In mice xenografted with myeloma cells, melflufen showed a more potent tumor growth inhibition and longer survival time than mice receiving equimolar doses of melphalan. Mechanistic studies showed that APN (a peptidase mediating melflufen hydrolysis to melphalan) is highly expressed in MM cells, and knockdown of APN with siRNA attenuated melflufen-induced cytotoxicity.

1.2.5 Clinical Experience

The experience of treating humans with melflufen is limited. In total of 45 patients have been treated with the drug in one extensive Phase I/II study consisting of three parts, one Phase I part (7 patients) and two Phase IIa parts (22 and 16 patients respectively).

1.2.5.1 Phase I Clinical Experience

A Phase I/IIa dose finding human clinical study has been conducted with melflufen, where in the Phase I part seven patients with advanced solid tumors were administered melflufen (25-

130 mg) as a 30-minute intravenous infusion every 3rd week in a total of 25 treatment cycles. The primary objective of the phase I part of the study was to identify the recommended Phase II dose. The majority of the adverse events reported during phase I were blood and lymphatic system disorders (46 events), gastrointestinal disorders (35 events) and general disorders (fatigue, pyrexia, chills and chest pain (22 events). Nausea in relation to or shortly after drug infusion, as well as asthenia or fatigue was also commonly observed in this population of terminally ill cancer patients. No hypersensitivity or allergic reactions were observed. Dose limiting toxicity was found to be bone marrow related, i.e. neutropenia and thrombocytopenia, mainly occurring at doses of 75 mg or above. The dose recommended for Phase II was established at 50 mg.

This side effect profile was expected based on experience from pre-clinical toxicity testing of melflufen and from known information from other alkylating agents, and are similar to what is observed for melphalan.

1.2.5.2 Phase II Clinical Experience

In the Phase IIa parts conducted in Sweden and Russia. A total of 38 patients (22 in Sweden, 16 in Russia) were treated with a total of 116 infusions (SWE: 65 cycles at doses 25-75 mg + RU: 51 cycles at doses 30-50 mg).

In the Swedish patients, doses of 25 – 75 mg were tested. The most frequently reported related adverse events of any common terminology criteria for adverse events (CTCAE) grade were neutropenia, leukopenia and thrombocytopenia experienced by 19 out of 22 patients. Neutropenia occurred in (16 patients, 27 events), leukopenia in (15 patients, 24 events) and thrombocytopenia in (11 patients, 20 events). These events were often seen in combination (16 patients, 28 episodes). The onset of the events was generally within 3 weeks after administration of study drug. The events resulted in dose reduction in next treatment period for 10 patients that continued treatment. Generally, the events were resolved within 1- 4 weeks of onset.

Of the 22 patients, 14 were evaluated for tumor response after 3 cycles of melflufen. Of these, one patient had a partial response (PR), 8 had stable disease (SD), and 5 had progressive disease (PD). Reasons for discontinuation prior to evaluation (eight patients) was due to disease progression after 1 (4 patients) or 2 cycles (2 patients), or hematological toxicity (2 patients).

In conclusion, reversible leukopenia/neutropenia and thrombocytopenia, was confirmed to be the dose-limiting toxicity of melflufen. During the Phase IIa part, the starting dose was reduced to 50 mg (from 75 mg), as hematological toxicity rendered dose reduction in several patients. The data suggested that several courses of previous chemotherapy was pre-disposing to bone marrow toxicity, and in general patients in Phase IIa were more pre-treated than those in phase I.

Sixteen patients were included in the Phase IIa part of the trial conducted in St Petersburg, Russia. The patients were diagnosed with ovarian cancer (n=8) or non-small cell lung cancer (NSCLC n=8, 2 females, 6 males) all without remaining standard treatment options. All patients had been treated with chemotherapy prior to study inclusion and in general ovarian cancer

patients had received more chemotherapy than NSCLC patients (3-5 different regimens for ovarian cancer, 2-4 different regimens for NSCLC).

The 16 patients were administered melflufen with a starting dose of 50 mg as a 30-minute infusion in a total of 51 treatment cycles. The Russian experience confirmed hematologic toxicity as the dose limiting toxicity of melflufen.

Out of 16 included patients 11 were evaluated for tumor response after nine weeks (2-3 cycles) of melflufen. These 11 included 5 ovarian cancer patients of who 4 had SD, and 1 PD. For the 6 NSCLC patients, evaluation showed SD in 4 and PD in 2. The three non-evaluable ovarian cancer patients discontinued the study before the third cycle due to hematological toxicity, one of these received supportive G-CSF (exclusion criteria). The two non-evaluable NSCLC patients discontinued the study before the third cycle due to death related to progression, and hematological toxicity (and G-CSF treatment), respectively.

Four patients died during the course of the Phase II studies. The cause of death was disease progression in three of the patients, and this was assessed by investigator as not related to melflufen therapy. One patient (male breast cancer, previously treated with six palliative chemotherapy regimens) presented with hematological nadir (neutrophils 0.6 WBC 1.3 x 109/L) 15 days after his first dose of melflufen 50 mg. Blood values improved by Day 22 (neutrophils 2.1, WBC 3.1 x 109/L), but on the same day the patient developed fever. He was admitted to hospital on Day 24, and was diagnosed with pneumonia with effusions and developed a neutropenic sepsis, from which he died on the 26th day after melflufen treatment in spite of treatment for the infection. This patient had liver metastases and was included in the study with slightly abnormal liver function tests (ALAT, ASAT, PK-INR and LDH) that worsened during the cycle and especially during his hospitalization.

In the Swedish patients, it was observed that previous chemotherapy treatment appeared predisposing to hematological toxicity. The study population was however heterogeneous with respect to diagnoses included and drugs given, and so no detailed analysis was possible. In the Russian Phase IIa patients, it was easier to identify two separate groups of patients that were different in this respect, and where all patients started with 50 mg melflufen. The ovarian cancer patients (n = 8) had received an average of 3.9 prior chemotherapy regimens, while the NSCLC patients only had received only 2.5. Dose reductions were done in six of seven ovarian cancer patients receiving more than one dose of melflufen (the remaining patient received only one dose), but not in any of the NSCLC patients (however, one patient discontinued after the 2nd dose due to the need for G-CSF support). When all patients in the Phase IIa part were considered (Sweden + Russia, n = 38), there were 8 patients that had received only 2 prior chemotherapy regimens. Among these 8 patients, hematological toxicity of grade 3 or 4 was seen in 3 patients receiving in average of 3.6 cycles of melflufen. In contrast, among 16 patients that had received 5 or more prior chemotherapy regimens, the incidence of hematological toxicity grade 3-4 was higher (14 of 16 patients), and the number of given doses of melflufen lower (average 2.6 cycles).

1.2.6 Clinical Pharmacokinetics

The pharmacokinetics (PK) of melflufen and the active metabolite melphalan were evaluated after melflufen doses ranging from 25 to 130 mg administered as an IV infusion over 30 minutes

to patients with advanced solid tumors during the Phase I-IIa trials in Sweden. Plasma concentration data of melflufen and melphalan were followed up to 6 hours after start of the 30-minute infusion. Concentration profiles were evaluated using non-compartmental methods.

It was concluded that administration of melflufen as an IV infusion resulted in a rapid and extensive formation of melphalan, which was thereafter eliminated from plasma in accordance with the pattern seen after direct administration of melphalan. Melphalan exposure increased approximately in relation to the given dose and the inter-occasion variability in exposure between treatment cycles was limited after administration of the same dose amount. Gender and body weight had no influence on the PK parameters of released melphalan. Consequently, the PK data supports an absolute dosing regimen of melflufen as proposed in the current clinical trial. Furthermore, the established PK profile of melflufen and its active metabolite melphalan supports that no further PK measurements are required in the current Phase I/IIa clinical trial given the low correlation between plasma concentrations and the efficacy and toxicity profile of melflufen. In the PK studies of melflufen, the dose 50 mg was the most frequently administered (32 occasions). It would be anticipated that a large patient would have a smaller Cmax and AUC than a smaller patient, if both patients were given the same dose. However, when these parameters were measured and were analyzed in relation to the patient´s weight, no significant relation could be detected, thereby justifying continuous use of flat-fixed dosing schedules.

2 Rationale

2.1 Study Rationale and Purpose

Melphalan has been clinically used for the treatment of malignant diseases for over fifty years, and has demonstrated activity in a variety of solid tumors like breast cancer, ovarian cancer and testicular cancer as well as in, multiple myeloma.[19,20] The clinical experience of melphalan in the treatment of multiple myeloma is extensive, both as low dose palliative treatment as well as high dose regimens supported by autologous or allogenic stem cell transplantation.

The in vitro studies demonstrated that melflufen provides targeted delivery of melphalan to the cancer cells and therefore higher concentrations are achieved in tumors. In preclinical animal studies, melflufen shows equimolar bone marrow toxicity profile to melphalan with better tumor growth suppression. The Phase I-II trial conducted in advanced cancer patients has established the recommended Phase two dose (RPTD) of melflufen, with an acceptable safety profile, to be 50 mg every 3 weeks, at least in previously treated patients with solid tumors. Melphalan is currently used clinically in MM. Cell culture studies demonstrate a greater cytotoxic potency of melflufen versus melphalan against MM cells without significant toxicity in normal cells. Overall, these preclinical and clinical studies provide the rationale for clinical protocols evaluating melflufen in MM.

2.2 Rationale for the Study Design

In the previous clinical trials performed with melflufen, no obvious interactions or other associated risk factors were observed by the investigators, except a noted tendency that patients with several lines of previous chemotherapy treatments appeared to be more vulnerable to bone

marrow toxicity than patients with less previous treatments. In addition, multiple myeloma is a disease state that adversely affects the bone marrow. Therefore, a Phase I/IIa study design was chosen to evaluate the toxicity profile in this select patient population. This is an open-label, Phase I/IIa, multicenter study which will enroll patients with relapsed and or relapsed-refractory multiple myeloma. The Phase I part of the trial will follow the standard 3 + 3 modified Fibonacci design with 3 to 6 patients, depending on dose limiting toxicity (DLT) observed, at each dose level to be tested.

Once the maximum tolerated dose (MTD) has been determined in Phase I, an additional 49 patients will be enrolled and treated at the MTD in the Phase IIa portion of the study to further evaluate toxicity and efficacy.

2.3 Rationale for Dose Selection

The primary objective of the Phase I portion of the study is to determine the MTD of the combination of melflufen and dexamethasone in subjects with relapsed and/or relapsed-refractory multiple myeloma. Dose levels have been selected based on safety and tolerability results from the previous Phase I/II trial with melflufen in solid tumor patients.

PK analyses conducted in patients with solid tumors concluded that administration of melflufen as an IV infusion resulted in a rapid and extensive formation of melphalan, which was thereafter eliminated from plasma in accordance with the pattern seen after direct administration of melphalan. For patients receiving 50 mg of melflufen the weight of the patients had no apparent effect on the observed Cmax or area under the curve (AUC) of neither melflufen nor melphalan. Consequently, the PK data support a fixed dosing regimen of melflufen as proposed in the current clinical trial synopsis.

Data show that melflufen is well tolerated when used at 50 mg for first cycle treatment in patients with lung cancer, while more pre-treated patients (patients with ovarian cancer) where more sensitive to melflufen. Since patients with MM are often both heavily pre-treated and have a disease that could weaken the bone marrow, this study will start at a dose that is lower than the identified RPTD. Once the first cohort of patients has been successfully treated with this lower dose, the dose will be escalated in a stepwise procedure to a maximum dose that is approximately the previously recommended Phase 2 dose. Up to 5 dose levels will be tested; IV melflufen given as a 30-minute infusion on Day 1 at 15 mg, 25 mg, 40 mg, 55 mg and 70 mg in combination with a fixed dose of dexamethasone 40 mg PO or IV on Days 1, 8 and 15 of each 21 day cycle. This was performed in the completed Phase I component of the study. Dose escalation of melflufen will occur only after that the Data Safety Monitoring Committee (DSMC) has reviewed each cohort and made a recommendation. Intra-patient dose escalation is permitted, according to guidelines in Section 7.8.1, for patients that are tolerating treatment and have achieved only a SD or MR as best response in order to maximize response and minimize toxicity in individual patients.

2.4 Rationale for Amendment 4

2.4.1 Rationale for 28-day cycle

As of 20 May 2015, 29 patients had been dosed with 40 mg of melflufen in the ongoing Phase II portion of the trial. A total of 89 full cycles of therapy have been administered with a median cycle length of 23 days. However, 41 of 89 (46%) completed cycles were delayed ≥ 5 days with the large majority due to delayed hematologic recovery.

The Data Safety Monitoring Committee (DSMC) convened on 18 May 2015 and reviewed the current safety data related to the 40 mg cohort of patients. Overall the safety profile is consistent and as expected with neutropenia and thrombocytopenia as the main toxicities. No new safety concerns were identified. A detailed review of the cycle length, dose intensity and response was completed. As a result of this assessment, the DSMC recommended to allow additional time for hematologic recovery and for some flexibility in dose modifications in order to maximize exposure and minimize toxicity in any given patient based on tolerability. The main objective is to allow more patients to stay on the scheduled dosing interval as well as allowing more patients to stay longer on treatment while decreasing the risk of bone marrow failure. These changes were implemented immediately, as they were seen as a safety precaution, prior to the formal amendment.

2.4.2 Rationale for Single Agent Melflufen Cohort

Dexamethasone alone is not regarded an effective treatment for multiple myeloma. When combined with other anticancer agents, two aims are to achieve an antiemetic effect and to support adrenal function. Oncopeptides AB conducted a face-to-face meeting with the FDA on 18 June 2015 where preliminary data from melflufen-dexamethasone combination in the ongoing study O-12-M1 were presented. The FDA representatives stressed that the interpretation of the therapeutic benefit of the combination was pending the availability of single-agent data from melflufen treated patients to isolate the effect of the melflufen component. The FDA would accept data from ≥20 single-agent treated patients in the presently ongoing study. If the exploratory cohort shows that the main activity of the combination of melflufen and dexamethasone arise from melflufen, future patients may be treated with melflufen without dexamethasone, thus avoiding the well-known dexamethasone side effects.

2.5 Rational for Amendment 5

2.5.1 New vial strength

Due to unexpectedly slow recruitment in the trial over the last months, the trial will have to continue beyond the expiry date of the IMP batches currently in use. The expiry date cannot be extended further since the stability studies with those batches are completed and there are no more vials available to extend the duration of the stability studies. As a consequence, a new batch will have to be shipped to the study sites. This batch will consist of 20 mg vials since the sponsor has decided to introduce this vial strength to be used in future clinical trials. Hence, the

protocol has been updated to include all three strengths (15, 20 and 25 mg). It also clarifies that the use of the 55 mg and 70mg doses are not applicable during the Phase 2 part of the study.

2.5.2 DSMC review of single agent cohort

In the event that the DSMC, at any time, determines that the risk-benefit balance of single agent melflufen is sub optimal, they will have the possibility to recommend that subsequent patients will be treated with the combination of melflufen with weekly 40 mg dexamethasone in order to optimize efficacy, without any further amendment. In this case, patients will follow the same dexamethasone dose, schedule and dose modification guidelines as the combination cohort previously described in accordance with protocol version 4.0 Amendment 3 dated 27 January 2015. A total of 40 patients have to date been treated with this combination. Patients ongoing in the single agent cohort may then have weekly dexamethasone added at the investigators discretion.

2.6 Rationale for Amendment 6

Study O-12-M1 was initiated in 2013 with the objective to assess the benefits and risks of melflufen including overall response rate (ORR), progression free survival (PFS) and overall survival (OS) in a treatment experienced relapsed-refractory multiple myeloma (RRMM) population. Based on clinical data in similar populations available at that time, showing 10-15 months OS with e.g. carfilzomib and pomalidomide (Mohty 2012), it was anticipated that it would be sufficient to follow patients for 24 months after last treatment with study drug (melflufen+dexamethasone) to appropriately document OS in the study.

The results of this study, in a population with median 4 prior lines of therapy (range 2-14), 93% last-line refractory and 67% double-refractory to an IMiD and a PI, show a surprisingly powerful clinical benefit including, but not limited to, a median OS of 20.7 months with median 28.4 months of follow-up based on data cut 9 Nov 2017. Approximately 40% of the treated patients in Phase 2 were still alive at 24 months after end of treatment or progression and could not be followed any further within the present protocol. It is of importance, not only for Oncopeptides but also for the medical community, that the majority of surviving patients in this study are followed beyond 24 months so that updated OS data can establish the real magnitude of benefit. Following these patients would further provide understanding of which patients may have the highest probability of long survival (the patients with the highest benefit/risk ratio) after treatment with melflufen. The protocol is therefore amended to allow for an extended OS follow-up assessment period beyond 24 months. This will be performed once, and after that the study will be closed for all patients and the results will be reported. There are currently 4 patients that are still in long-term follow-up, and they will then stop the study early. They have already lived longer than the median OS, and will be part of the few remaining late-stage censored patients.

3 Objectives and Endpoints

3.1 Primary Objectives

3.1.1 Phase I

The primary objective of the Phase I portion of the study is to determine the MTD of the combination of melflufen and dexamethasone in patients with relapsed and or relapsed-refractory MM.

3.1.2 Phase IIa

To evaluate the objective response rate (≥ PR) and the clinical benefit (≥ MR) to the combination of melflufen and dexamethasone and melflufen as single agent at the MTD determined in Phase I.

3.2 Secondary Objectives

To evaluate the overall response including the complete response/stringent complete response (CR/sCR), very good partial response (VGPR) partial response (PR) and clinical benefit (≥ MR), the time to progression (TTP), duration of response (DOR), progression free survival (PFS) and overall survival (OS) in all evaluable patients.

To further explore the safety and tolerability of the combination of melflufen and dexamethasone and of melflufen as single agent at the MTD.

3.3 Exploratory Objective(s)

3.3.1 Correlative Studies Objective(s)

To identify mechanisms of response and or resistance to melflufen.

Pharmacokinetics will be evaluated on patients enrolled at a select site that will be trained in the process of sample handling.

ECG assessments to screen for major effects on the QTc interval will be conducted at select sites. Should a signal be detected further evaluations will be conducted in future studies.

4 Study design

4.1 Description of Study Design

This is an open-label, Phase I/IIa, multicenter study that will enroll patients with relapsed and or relapsed-refractory MM. Phase I will follow the standard 3 + 3 modified Fibonacci design with 3 to 6 patients, depending on dose limiting toxicity (DLT) observed, at each dose level to be tested. Up to 5 dose levels will be tested; IV melflufen given as 30-minute infusion on Day 1 at 15 mg, 25 mg, 40 mg, 55 mg and 70 mg in combination with a fixed dose of dexamethasone 40mg PO on Days 1, 8 and 15 of each 21-day cycle. Alternate dose level of dexamethasone 20 mg PO on Days 1, 8 and 15, may be explored in the event that the DLT at any dose level is thought to be specifically related to the treatment with dexamethasone 40 mg (PO or IV).

Once the MTD has been determined in Phase I, an additional 49 patients will be enrolled and treated at the MTD. The evaluation of the MTD will be based on the toxicity observed during Cycle 1 of Phase I.

For both Phase I and Phase II, a treatment cycle was 21 days, however 18 May 2015 the cycle length was increased by the DSMC to 28 days. Patients will be assessed for response after each cycle with confirmation of response according to the IMWG response criteria regardless of dose level treated. Patients may receive up to 8 cycles of therapy. Doses of melflufen or dexamethasone may be interrupted or reduced in an attempt to manage toxicity according to the protocol guidelines. However, patients who have benefit from the therapy may continue treatment at the discretion of the investigator and after approval by the study sponsor for each individual case. In this case, patients will be treated with the dose last tolerated in cycle 8 or as modified based on cycle 8 toxicity requiring dose modification.

Patients in the single agent cohort will receive melflufen 40 mg on day one of each 28-day cycle. All study procedures will remain the same except for the administration of dexamethasone. Dexamethasone will be used at lower doses as an anti-emetic medication.

Dexamethasone alone is not regarded as an effective treatment. If the exploratory cohort shows that the main activity of the combination of melflufen and dexamethasone arise from the melflufen component, future patients may be treated with melflufen without dexamethasone, thus avoiding the well-known dexamethasone side effects. In the event that the DSMC, at any time, determines that the risk-benefit balance of single agent melflufen is sub optimal, they will have the possibility to recommend that subsequent patients will be treated with the combination of melflufen with weekly 40 mg dexamethasone in order to optimize efficacy, without any further amendment. In this case, patients will follow the same dexamethasone dose, schedule and dose modification guidelines as the combination cohort previously described in accordance with protocol version 4.0 Amendment 3 dated 27 January 2015. Patients ongoing in the single agent cohort may then have weekly dexamethasone added at the investigators discretion.

5 Patient Population

This trial will enroll patients with a diagnosis of relapsed or relapsed-refractory MM. Up to 36 patients will be enrolled in Phase I with 5 dose levels of melflufen to be tested. However, in the event the DSMC, upon review of all other toxicities noted for the given cohort, determines a reduced dose of dexamethasone (eg; 20mg) will be implemented for subsequent cohorts, then the lower dose of dexamethasone is to be tested with the dose level of melflufen, at which the dexamethasone caused the DLT. In this case up to 6 additional patients may be enrolled, for a maximum of 36 patients. An additional 49 patients will be enrolled in the Phase IIa part at the MTD determined in Phase I, for a total of 55 patients treated at the MTD. Patients will be enrolled from approximately 6 – 8 sites in the United States and Europe.

Amendment 4 will enroll a cohort of ≥20 patients to single agent melflufen 40 mg on day 1 of each 28-day cycle. All patients following approval of the amendment will be treated with single agent melflufen until the 20 efficacy-evaluable single-agent cohort has been completed. The objective is to treat a total of 55 efficacy-evaluable patients with 40 mg of melflufen. The 55 efficacy-evaluable patients will therefore also include the cohort of 20 single agent

patients. When 55 evaluable patients have been obtained, further recruitment will be stopped but all patients that have signed informed consent will be allowed to continue. If the 20 efficacy-evaluable single-agent cohort has NOT been fulfilled within the total of 55 patients, recruitment will continue until this cohort is complete.

5.1 Patient Screening

Written informed consent must be obtained before any protocol-specific screening tests or procedures are performed. Patients must have received at least 2 prior therapies for their disease and meet all the entry criteria detailed in Section 5.3 and 5.4. After informed consent is obtained, the screening assessments will be performed as detailed in Section 8 of the protocol. Table 8-1 lists all of the screening assessments including frequency and time lines of when assessments are to be performed. Laboratory tests noted in the inclusion criteria must be within the limits specified prior to patient registration. Testing may be repeated for this purpose. The last result obtained prior to start of study treatment will be used to determine eligibility. Assessments performed as part of the subject'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 registration.

5.1.1 Information to Be Collected on Screening Failures

Patients who sign an informed consent but fail to be started on treatment for any reason will be considered screen failures. The reason for not being started on treatment will be entered in the screening log and the eCRF.

5.2 Patient Eligibility

The investigator or designee must ensure that patients meet all the following inclusion and exclusion criteria.

5.2.1 Inclusion Criteria

Eligible patients will be considered for inclusion in this study if they meet **all** of the following criteria:

1. Male or female, age 18 years or older.

2. Patient has a diagnosis of multiple myeloma with documented relapsed and/or relapsed-refractory disease.

3. Patient has measurable disease defined as any of the following:

    a. Serum monoclonal protein ≥ 0.5 g/dL by protein electrophoresis.

    b. ≥ 200 mg of monoclonal protein in the urine on 24-hour electrophoresis

c. Serum immunoglobulin free light chain ≥ 10 mg/dL AND abnormal serum immunoglobulin kappa to lambda free light chain ratio.

d. If no monoclonal protein is detected (non-secretory disease), then ≥ 30% monoclonal bone marrow plasma cells.

4. Patient has had at least 2 or more prior lines of therapy including lenalidomide and bortezomib and has demonstrated disease progression on or within 60 days of completion of the last therapy. (See Appendix D for the definition of lines of therapy);

5. Life expectancy of ≥ 6 months;

6. Patient has an ECOG performance status ≤ 2. (Patients with lower performance status based solely on bone pain secondary to multiple myeloma will be eligible);

7. Females of childbearing potential (FCBP)† must have a negative serum or urine pregnancy test prior to initiation of therapy;

8. Female patients of child bearing potential and non-vasectomized male patients agree to practice appropriate methods of birth control;

9. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information;

10. The patient has, or accepts to have, an acceptable infusion device for infusion of melflufen (Port-a- Cath, PICC line or central venous catheter);

11. 12 lead ECG with QtcF interval ≤ 470 msec. (see Appendix G)

12. The following laboratory results must be met within 21 days, or as specified in the table of assessments, of initiation of therapy:

- Absolute neutrophil count (ANC) ≥ 1,000 cells/ mm^3 (1.0 x 10^9/L) (Growth factors cannot be used within 14 days of initiation of therapy);
- Platelet count ≥ 75,000 cells/ mm^3 (75 x 10^9/L) (platelet count ≥ 50,000/ mm^3 for patients in whom ≥ 50% of bone marrow nucleated cells are plasma cells (without transfusion during the previous 7 days to initiation of therapy);
- Hemoglobin ≥ 8.0 g/dL (RBC transfusions are permitted);
- Total Bilirubin ≤ 1.5 x upper limit of normal (ULN);

- Renal function: Estimated creatinine clearance ≥ 45 ml/min and serum creatinine ≤ 2.0 mg/dL; (See Appendix F);
- AST (SGOT) and ALT (SGPT) ≤ 3.0 x ULN.

† 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. Patient has evidence of mucosal or internal bleeding and/or is platelet transfusion refractory (i.e., unable to maintain a platelet count ≥ 50,000 cells/mm^3);

2. Any medical conditions that, in the Investigator's opinion, would impose excessive risk to the patient or would adversely affect his/her participation 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), renal insufficiency (unless felt to be secondary to MM);

3. Known active infection requiring parenteral or oral anti-infective treatment;

4. Other malignancy within the past 3 years with the exception of adequately treated basal cell carcinoma, squamous cell skin cancer, carcinoma in-situ of the cervix;

5. Other ongoing anti-myeloma therapy. Patients may be receiving concomitant therapy with bisphosphonates and low dose corticosteroids (e.g., prednisone up to but no more than 10 mg PO q.d. or its equivalent) for symptom management and comorbid conditions. Doses of corticosteroid should be stable for at least 7 days prior to initiation of therapy;

6. Pregnant or breast-feeding females;

7. Serious psychiatric illness, active alcoholism, or drug addiction that may hinder or confuse follow-up evaluation;

8. Known HIV or hepatitis B or C viral infection;

9. Patient has concurrent symptomatic amyloidosis or plasma cell leukemia;

10. POEMS syndrome (plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein and skin changes);

11. Previous cytotoxic therapies, including cytotoxic investigational agents, for multiple myeloma within 3 weeks (6 weeks for nitrosoureas) prior to start of study treatment. Biologic, novel therapy (including investigational agents in this class) or corticosteroids within 2 weeks prior to initiation of therapy. Patient has side effects of the previous therapy > grade 1 or previous baseline.

12. Prior peripheral stem cell transplant within 12 weeks of initiation of therapy;

13. Radiotherapy within 21 days prior to Cycle 1 Day 1. However, if the radiation portal covered ≤ 5% of the bone marrow reserve, the patient may be enrolled irrespective of the end date of radiotherapy;

14. Known intolerance to steroid therapy.

6 Patient Registration, Numbering and Treatment Assignment

6.1 Patient Registration

The investigator or designated staff will contact Oncopeptides AB's Contract Research Organization (CRO), and provide the requested eligibility and identifying information for the patient to register (Registration form). The form will be faxed to the CRO using a dedicated fax line (Refer to the Study Reference Manual for procedure details). Patient's eligibility will be checked by the CRO once all screening procedures are completed prior to registration and cohort assignment. Patients that do not meet all the eligibility criteria will be considered screen failures and will not be registered into the trial.

6.2 Patient Numbering

Each patient will initially receive a screening number. A Patient Number is assigned when the patient is registered in the study and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Patient Number consists of the Center Number with a sequential patient number suffixed to it, so that each patient is numbered uniquely. The time point of confirmation of eligibility and assignment of the patient number will be considered "registration" into the trial.

Once assigned, the Patient Number must not be reused for any other patient and the Patient Number for that individual must not be changed.

6.3 Treatment Assignment

During Phase I, the assignment of a patient to a particular dose level will be coordinated by the CRO. Confirmation of patient registration and the dose level assignment for a particular patient will be communicated by the CRO to the sites via return FAX and email of the patient Registration Form. During Phase IIa, confirmation of patient registration and the dose selected for the Phase IIa will also be communicated to the sites via return FAX and email of the patient Registration Form. Treatment may not begin prior to receipt of the confirmation of registration. Once registered, treatment must begin within the remaining days of the screening period. If the patient fails to start treatment for any reason, the patient will be considered a screen failure.

6.4 Replacement Policy

6.4.1 Phase I

Patients will not be replaced on study during Phase I unless they fail to start treatment, withdraw from study for reasons other than an adverse event during Cycle 1 and are considered as non-evaluable for the purposes of determining toxicity for the current cohort. Enrollment of a new patient to the current cohort will only be considered if there is less than the required number of evaluable patients to determine toxicity for the cohort. (For example; of 3 patients in a cohort, one withdraws due to disease progression but 2 others have DLT, there is no need to replace the patient for the given cohort as the MTD has already been exceeded. Alternatively; of 3 patients in a cohort, one withdraws due to disease progression but 2 others have not experienced a DLT, the patient will be replaced to fully evaluate the cohort with three evaluable patients). Decisions regarding replacement of patients will be made by the Data Safety Monitoring Committee.

6.4.2 Phase IIa

In Phase IIa patients will not be replaced if they are considered evaluable for response. All patients who have baseline evaluation, receive at least 2 cycles of therapy followed by at least one efficacy measurement will be considered evaluable for response. The Phase IIa portion of the study uses a one-stage design and will enter 49 eligible patients for a total of 55 evaluable patients (including the 6 patients treated at the MTD in the Phase I portion). If sufficient numbers of evaluable patients are not available to evaluate response, additional patients may be enrolled in order to meet the secondary endpoint. Decisions regarding replacement of patients will be made by the Data Safety Monitoring Committee.

Amendment 4 will enroll a cohort of 20 patients to single agent melflufen 40 mg on day 1 of each 28-day cycle. Replacement rules for this cohort will be the same as those described above.

7 Treatment

7.1 Study Treatment

Treatment will be given in an outpatient treatment setting in cycles. Each cycle is 21 days. As described in Amendment 4, DSMC 18 May 2015 increased the cycle length to 28 days.

Ongoing patients may increase to a 28-day schedule at investigator discretion; new patients will start with 28-day cycles.

Patients enrolled in the single agent cohort of melflufen will follow the same guidelines for drug administration as the combination cohorts.

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

Prior to initiation of therapy on Cycle 1 Day 1, CBC results must continue to meet the entry criteria:

- Absolute neutrophil count (ANC) ≥ 1,000 cells/ mm^3 (1.0 x 10^9/L) (Growth factors cannot be used within 14 days of initiation of therapy);
- Platelet count ≥ 75,000 cells/ mm^3 (75 x 10^9/L) (platelet count ≥ 50,000/ mm^3 for patients in whom ≥ 50% of bone marrow nucleated cells are plasma cells) (without transfusion during the previous 7 days to initiation of therapy).

Melflufen will be administered as a 30-minute intravenous (IV) infusion every 21 days. As described in Amendment 4, DSMC 18 May 2015 increased the cycle length to 28 days. Ongoing patients may increase to a 28-day schedule at investigator discretion; new patients will start with 28-day cycles. (See protocol section 7.10 for complete guidelines on drug preparation and administration).

Dexamethasone will be administered as oral tablets or IV infusion, at the investigators discretion according to the regional Package Insert.

7.2 Phase I (Phase I is completed)

7.2.1 Dosing Levels

Table 7-1 Dose levels to be tested

Dose Level	Melflufen Dose (IV)	Dexamethasone dose (PO or IV)
Cycle = 21 days	Day 1	Days 1, 8 and 15
Level 1	15 mg	40 mg
Level 2	25 mg	40 mg
Level 3	40 mg	40 mg
Level 4	55 mg	40 mg
Level 5	70 mg	40mg

7.3 Phase IIa

Patients will be treated at the dose determined in Phase I administered according to the same schedule; melflufen on Day 1 and dexamethasone on Days 1, 8 and 15 of each 21 day cycle or the recommended Phase II dose and schedule as determined by the DSMC. As described in Amendment 4, DSMC 18 May 2015 increased the cycle length to 28 days. Ongoing patients may increase to a 28-day schedule at investigator discretion; new patients will start with 28-day cycles.

Amendment 4 will enroll a cohort of ≥20 patients to single agent melflufen 40 mg on day 1 of each 28-day cycle. Dexamethasone will NOT be administered as an anti-tumor compound. However, all patients will be treated with dexamethasone as an anti-emetic prophylaxis with 8 mg of dexamethasone on days 1 and 2 of every cycle. An additional 4 mg of dexamethasone may be given on days 3 and 4 if needed, at the discretion of the investigator. The total dose of dexamethasone may not exceed 24 mg in any cycle. In the event that the DSMC, at any time, determines that the risk-benefit balance of single agent melflufen is sub optimal, they will have the possibility to recommend that subsequent patients will be treated with the combination of melflufen with weekly 40 mg dexamethasone in order to optimize efficacy, without any further amendment. In this case, patients will follow the same dexamethasone dose, schedule and dose modification guidelines as the combination cohort previously described in accordance with protocol version 4.0 Amendment 3 dated 27 January 2015. Patients ongoing in the single agent cohort may then have weekly dexamethasone added at the investigators discretion.

7.4 Concomitant Therapy

All baseline medications that the patient is taking within 7 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.

7.4.1 Recommended Concomitant Therapy

Prophylactic treatment with anti-emetic(s) prior to melflufen administration is recommended. Subsequent anti-emetic drugs against delayed emesis will be administered at the discretion of the investigator.

Patients should receive full supportive care, including transfusions of blood and blood products (including platelets), antibiotics, anti-diarrheals, analgesics, etc. and prophylactic treatment for tumor lysis syndrome when appropriate.

Bisphosphonate therapy IV or PO should be administered if indicated in accordance with institutional guidelines.

The prophylactic use of growth factors and platelet transfusions in cycle one of the dose escalation cohorts in Phase I is not permitted. However, at the discretion of the investigator, the use of growth factors and platelet transfusions to facilitate retreatment is permitted.

7.4.2 Contraindicated Concomitant Therapy

Concurrent therapy with any approved or investigative anticancer therapeutic drug with activity against multiple myeloma is not allowed.

Corticosteroids for non-malignant conditions (e.g., asthma, inflammatory bowel disease) > prednisone 10 mg/day (or its equivalent) are not permitted.

Amendment 4 single agent melflufen cohort may not exceed a total dose of 24 mg of dexamethasone per cycle

Other investigative agents should not be used during the study.

7.5 Phase I Dose Escalation Guidelines (Phase I is completed)

The first cohort of patients enrolled in the Phase I portion of the study will receive dose level 1. A full safety evaluation will be conducted when these patients have completed one cycle (21 days) of combination therapy. Based on the evaluation after the first cycle, the dose escalation for subsequent patients will proceed as follows:

- If no DLT is reported in the first three patients at a dose level, that dose level will be considered safe and three patients will be enrolled at the next dose level.

- If 1/3 patients in a cohort at a dose level has a DLT, the dose level will be expanded to obtain six evaluable patients.

- If 2/3 patients in a cohort at a dose level has a DLT, that dose level will not be considered safe, no further dose escalation will take place, and the MTD will have been exceeded*.

- If there is ≤ 1 patient with a DLT among the expanded cohort of six evaluable patients a cohort of three patients will be enrolled in the next higher dose level.

- If there are 2 or more patients with a DLT among the expanded cohort of six evaluable patients, that dose level will not be considered safe, no further dose escalation will take place, and the MTD will have been exceeded*.

* When the MTD has been exceeded:

If less than 6 patients have been treated in the next lower dose level (the possible MTD level), additional patients will be entered into this dose level until there are 6 patients treated. If ≤ 1 of these 6 patients encountered DLT, then this dose level will be declared to be the MTD. If 2 or more of the 6 patients encounter DLT, then the MTD has been exceeded.

NOTE: If a patient discontinues treatment for reasons unrelated to adverse events such that safety in cycle one cannot be fully evaluated, an additional patient may be enrolled; this will be

reviewed on a case by case basis in conjunction with The Data Safety Monitoring Committee. (See Section 6.4.1)

7.6 Definition of Maximum Tolerated Dose (Phase I only. Phase I is completed)

The MTD of the combination of melflufen and dexamethasone in multiple myeloma patients shall be defined as the highest dose level resulting in ≤ 1 out of 6 patients experiencing DLT in Cycle 1. The dose will be escalated in a new cohort until an MTD is identified or the maximum planned dose is achieved.

7.7 Definition of DLT (Phase I only. Phase I is completed)

A dose-limiting toxicity (DLT) is defined as an adverse event or abnormal laboratory value assessed as related or possibly related to study drug that occurs within the first 21 days of treatment and meets any of the criteria outlined below. National Cancer Institute CTCAE version 4.03 will be used for all grading.

- Grade 3 or greater non-hematologic toxicity possible/probable/definite related to treatment with melflufen or the combination of melflufen and dexamethasone. (*If a patient experiences a grade 3 or greater non-hematologic toxicity (see Table 7-5 for list of toxicities that would be considered attributable to dexamethsone) that is clearly and solely related to dexamethasone during cycle one of therapy – this will not necessarily be counted as a DLT. The event will be considered by the DSMC upon review of all other toxicities noted for the given cohort and the DSMC will determine if dose escalation should continue or if a reduced dose of dexamethasone (20mg) will be implemented for subsequent cohorts).*
- Grade 3-4 thrombocytopenia (platelet count < 50,000/ mm^3) with clinically significant bleeding.
    - Platelet transfusions in the absence of bleeding will not be considered a DLT because thrombocytopenia is an anticipated effect of the disease and side effect of treatment, particularly in a heavily pretreated patient population and patients can enter the study with pre-existing thrombocytopenia.
- Grade 4 neutropenia must occur for more than 5 days to be considered a DLT. A grade 4 neutropenia with duration of less than 5 days or grade 3 neutropenia must result in neutropenic fever with elevated temperature (defined as ANC < 1000/mm3 with a single temperature of > 38.3°C or sustained temperature of ≥ 38°C for more than one hour) to be considered dose-limiting.
- Other grade 4 hematological toxicity (other than thrombocytopenia, neutropenia and lymphopenia)
- Inability to receive Day 1 dose for Cycle 2 within 14 days of planned Day 1 Cycle 2, due to continued drug related toxicity from cycle one or drug related toxicity newly encountered on Day 1 of Cycle 2.

Patients must meet the criteria as outlined in the protocol (Section 7.9.7, Initiation of a New Cycle of Therapy), including platelet count ≥ 50,000/ mm^3 and Neutrophils ≥ 1,000 cells/mm^3, to begin cycle 2 or subsequent cycles of therapy. The prophylactic use of growth factors and platelet transfusions in cycle one of the dose escalation cohorts in Phase I is not permitted. However, at the discretion of the investigator, the use of growth factors and platelet transfusions to facilitate retreatment is permitted.

7.8 Guidelines for Dose Escalation Decisions (Phase I only. Phase I is completed)

For the purposes of dose escalation decisions, each cohort will consist of 3 to 6 newly enrolled patients who will be treated at the specified dose level.

Patients must complete a minimum of 1 cycle of treatment (21 days) with the minimum safety evaluation or have had a DLT within the first cycle of treatment to be considered evaluable for dose escalation decisions.

Dose escalation decisions will be made by the DSMC and will be based on data from the first cycle. Additional data from all other ongoing dose levels may also be included in the dose escalation decision at the discretion of DSMC. If a patient experiences a grade 3 or greater non-hematologic toxicity that is clearly and solely related to dexamethasone (see Table 7-5 for list of toxicities that would be considered attributable to dexamethasone) during cycle one of therapy – this will not necessarily be counted as a DLT. The event will be considered by the DSMC upon review of all other toxicities noted for the given cohort and the safety committee will determine if dose escalation should continue or if a reduced dose of dexamethasone (eg. 20mg) will be implemented for subsequent cohorts. The DSMC may at its own discretion alter the dose or schedule of melflufen. In the event that a lower dose of dexamethasone is to be tested, the dose level of melflufen, at which the dexamethasone caused the DLT, will be repeated.

Drug administration at the next higher dose level may not proceed until the DSMC determines that the results of the previous dose level were evaluated and that it is permissible to proceed to a higher dose level.

7.8.1 Intra-Patient Dose Escalation (Phase I only. Phase I is completed)

Intra-patient dose escalation is not permitted at any time within the first 2 cycles of treatment. After the second cycle is completed, individual patients may be considered for treatment at a dose of melflufen higher than the dose to which they were initially assigned. In order for a patient to be treated at a higher dose he or she must have tolerated the lower dose for at least 2 cycles of therapy without experiencing a DLT or requiring a dose reduction in Cycle 2 or subsequent cycles and have achieved only a stable disease (SD) or minor response (MR) as best response. In addition, the higher dose with which the patient is to be treated must be a dose that has completed the safety evaluation and has not exceeded the MTD. Patients may only escalate from one dose level to the next, without skipping a dose level. For any further increase after the initial intra-patient dose escalation, the following rules apply: the patient must not have experienced a CTCAE grade ≥ 2 drug related toxicity over at least two cycles of therapy at the lower dose, and the higher dose being considered must have been fully evaluated and shown

not to exceed the MTD. Consultation and agreement with the DSMC must occur prior to any intra-patient dose escalation occurring.

7.9 Dose Modifications

7.9.1 Phase I and Phase IIa Dose Modification and Dose Delay

Dose reductions are not permitted during Cycle 1 of Phase I unless the patient experiences a DLT. The patient may continue on protocol therapy if the toxicity resolves and the patient can be managed by a dose modification as detailed in this section. However, the occurrence of the DLT will be counted toward the assessment of the MTD. Dose reductions are permitted in subsequent cycles of Phase I and during cycle 1 and subsequent cycles of Phase IIa.

The prophylactic use of growth factors and platelet transfusions in cycle one of the dose escalation cohorts in Phase I is not permitted. However, at the discretion of the investigator, the use of growth factors and platelet transfusions to facilitate retreatment is permitted. Dose adjustments are permitted according to rules described in this section. Dose modifications different from those stated in the protocol should only be made in consultation with the medical monitor of the designated CRO –and/or the DSMC; unless required for immediate patient safety.

Administration of the study drugs will be discontinued in the event of a treatment-related toxicity that persists despite appropriate dose reductions or any other toxicity that, in the opinion of the Investigator, warrants discontinuation.

Toxicity will be assessed using the CTCAE version 4.03 (Appendix B).

All interruptions or changes to study drug administration must be recorded in the eCRF.

All dose modifications should be based on the worst preceding toxicity.

7.9.2 Dose Reduction Steps

7.9.3 Dose Reduction Steps for Melflufen

Table 7-2 outlines the dose reduction steps for melflufen based on the starting dose for Cycle one or subsequent cycles. Multiple dose reductions are permitted however, the lowest dose permitted is 15 mg. If a patient is unable to tolerate the lowest dose of melflufen due to drug related toxicity the patient must be withdrawn from study.

Table 7-2 Dose reduction steps for melflufen (Phase I/IIa)

Starting Dose	Dose reduction step - 1	Dose reduction step – 2	Dose reduction step - 3	Dose reduction step - 4
70 mg	55 mg	40 mg	25 mg	15 mg
55 mg	40 mg	25 mg	15 mg	
40 mg	25 mg	15 mg	-	-
25 mg	15 mg	-	-	-
15 mg	-	-	-	-

7.9.4 Dose Reduction Steps for Dexamethasone

Table 7-3 outlines the dose reduction steps for dexamethasone based on the starting dose for Cycle one or subsequent cycles. Multiple dose reductions are permitted. If a patient is unable to tolerate dexamethasone due to dexamethasone related toxicity, dexamethasone may be discontinued. However, the patient may continue on treatment with single agent melflufen, at the investigators discretion.

Table 7-3 Dose reduction steps for dexamethasone (Phase I/IIa)

Starting Dose	Dose reduction step - 1	Dose reduction step - 2
40 mg	20 mg	12 mg
20 mg	12 mg	-
12 mg	-	-

Amendment 4 will change the dexamethasone dosing schedule for all new patients to 8 mg given on Days 1 and 2 of each cycle. An additional 4 mg allowed at the discretion of the investigator on Days 3 and 4 only, if needed. The ongoing patients should continue with the initial schedule. In the event that the DSMC, at any time, determines that the risk-benefit balance of single agent melflufen is sub optimal, they will have the possibility to recommend that subsequent patients will be treated with the combination of melflufen with weekly 40 mg dexamethasone in order to optimize efficacy, without any further amendment. In this case, patients will follow the same dexamethasone dose, schedule and dose modification guidelines as the combination cohort previously described in accordance with protocol version 4.0 Amendment 3 dated 27 January 2015. Patients ongoing in the single agent cohort may then have weekly dexamethasone added at the investigators discretion.

7.9.5 Dose Modification Guidelines for Melflufen

Amendment 4 Dose Modifications:

The Data Safety Monitoring Committee (DSMC) convened on 18 May 2015 and reviewed the current safety data related to the 40 mg melflufen treatment cohort of patients. Overall the safety profile is consistent and as expected with neutropenia and thrombocytopenia as the main toxicities and no new safety concerns were identified. A detailed review of the cycle length, dose intensity and response was completed. As a result of this assessment, the DSMC made recommendations to allow additional time for hematologic recovery and for some flexibility in dose modifications in order to maximize exposure and minimize toxicity in any given patient based on tolerability. The main objective is to allow more patients to stay on the scheduled dosing interval as well as allowing more patients to stay longer on treatment while decreasing the risk of bone marrow failure.

Amendment 4 details the revised dose modifications of melflufen implemented as a safety precaution for all patients treated in Phase II as of 18 May 2015 and all new patients enrolled in the study.

Dose modifications of melflufen for the Amendment 4 single agent cohort will follow the same rules detailed below for melflufen.

Dose modifications are permitted for melflufen according to the following guidelines. If a patient is unable to tolerate the lowest dose of melflufen due to drug related toxicity the patient must be withdrawn from study.

Prior to each cycle of melflufen the criteria for initiation of therapy must be met. (See section 7.9.7). The dose of melflufen to be administered is based on the time to recovery of the adverse event.

The cycle length is changed from 21 to 28 days. Patients currently tolerating a 21-day cycle may continue with a 21-day or increase to a 28-day cycle length at the investigators discretion. All new patients enrolled in the study will commence with a 28-day treatment cycle.

Hematologic Toxicity:

The following guidelines for dose modification should be followed:

- If the criteria for initiation of a new cycle of therapy (See Section 7.9.7) are not met on the next scheduled Day 1 of any given cycle, re-evaluate weekly.
- If the criteria for initiation of a new cycle of therapy are met on Day 29, 36 and/or Day 43, continue therapy at the same dose level.
- If the criteria for initiation of a new cycle of therapy are met on Day 29 or Day 36, an additional week may be added to the cycle length at the investigators discretion to allow additional bone marrow recovery. However, in this circumstance, treatment must be initiated by 6 weeks (42 days).
- If the criteria for initiation of a new cycle of therapy are not met on Day 36, but are met by Day 43, a one level dose reduction may be implemented at the investigator's discretion but is not required. If the patient does not fulfill the retreatment criteria at Day 43, a dose reduction is required.
- If the criteria for initiation of a new cycle of therapy are not met by day 43, continue to re-evaluate weekly for an additional 2 weeks.
- If the criteria are met on days 50 or 57, a one level dose reduction of melflufen is required.
- 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 the study; unless in the investigators opinion the patient is benefitting from therapy, continuation may be discussed with the medical monitor or sponsor on a case by case basis.

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

Patients who discontinue the study for a study related adverse event including abnormal laboratory value must be followed as described in Section 8.2.6.

The prophylactic use of growth factors and platelet transfusions is not permitted within 14 days of initiation of treatment (C1D1). However, at the discretion of the investigator, growth factors and platelet transfusions are permitted as per institutional guidelines for the treatment of hematologic toxicity.

Non-hematologic toxicity

The resolution of all non-hematologic toxicity must be to ≤ Grade 1 or baseline and will follow the same criteria and time lines for dose reduction as hematologic toxicity noted above.

7.9.6 Dose Modification Guidelines for Dexamethasone

Table 7-5 Dose modifications for toxicity related to dexamethasone

Body System	Symptom	Recommended Action
Gastrointestinal	Dyspepsia, gastric or duodenal ulcer, gastritis Grade 1–2 (requiring medical management)	Treat with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, decrease dexamethasone dose by 1 dose level.
Gastrointestinal	> Grade 3 (requiring hospitalization or surgery)	Hold dexamethasone until symptoms adequately controlled. Restart and decrease one dose level of current dose along with concurrent therapy with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, discontinue dexamethasone and do not resume.
Gastrointestinal	Acute pancreatitis	Discontinue dexamethasone and do not resume
Cardiovascular	Edema > Grade 3 (limiting function and unresponsive to therapy or anasarca)	Diuretics as needed, and decrease dexamethasone dose by 1 dose level; if edema persists despite above measures, decrease dose another dose level. Discontinue dexamethasone and do not resume

		if symptoms persist despite second reduction.
Neurology	Confusion or Mood alteration > Grade 2 (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 2 (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 dose level. Discontinue dexamethasone and do not resume if symptoms persist.
Metabolic	Hyperglycemia > Grade 3 or higher	Treatment with insulin or oral hypoglycemics as needed. If uncontrolled despite above measures, decrease dose by one dose level until levels are satisfactory.

7.9.7 Initiation of a New Cycle of Treatment

Patients should be assessed at the beginning of each cycle according to the tests and evaluations outlined on Day 1 of each cycle in Table 8-1. To begin a new cycle of treatment the following criteria must be met:

- ANC must be $\geq 1.0 \times 10^9$/L ($\geq 1{,}000/mm^3$)
- Platelet count must be $\geq 50.0 \times 10^9$/L ($\geq 50{,}000/mm^3$)
- All non-hematologic toxicities must be $\leq$ Grade 1 or returned to baseline (except alopecia
- Absence of any other DLT's

If these criteria are not met on the next scheduled Day 1, re-evaluate weekly. If these criteria are not met on the scheduled Day 1, the new cycle should be held and can only be initiated when the criteria are met according to the dose modifications and timelines outlined in Section 7.9.5. Dose Modifications.

7.9.8 Treatment Duration

Patients may continue treatment in both Phase I and Phase IIa with the study drug for up to 8 cycles or until the patient experiences unacceptable toxicity, disease progression or withdraws consent, and/or treatment is discontinued at the discretion of the investigator. However, patients who have benefit from the therapy at the end of 8 cycles may continue treatment at the discretion of the investigator and after approval by the study sponsor for each individual case. In this case, patients will be treated with the dose last tolerated in Cycle 8 or as modified based on Cycle 8 toxicity requiring dose modification.

7.10 Study Drug Preparation and Administration

7.10.1 Melflufen Packaging and Labeling

The study drug is packaged in 50 ml glass vials containing 15, 20 or 25 mg of melphalan flufenamide (melflufen). The vials will be delivered either in separate paper boxes with respective doses of 15, 25, 40 or 55 mg, or in paper boxes with 16 vials of 20 mg. The Phase 2 dose of 40 mg will consist of two vials (either one 15 mg + one 25 mg or 2 x 20 mg) and the 55 mg dose will consist of 3 vials (two 15 mg + one 25mg). The 70 mg dose will be prepared from two dose boxes of 40 mg (volume infused calculated to ensure correct dose given). Note: The 55 mg and 70 mg doses are not applicable to the Phase 2 part of the study thus use of the 20 mg vial for these doses is also not applicable.

Medication labels on the vials will be in the local language and comply with the legal requirements of each country.

The labeling of the infusion bag for each patient is performed in connection with the preparation of the infusion solution at the hospital pharmacy.

7.10.2 Melflufen Supply

Melflufen is formulated as a sterile lyophilized powder for solution for infusion (containing melflufen and the excipient sucrose). The product, lyophilized melflufen for solution for infusion, is filled in 50 mL glass vials. Each vial contains 15, 20 or 25 mg of melflufen.

7.10.3 Melflufen Storage

Study treatments 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 melflufen shall be stored at +2 - 8°C (refrigerated).

7.10.4 Preparation of Melflufen Solution for infusion

The prescribed dose of melflufen will be prepared in a designated pharmacy. Safety precautions regarding preparation and handling of alkylating agents should be followed according to standard operating procedures at the pharmacy.

Melflufen powder will be diluted in a 250 mL 5% glucose solution infusion bag (called 5% glucose below). The melflufen solution for infusion will be administered to the patient as a 30-

minute IV infusion and the infusion **must start within 30 minutes from start of preparation (initial dilution)**.

This means that a well-planned preparation and handling procedure is required due to the relatively rapid degradation of the melflufen drug substance in water solutions.

The melflufen solution is prepared by dilution of melflufen powder in 250 mL 5% glucose according to the prescribed dose and the dosing table below.

7.10.4.1 Materials

Melflufen Powder:	15, 20 or 25 mg in a glass vial. Delivered in paper boxes Store at +2 to +8 °C (refrigerated) until preparation. Only take out the number of vials to be used. Allow the vial/s to equilibrate to room temperature (15-25°C) for 30 minutes before mixing with 5% glucose.
5% glucose:	Plastic infusion bag, 250 mL. **Note!** The solution should have reached room temperature (15-25°C) at the time point for preparation.
Syringe:	PP (Poly Propylene) syringes should be used when handling the Melflufen Solution. The Melflufen Solution should be injected directly into the glucose bag from the syringe through one of the injection ports. A transfer device should not be used.
Infusion tubing set:	Sites can use their standard infusion tubing sets.

NOTE: The infusion tubing set should be pre-filled with 5% glucose. Use of saline is prohibited due to the risk for precipitation.

7.10.4.2 Preparation procedure:

1. The investigator will prescribe the melflufen dose, according to protocol.

2. Prepare the labels, see below; one label should be placed on the infusion bag and one label should be placed in the patient's medical records. It is also to be filled in electronically in the eCRF at the clinic after the infusion is finished.

3. Take out the melflufen vial/s from the corresponding dose/paper box. The number of vials will depend on the dose, as listed in the table below. Allow the vials to equilibrate to room temperature (15-25°C) for 30 minutes before preparation.

4. Note the dose and batch number for the Melflufen Powder in the preparation protocol.

5. Notify the clinic that the preparation is about to begin, to make sure that the prepared infusion bag of Melflufen Solution will be collected immediately after preparation. The infusion must start within 30 minutes from start of preparation i.e the infusion must be completed within 60 minutes.

6. Use standard safety precautions for preparing chemotoxic drugs (Gown, face and eye protection, gloves and work under a LAF).Shake or vortex the vial/s to disintegrate the freeze-dried melflufen powder-cake. Add 40 mL of glucose solution from the infusion bag, using a polypropylene (PP) syringe, to the/each Melflufen Powder vial. Mix thoroughly by shaking the vial/vials until clear solution. If the solution is not clear within 10 minutes, discard and take out a new dose and start over. For 40 mg doses transfer the solutions to the 5% glucose infusion bag. For 15 and 25 mg doses the volume transferred to the infusion bag must be adjusted to ensure correct dose. For a 25 mg dose, either use one 25 mg vial and transfer the full volume (40 mL) to the infusion bag, or use two 20 mg vials and transfer the full volume (40 mL) from the first vial to the infusion bag, but only transfer 10 mL from the second vial to the infusion bag. For a 15 mg dose, use only one vial, either 15 mg or 20 mg. If 20 mg vial is used, only transfer 30 mL to the infusion bag. If 15 mg vial is used transfer the full 40 mL to the infusion bag. Do not use a transfer device, inject directly into the bag. Be careful to make sure that the dissolved melflufen solution is transferred correctly to the glucose infusion bag.

7. Turn the infusion bag upside down at least five times to ensure a good mixing of the solutions. Carefully check that the infusion solution is clear, without visible particles or colour. A non-clear solution should not be used. The Melflufen Solution should be kept at room temperature (15- 25°C).

8. Note the exact time point (hour, min) for preparation (i.e. when the 40mL glucose solution is added to the Melflufen Powder) of the Melflufen Solution in all the labels, both paper and electronic.

Table 7 – 6 List of Melflufen Powder Vials List of vials of 'Melflufen Powder' to be added to 250 mL 5% glucose solution for each melflufen dose planned to be used in the clinical trial.

Melflufen Dose (mg)	**Melflufen Powder to be added to 250 mL 5% glucose**	**No of vials that will be needed**
15	1 x 15 mg vial or 1 x 20 mg vial	1
25	1 x 25 mg vial or 2 x 20 mg vials	1 or 2
40	1 x 15 mg vial + 1 x 25 mg vial or 2 x 20 mg	2
55*	2 x 15mg vials + 1 x 25mg vial	3
70*	2 x 15mg vials + 2 x 25mg vial	4

*Note: the 55 mg and 70 mg doses are not applicable during the Phase 2 part of the study thus use of the 20 mg vial is also not applicable for these doses.

7.10.5 Labeling

The glucose bag should be labelled according to the description below. A second label should be detached and transferred to the medical records at the clinic, and be filled in electronically in the eCRF.

For Clinical trial only Protocol No: O-12-M1 **Melflufen Solution for i.v. Infusion** **Patient number [*X*]** **[*Y*] mg; Cycle number [Z]** Infusion should start within 30 minutes from start of preparation Infusions time: 30 min. Store at 15-25°C Date YYYY/MM Time of preparation xx h: xx min Sign. Investigator Name: Sponsor: Oncopeptides AB, *Phone+46 (0)70 6340211*	For Clinical trial only Protocol No: O-12-M1 **Melflufen Solution for i.v. Infusion** **Patient number [*X*]** **[*Y*] mg; Cycle number [Z]** Date YYYY/MM Time of preparation xx h: xx min Sign. Investigator Name: Sponsor: Oncopeptides AB, *Phone +46 (0)70 6340211*
This label should be placed on the infusion bag.	**This label should be placed in the medical record and the information completed on the appropriate eCRF**

7.10.6 Handling and storage of the Melflufen Solution for infusion

The labelled Melflufen solution for infusion bag should be kept at room temperature (15-25°C) and be transported immediately to the clinic for start of the infusion to the patient within 30 minutes from start of preparation (initial dilution).

Labels for vials (example):

For Clinical trial only Protocol No: O-12-M1 **Melflufen Powder for Solution for i.v. infusion** **X* mg** Batch number: xxxxx

Expiry date: YYYY/MM Store at 2-8°C (refrigerated) Sponsor: Oncopeptides AB, *Phone+46 (0)70 6340211*

*** 15, 20 or 25 mg**

In the US an additional cautionary statement will be added on the labels:
Caution: new drug limited by United States law to investigational use.

7.10.7 Melflufen Administration

The study treatment will be administered via an acceptable infusion device, which will be inserted according to standard local practice. All patients must have an acceptable infusion device for infusion prior to the initiation of the first dose of melflufen. (Port A Cath, PICC line or central venous catheter). The infusion tubing set should be pre-filled with 5% glucose.

NOTE: **Flushing the tubing set with saline is not allowed at any time due to the risk for precipitation. Glucose 5% must be used.**

The time from start of preparation to end of infusion should not exceed 60 minutes, i.e;

- The infusion should start as soon as possible, but not later than 30 minutes from the start of preparation.
- The investigational product should be administered as a 30-minute intravenous infusion.

The exact preparation time, the administered dose as well as the start and stop time for the infusion, should be documented on the appropriate eCRF page.

For the 70mg dose, the volume to be infused must be calculated to ensure the correct dose is given. Two dose boxes of 40mg should be used. Four vials (2 x 15mg and 2 x 25mg) should be dissolved in a 250 ml glucose bag according to the procedure above. From that prepared 80mg dose, only 87.5% or 218.75 ml should be infused in order for the patient to receive a 70mg dose.

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

Vital signs will be recorded pre and post infusion.

7.11 Dexamethasone

7.11.1 Dexamethasone Packaging and Labeling

Dexamethasone is a commercially available drug, available as both tablets and as various sterile formulations for intravenous administration. Where not readily available, oral dexamethasone will be supplied by Oncopeptides AB.

7.12 Dexamethasone Storage

Dexamethasone is to be stored at controlled room temperature 20 – 25°C (68-77°F). Consult the package insert for the respective product for additional storage and usage instructions.

7.12.1 Dexamethasone Administration

Dexamethasone may be administered orally or intravenously at the investigators discretion. Sites are responsible to record administration and patient compliance regarding dexamethasone dosing in the eCRF. Consult the package insert for the respective product for additional instructions for dexamethasone administration.

7.13 Study Drug Compliance and Accountability

7.13.1 Study Drug Compliance

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

7.13.2 Study Drug Accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Drug accountability will be noted by the field monitor during site visits and at the completion of the study.

For sites where dexamethasone is provided by the sponsor, sites will be asked to return all unused dexamethasone on a regular basis, at the end of the study or at the time of study treatment discontinuation.

At study close-out, and as appropriate during the course of the study, the investigator will return all used and unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Oncopeptides AB's selected CRO monitor.

8 Visit Schedule and Assessments

8.1 Study Flow and Visit Schedule

Table 8-1 lists all of the assessments and indicates with an "X", when they are to be performed. All data obtained from these assessments must be supported in the patient's source documentation.

Table 8 – 1 Visit Schedule and Assessments

Visit Schedule and Assessments for Phase I and Phase II											
PROCEDURES	**Screen**	**Cycle 1 (Days 1 – 28)**				**Cycle 2 - 8[16] (Days 1 – 28)**				**[14]End of Treatment**	**[15]Post Study Follow Up**
	-21d to -1d	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 1**	**Day 8**	**Day 15**	**Day 22**		
Informed Consent	X										
Medical History, Demographics	X										
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	
PE, Weight, Height, ECOG[1]	X	X				X				X	
Toxicity Evaluation		X	X	X	X	X	X	X	X	X	
Vital Signs (HR, Temp, RR, BP) [2]	X	X				X				X	
ECG [3]	X	X[3]				X[3]				X	
CXR	X									X	
CBC [4]	X	X[4]	X	X	X	X [4]	X	X	X	X	
Serum Chemistry [5]	X	X[5]				X [5]				X	
PT/PTT	X									X	
Urinalysis	X									X	
Correlative Studies [6,11]	X[6]	X (Day 2)[6]				X [6]				X[6]	
Pharmacokinetics[7]		X									
Pregnancy test [8]	X					X				X	
Extramedullary disease [9]	X	X[9]				X[9]				X	X[15]
Skeletal Survey [10]	X					X[10]				X	
Bone Marrow Aspiration [6,11]	X	X(Day 2)[6]				X[6,11]				X[6,11]	X[15]
Myeloma-specific lab tests including 24 hour urine collection[12]	X[12]	X				X[12]				X	X[15]
Melflufen Administration[13]		X				X					
40 mg Dexamethasone Administration[13]		Days 1, 8, 15 and 22 [13]				Days 1, 8, 15 and 22 [13]					

Dexamethasone in single-agent cohort		8 mg in days 1 and 2 mandatory, 4 mg in days 3 and 4 optional				8 mg in days 1 and 2 mandatory, 4 mg in days 3 and 4 optional					
Disease status/survival/SPM[14]											X

1. Physical exam: a complete physical examination (PE) is required at screening, Cycle 4 and 8 and end of study visit (including neurological exam and baseline symptom assessment). A symptom directed PE should be done prior to the administration of study drug on Day 1 of each cycle and at any other time at the investigators discretion. Height required at screening only.
2. Vital signs to be performed pre and post melflufen administration or as indicated by symptoms.
3. ECG: Screening and end of study 12 lead ECG will be required on all patients. Additional ECG assessments to screen for major effects on the QTc interval **will be conducted at select sites** during Cycles 1 - 3**.** (See Section 8.2.3 and Study Reference Manual for details on procedures).
4. CBC to be performed and reviewed by clinician within 24 hours of day of dosing (first day of each cycle). . To include complete blood count with differential and platelet count. Cycle 1, Day 1 lab values must remain within the entry criteria to proceed with treatment. Following Cycle 2 Day 1, a clinic visit is optional at the investigators discretion as long as the investigator reviews the CBC results and toxicity on day 8 and 15.
5. Serum Chemistry to be performed and reviewed by the investigator within 24 hours of day of dosing (first day of each cycle). Screening chemistry may be used for Cycle 1 Day 1 if within 72 hours of initiation of therapy but lab values must remain within the entry criteria to proceed with treatment. Chemistry includes: glucose, calcium, albumin, total protein, sodium, potassium, CO_2, chloride, BUN, creatinine, ALP, ALT, AST, bilirubin and LDH. Calculate creatinine clearance according to the Cockcroft-Gault equation. (See Appendix F)
6. Correlative studies: - Peripheral blood and bone marrow aspirate samples will be collected at pre-therapy, Cycle 1 Day 2, at confirmation of CR and end of therapy. In addition, collection of a sample is highly encouraged at any time a bone marrow aspirate is to be performed on a consenting patient. (BMA samples are optional on Cycle 1, Day 2 and at end of therapy). **US sites only.**
7. Pharmacokinetics: **PK samples will only be collected at one to two designated sites.** Plasma samples for determination of melflufen and melphalan concentrations will be drawn in connection to the first treatment cycle prior to start of infusion (baseline), at 15 and 25 minutes post start of infusion, immediately before end of infusion, and at 5, 10, 15, 30, 60, 120 and 210 minutes post end of infusion.
8. Pregnancy test required for females of child bearing potential.
9. Extramedullary Disease: evaluation required prior to study (28 days), to confirm response as indicated by IMWG criteria, at End of Treatment visit or upon clinical suspicion of progressive disease. This may include MRI/CT/PET scan of the abdomen/pelvis, CT or x-ray of the chest, ultrasound of the liver/spleen or abdomen. Plasmacytomas evaluable by PE should be assessed each cycle.
10. Skeletal survey (including skull, all long bones, pelvis and chest) with tumor measurements if plasmacytomas present. Required if previous survey > 12 weeks from study entry, at any time when clinically indicated or for symptoms suggesting of new or progressing bone lesions and End of Treatment. (CT/PET scan may be added to conventional X-ray of spine, ribs and pelvis with the same technique to be used with each evaluation).
11. A bone marrow aspiration is required at screening. A portion of the specimen should be sent to CCI for cell count and another portion should be tested at the local lab to include cytogenetics (standard karyotype) and FISH. Repeat bone marrow aspirate if CR, sCR is suspected and as appropriate to confirm achievement of response (aspirate only—biopsy not required) (See section 9.1 and also footnote 6 – correlative studies).
12. Myeloma lab tests: B2Microglobulin (collected at screening only); serum immunoelectrophoresis, immunoglobulin assay, M band quantitation by immunofixation, free light chain and 24 hour urine collection for Bence Jones protein to be performed at screening prior to study, Cycle 1 Day 1 and prior to each cycle thereafter and at time of study discontinuation (if last tests were > 4 weeks ago). These evaluations are to be sent to the central lab. However, local lab results can be used whenever needed and as clinically indicated before delivery of central lab results.
13. See Section 7 for study specific drug preparation and administration guidelines. Melflufen to be infused over 30 minutes. Record start and stop time of infusion. Dexamethasone 40 mg weekly dosing is only for the ongoing combination therapy cohort and NOT to be administered to patients in Amendment 4 single agent melflufen cohort. Patients in the single agent cohort will receive dexamethasone 8 mg on Days 1 and 2, with an optional 4 mg on Days 3 and 4, with the total dose not to exceed 24 mg/cycle. In the event that the DSMC, at any time, determines that the risk/efficacy balance of single agent melflufen is sub optimal, they

will have the possibility to recommend that subsequent patients will be treated with the combination of melflufen with weekly 40 mg dexamethasone in order to optimize efficacy, without any further amendment. In this case, patients will follow the same dexamethasone dose, schedule and dose modification guidelines as the combination cohort previously described in accordance with protocol version 4.0 Amendment 3 dated 27 January 2015. Patients ongoing in the single agent cohort may then have weekly dexamethasone added at the investigators discretion.

14. End of Treatment visit should be done within 30 days and prior to initiation of any subsequent therapy (whichever occurs first). Serious Adverse events should be followed until resolution or stable with no expectation of resolution. Patients that discontinue therapy for reasons other than progression at any time will continue to have disease assessments done monthly (for according to IMWG for confirmation of response/PD) until progression or initiation of subsequent therapy.
15. Following disease progression or initiation of subsequent therapy, Post study follow up includes documentation of second primary malignancies, subsequent therapy, disease status and survival. Follow-up should occur every 3 months for up to 2 years. For patients who were alive at their original End of Study, one additional OS follow-up will be made as part of Amendment 6.
16. Patients that continue therapy beyond 8 cycles will continue to follow the same schedule of assessments as required for Cycles 2 – 8.

A +/- 3-day window is permitted for all time points, following screening, to allow for holidays/weekends and scheduling difficulties. *Additional tests may be performed at the beginning of each cycle and at any reasonable time point during treatment if indicated for monitoring of drug profile/safety or for disease/health status at the discretion of the clinical investigator.

8.2 Study Assessments

All assessments will be done according to the timelines outlined in Table 8-1; Visit Schedule and Assessments.

8.2.1 Efficacy Assessments

Efficacy Assessments

- M-protein determination using both of the following procedures:
  - Serum protein electrophoresis (SPEP) and serum protein immunofixation with quantitative immunoglobulins; and
  - Urine protein electrophoresis (UPEP) and urine protein immunofixation (all using the same 24-hour urine collection);
- Serum free light chains (SFLC);
- Plasmacytoma evaluation;
- Bone marrow aspirate to quantify percent myeloma cell involvement;
- Beta2 microglobulin.
- 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. (CT/PET scan may be substituted for conventional X-ray of spine, ribs and pelvis with the same technique to be used with each evaluation).

Starting with Cycle 2, response to treatment will be assessed every cycle by M protein quantitation and immunofixation from serum, a 24-hour urine collection and SFLC. Full disease response assessment, including skeletal survey and or CT/PET scan will be performed according to the International Myeloma Working Group (IMWG) response criteria[21] to confirm response and end of treatment visit. Bone marrow aspirate will be performed to confirm CR in patients who have achieved a CR by immunofixation. Additional skeletal survey and/or CT/PET scan may be performed if the patient has bone symptoms suggested by pain and/or progression of lesions documented at baseline. If soft tissue plasmacytomas are present and measurable on physical examination they will be assessed at every cycle. Those extramedullary plasmacytomas documented and measurable only by MRI and/or CT/PET scans will be assessed by the relevant modality to confirm response according to the IMWG response criteria and end of treatment visit.

8.2.2 Safety and Tolerability Assessments

Safety Assessments:

- Serial physical examinations with vital signs and assessment of performance status;
- Routine safety laboratory tests (CBC with differential and platelets; clinical chemistry, coagulation tests) with calculation of creatinine clearance according to the Cockgroft-Gault equation);
- Chest X-ray;

- Pregnancy testing;
- Electrocardiogram; (see section 8.2.3 for details on ECG assessments)
- Neurological assessments;
- Assessment and grading of adverse events.

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

8.2.3 Electrocardiogram Assessments

At screening a 12-lead Electrogardiogram (ECG) assessment will be performed on all patients to assess the QTcF interval (Note: the QTcF interval at screening must be ≤ 470msec for the patient to be eligible for participation in the trial). (See Appendix G)

Additionally, at three select sites further ECG assessments will be done to provide data to guide future need for QTc monitoring. ECGs will then be performed via Holter monitor in Cycles 1, 2 and 3, from baseline prior to the infusion and up to 120 minutes after end of infusion. All ECGs, obtained at the select sites, will be read centrally. Please refer to the ECG section of the Study Reference Manual.

All cardiac events should be treated as per the local standard of care and referred to a specialist if clinically indicated. Treatment decisions may be based on local interpretation of the QTc. The centralized readings of ECG's by an independent ECG expert will use the Fridericia correction: QTcF.

8.2.4 Pharmacokinetic Assessments

PK samples will only be collected at one to two designated sites that will receive training in the methods of sample processing.

Plasma samples for determination of melflufen and melphalan concentrations will be drawn in connection to the first treatment cycle (Cycle 1, Day 1) prior to start of the infusion (baseline), at 15 and 25 minutes post start of infusion, immediately before end of infusion, and at 5, 10 15, 30, 60, 120 and 210 minutes post end of infusion. Additional specimen handling instructions will be provided in a site specific PK collection manual.

8.2.5 Correlative Sample Assessments

Correlative samples will be collected to identify mechanisms of response/resistance to melflufen.

Peripheral blood and bone marrow aspirate samples will be collected at screening, Cycle 1 Day 2, at time of confirmation of response and end of therapy. Cells will be subjected to proteomic study, microarray analysis, enzymatic assays, and Tissue Microarray Analysis (TMA). Cycle 1 Day 2 and end of therapy samples are optional for consenting patients.

8.2.6 Follow Up Assessments

All patients must have safety evaluations within 30 days after the last dose of study treatment.

Follow-up evaluations include review of concomitant medications and ongoing adverse events up to 30 days post treatment and any new disease related therapy. Serious Adverse Events should be followed until resolution or stabilized with no expectation of resolution. Assessment for second primary malignancies, disease status and survival will be done every 3 months for up to 2 years. For patients who were alive at their original End of Study, one additional OS follow-up will be made as part of Amendment 6.

8.2.6.1 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.

8.3 End of Treatment Visit Including Post Study Follow-Up and Premature Withdrawal

At the time patients discontinue study treatment, a visit should be scheduled as soon as possible (within 30 days or prior to initiation of subsequent therapy – whichever occurs first), at which time the End of Treatment (EOT) visit will be performed as described in Table 8-1 Visit schedule and Assessments. This will be followed by the Post Study Follow-Up assessments.

At a minimum, all patients who discontinue study treatment, including those who refuse to return for a final visit, will be contacted for safety evaluations during the 30 days following the last dose of study treatment.

Patients that discontinue therapy for reasons other than disease progression at any time will continue to have disease assessments done monthly (or according to IMWG for confirmation of response/PD) until progression or initiation of subsequent therapy. Post study follow up includes documentation of second primary malignancies, subsequent therapy, disease status and survival. Following disease progression or subsequent therapy, follow-up should occur every 3 months for up to 2 years. For patients who were alive at their original End of Study, one additional OS follow-up will be made as part of Amendment 6.

8.3.1 Criteria for Premature Patient Withdrawal

Patients may voluntarily withdraw from the study or be dropped from it at the discretion of the investigator at any time. The study can be terminated at any time for any reason by Oncopeptides AB. Patients may be withdrawn from the study if any of the following occur:

1. Disease Progression.
2. Patients may choose to withdraw from the study at any time.
3. Adverse Event(s) (AEs) that, in the judgment of the investigator, may cause severe or permanent harm or which rule out continuation of study drug.

4. Clinical judgment of the Investigator: A patient may be withdrawn from the study, if in the opinion of the investigator, it is not in the patient's best interest to continue.
5. Requiring other anti-neoplastic therapies.
6. Major violation of the study protocol (i.e., unable to adhere to study schedule).
7. Withdrawal of consent.
8. Lost to follow-up.
9. Death.
10. Confirmed pregnancy.
11. Discontinuation of the study by Oncopeptides AB.

9 Central Lab and Correlative Sample Collection and Handling

9.1 Central Lab Specimen Collection

All laboratory assessments required for assessment of response will be sent to CCI Central lab for processing. These evaluations include:

- M-protein determination using both of the following procedures:
  - Serum protein electrophoresis (SPEP) and serum protein immunofixation with quantitative immunoglobulins; and
  - Urine protein electrophoresis (UPEP) and urine protein immunofixation (all using the same 24-hour urine collection);
- Serum free light chains (SFLC);
- Bone marrow aspirate to quantify percent myeloma cell involvement;
- Beta2 microglobulin.

Local lab results can be used whenever needed and as clinically indicated before delivery of central lab results.

9.1.1 Central Lab Specimen handling and shipping

CCI will provide study specific lab kits that will contain specimen handling instructions and shipping information. Additional information can be found in the CCI study specific lab manual.

9.2 Correlative Specimen Collection and Handling

In the US sites, peripheral blood and bone marrow aspirate samples will be collected at screening, Cycle 1 Day 2, at time of confirmation of response and at end of therapy. Cycle 1 Day 2 and end of therapy samples are optional in patients providing consent. Cells will be subjected to proteomic study, microarray analysis, enzymatic assays, and Tissue Microarray Analysis (TMA).

9.2.1 Specimen Collection

Required samples:

- BM aspirate (10-15 ml in heparinized syringe/tube)
- Peripheral blood (3-10 ml green top tubes, 2 for cells and 1 for plasma)

9.2.2 Handling of Specimens

Sites located in the USA:
Samples should be sent fresh as soon as possible after sampling for receipt within 24 hours and will be processed by the receiving lab.

9.2.3 Labeling and Shipping of Samples

Fresh bone marrow and peripheral blood samples should immediately be sent (via Fed/ex or other traceable carrier) to CCI [redacted]. Samples must be received within 24 hours of collection.

Address:
450 Brookline Avenue,
Mayer 5th floor Room M553,
Boston, MA 02215.

Label all specimens with the following:

i) Subject initials
ii) Subject study number (will include protocol number)
iii) Visit at which sample was drawn (i.e. C1D2)
iv) Date sample drawn (i.e. mm/dd/yyyy)
v) Time sample drawn (24 hour clock)
vi) Sample type (e.g. plasma, bone marrow cells)

10 Safety Monitoring and Reporting

10.1 Adverse Events

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

An AE therefore can be any unfavorable and unintended sign (including laboratory finding), symptom or disease temporally associated with participation in an investigational study, whether or not considered drug-related. In addition to new events, any increase in the severity or frequency of a pre-existing condition that occurs after the patient begins study therapy is considered an AE. This includes any 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 IB would be considered "unexpected".

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

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

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

The investigator must appraise all abnormal laboratory results for their clinical significance. If any abnormal laboratory result is considered clinically significant, the investigator must provide details about the action taken with respect to the test drug and about the patient's outcome.

10.1.1 Adverse Event Reporting

All adverse events, from initiation of therapy, 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. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE Grade 1-5).
2. Its duration (Start and end dates).
3. Its relationship to the study treatment.
4. Action taken with respect to study or investigational treatment (eg. none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable).
5. Whether medication or therapy was given (eg; no concomitant medication/non-drug therapy or procedure, concomitant medication/non-drug therapy or procedure).

6. Outcome (eg; not recovered/not resolved, recovered/resolved, recovered/resolved with sequalae, fatal, unknown).
7. Whether it is a serious adverse event (SAE) as defined in Section 10.2.

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

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent up to 30 days post the last dose of study drug. Assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

Progression of malignancy should not be reported as an adverse event. Progression of malignancy with a fatal outcome should not be reported as a serious adverse event unless the event meets any of the other seriousness criteria as outlined in Section 10.2. Adverse events associated with but separate from the progression of malignancy (example, deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

10.1.2 Laboratory Test Abnormalities

10.1.2.1 Definitions and Reporting

Laboratory abnormalities that constitute an adverse event (are considered by the investigator to be clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Event eCRF.

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

10.2 Serious Adverse Events

10.2.1 Definitions

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

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

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

Note that hospitalizations for the following reasons should not be reported as serious adverse events:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
- Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
- Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event

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 at least 30 days after the patient has stopped study treatment must be reported to the Oncopeptides AB designated CRO, within 24 hours of the onset or after the investigator became aware of the SAE learning of its occurrence, via the Electronic Data Capture (EDC) system.

Any SAEs experienced after this 30-day period should only be reported to Oncopeptides AB designated CRO if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded in the EDC on the electronic Serious Adverse Event Report Form (eSAE); all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to study treatment, complete the eSAE Report Form within 24 hours to the Oncopeptides AB designated CRO Drug Safety department.

SAE reporting instructions can be found in the Data Management Entry Specification instructions for Inform.

In the event that the EDC system is non-functioning, fax transmission is possible. Regional Fax numbers are provided in the Study Reference Manual. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

Each re-occurrence, change in grade, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Oncopeptides AB study treatment, an Oncopeptides AB designated CRO Drug Safety department associate may urgently require further information from the investigator for Health Authority reporting. Oncopeptides AB may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

10.3 Pregnancies

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Oncopeptides AB designated CRO within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine 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.

Pregnancy should be reported by the investigator via the paper Pregnancy Report form and must be submitted to the Oncopeptides AB designated CRO Data Management department. Pregnancy follow-up should include an assessment of the possible relationship to the study treatment and any pregnancy outcome. Any SAE experienced during pregnancy (such as congenital anomaly/birth defect/spontaneous abortions) must be reported on the electronic Serious Adverse Event Report Form (eSAE).

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

10.4 Data Safety Monitoring Committee

A DSMC will be convened for this study and will primarily act to safeguard the interests of study subjects, assess safety and efficacy data, and for monitoring the overall conduct of the study. The committee will consist of Oncopeptides AB Chief Medical Officer, the Oncopeptides Medical Expert of the study, the CRO Medical Monitor and will be chaired by an independent multiple myeloma expert. All study investigators will be invited but are not mandatory participants. At the end of each cohort, the committee will meet and evaluate all the current safety data and make decisions regarding dose escalation or cohort expansion in the Phase I component of the study. The committee will also determine when the MTD has been reached and make recommendations on the Phase II dose and schedule. The DSMC may provide recommendations for stopping or continuing the study. The DSMC may also make recommendations related to the selection, recruitment, and retention of subjects, their management and the procedures for data management and quality control. Additional details regarding the DSMC may be found in the Oncopeptides AB DSMC Charter.

11 Data Collection and Management

11.1 Data Confidentiality

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

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

In the event that a patient revokes authorization to collect or use PHI, the Sponsor and its agents, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect follow-up safety information (e.g. has the patient experienced any new or worsened AEs) at the end of their scheduled study period.

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

11.2 Site Monitoring

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

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

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

11.3 Data Collection

An electronic Case Report Form (eCRF) is required and should be completed for each subject. The subject'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 Analysis Sets

12.1.1 Safety Analysis Set

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

12.1.2 Efficacy Analysis Set

All patients in the Phase IIa part (including the 6 patients on MTD in Phase I) who have baseline evaluation, receive at least 2 cycles of therapy and have at least one post dose efficacy measurement will be considered evaluable for response.

12.1.3 Correlative Studies Analysis

Correlative studies are an exploratory endpoint. Samples will be collected on consenting patients to identify mechanisms of response and resistance to melflufen.

12.2 Analysis of Objectives

12.2.1 Primary Objective

12.2.1.1 Phase I

The primary objective(s) of the Phase I portion of the study is to determine the MTD, after one treatment cycle, of the combination of melflufen and dexamethasone in patients with relapsed or relapsed-refractory MM.

12.2.1.2 Phase IIa

The primary objective of Phase IIa is to evaluate the objective response rate (≥ PR) and the clinical benefit (≥ MR) to the combination of melflufen and dexamethasone and melflufen as single agent at the MTD determined in Phase I.

12.2.2 Secondary Objective(s)

To evaluate the overall response including the complete response/stringent complete response (CR/sCR), very good partial response (VGPR), partial response (PR) and clinical benefit (≥ MR), the time to progression, duration of response, progression free survival and overall survival in all evaluable patients.

To further explore the safety and tolerability of the combination of melflufen and dexamethasone and melflufen alone at the MTD.

12.2.3 Exploratory Objective(s)

To identify mechanisms of response or resistance to melflufen.

Pharmacokinetic analysis will be evaluated on patients enrolled at a select site that will have training in specimen handling.

ECG assessments to screen for major effects on the QTc interval will be conducted at select sites. Should a signal be detected further evaluations will be conducted in future studies.

12.3 Analysis of Endpoints

12.3.1 Primary Endpoint Analysis Phase I

The frequency and grade of adverse events and dose limiting toxicities occurring in each cohort will be determined.

This dose escalation study will use a modified Fibonacci design with 3-6 patients at each dose level. Depending on the dose level at which DLT is observed, a maximum of 36 eligible participants may be enrolled.

Three to six patients will be entered at each dose level. If no DLT is observed in the first 3 patients, escalation will proceed. If 2 or 3 DLTs are observed in the first 3 patients, escalation stops. If 1 DLT is observed in the first 3 patients, an additional 3 patients will be entered. If no additional DLTs are observed in the three additional patients, escalation proceeds. If any DLTs are observed among the 3 additional patients (> 1 DLT among 6 patients), escalation stops.

The probability of escalating to the next dose for various true underlying rates is given in the following table.

True DLT rate	0%	5%	10%	15%	20%	25%	30%	35%	40%	45%	50%
Probability of dose escalation (i.e. 0/3 or 1/6 with DLT)	100%	97%	91%	81%	71%	60%	49%	40%	31%	23%	17%
Probability of MTD (i.e. at most 1/6 with DLT)	100%	97%	89%	78%	66%	53%	42%	32%	23%	16%	11%

12.3.2 Primary Endpoint Analysis Phase IIa

A true objective response rate of 15% of the patients would be considered promising in this population. The Phase IIa portion of the study originally used a one-stage design to enter 20 eligible patients for a total of 26 including the 6 patients treated at the MTD. It was calculated that if we saw 4 or more (≥ 15% including MR) responses among 26 evaluable patients, we would declare this treatment effective. Subjects are evaluable for response if they complete baseline evaluations; receive at least 2 cycles of therapy followed by at least one efficacy measurement.

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

Amendment 4 will enroll a cohort of ≥20 efficacy-evaluable patients to single agent melflufen to observe the ORR and CBR as an exploratory cohort**.** These patients will be assessed as part of the total efficacy analysis set (55 patients treated at MTD) as well as separately. An ORR rate of 15% or higher in the single agent cohort would suggest that melflufen has single agent activity.

12.3.3 Secondary Endpoint Analysis

The time to event secondary endpoints are defined as follows:

- Time to progression: time from first dose of study drug to progression, censored at date last known progression-free for those who have not progressed
- Progression-free survival: time from first dose of study drug to the disease progression or death from any cause, censored at date last known progression-free for those who have not progressed or died
- Duration of response: time from response to disease progression or death, or date last known progression-free and alive for those who have not progressed or died
- Overall survival: time from first dose of study drug to death or date last known alive

Overall survival, time to progression, progression free survival and the duration of response will be estimated using the method of Kaplan-Meier.

The overall response rate, as well as the different definitions of partial response will be presented for all evaluable patients in both absolute numbers and as a proportion with 95 % exact confidence interval.

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

12.4 Sample Size Calculation

12.4.1 Phase I

By using a modified Fibonacci design, cohorts of 3 to 6 evaluable patients will be enrolled in the dose-escalation part including at least six patients at the MTD level, as described in Section 4. Up to 5 dose levels will be tested. However, in the event the DSMC, upon review of all other toxicities noted for the given cohort, determine a reduced dose of dexamethasone (20mg) will be implemented for subsequent cohorts then the lower dose of dexamethasone is to be tested with the dose level of melflufen, at which the dexamethasone caused the DLT. In this case up to 6 additional patients may be enrolled, for a maximum of 36 patients. Therefore, for the Phase I portion of the study up to 36 patients may be treated in order to determine the MTD.

12.4.2 Phase IIa

Assuming a true response rate of 20 % there is approximately 80 % (exact probability: 79.31 %) probability to observe 4 or more responses with 26 evaluable patients. Amendment 3 increased the patient population to 55. Assuming an ORR for melflufen of 50% the study will have 80% power to show that the lower limit of a 95 % confidence interval is above 32%.

Amendment 4 will enroll a cohort of ≥20 efficacy-evaluable patients to single agent melflufen as an exploratory cohort. These patients will be assessed as part of the total efficacy analysis set (55 patients treated at MTD) as well as separately. An ORR rate of 15% or higher in the single agent cohort would suggest that melflufen has single agent activity.

Dexamethasone alone is not regarded as an effective treatment. If the exploratory cohort shows that the main activity of the combination of melflufen and dexamethasone arise from the melflufen component, future patients may be treated with melflufen without dexamethasone, thus avoiding the well-known dexamethasone side effects.

12.4.3 Pharmacokinetic methods

The concentration-time profiles for melflufen and melphalan will be evaluated using non-compartmental methods and the software WinNonlin Professional Version 5.3 (Pharsight Corporation).

Actual time points for drug administration and plasma sampling will be used.

The following PK parameters will be assessed where possible:

- Time of maximum observed concentration (tmax)
- Maximum observed concentration (Cmax)
- Area under the concentration versus time curve between 0h and end of drug infusion (AUC0-t)

- Area under the concentration versus time curve from 0h to infinity (AUCinf)
- Elimination phase half-life (t½)

Additional modeling may be performed based on the nature of the data.

Plasma concentrations reported to be below the limit of quantification (BLQ) will be treated as follows:

- Pre-dose concentrations and samples with BLQ concentrations before the first sampling time point with a quantifiable concentration will be set at zero.
- Concentrations reported as BLQ at time points where samples at both previous and subsequent time points show quantifiable concentrations will be estimated using interpolation if supported by the pattern of the entire concentration-time profile.
- Samples reported as BLQ at time points not followed by later time points with quantifiable concentrations will not be used for the PK evaluation. If the estimation of the terminal elimination half-life based on quantifiable concentrations indicates that the sample taken immediately subsequent to the last quantifiable sample should also have shown a quantifiable concentration, the concentration at this first BLQ value will be set equal to the LOQ value in the estimation of AUCinf and t½.

12.4.4 Statistical methods for PK parameters

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

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 SD 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.

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

13.2 Responsibilities of the Investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB must be given to Oncopeptide AB (or designated CRO) before study initiation. Prior to study start, the investigator is required

to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Oncopeptides AB (or designated CRO) monitors, auditors, Clinical Quality Assurance representatives, designated agents of Oncopeptides AB, IRBs/IECs/REBs and regulatory authorities as required.

13.3 Informed Consent Procedures

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

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

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

13.4 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.

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 institutional requirements

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

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

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

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

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

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 informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

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.

14 Protocol Adherence

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

14.1 Amendments to the Protocol

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

15 References

1 Gullbo J, Wickström M, Tullberg M, Ehrsson H, Lewensohn R, Nygren P, Luthman K, Larsson R. Activity of hydrolytic enzymes in tumour cells is a determinant for anti-tumour efficacy of the melphalan containing prodrug J1. Journal of Drug Targeting 2003, Jul;11(6): 355-363.

2 Wickström M, Fryknäs M, Hellman B, Larsson R and Gullbo J. The prodrug J1 is activated by aminopeptidase N, which results in high intracellular melphalan concentrations, DNA damage and apoptosis. Manuscript: Uppsala University, Medicinska vetenskapsområdet, Faculty of Medicine, Department of Medical Sciences

3 Chauhan D, Bandi M, Singh A, Podar K, Richardson P, Nikhil M, Viktorsson K, Lewensohn R, Spira J and Anderson K. Anti-Myeloma Activity Of Enzymatically Activated Melphalan Prodrug MELFLUFEN. (poster) ASH 2010.

4 Kaur G, Hollingshead M, Holbeck S. In vivo cultivation of tumor cells in hollow fibers. Life Science, 1995. 57: p. 131-41.

5 American Cancer Society. Cancer facts and figures 2005. Atlanta: American Cancer Society 2005.

6 Boyle P, Ferlay J. Cancer incidence and mortality in Europe, 2004. Ann Oncol 2005; 16: 481–488.

7 Kumar S., Rajkumar S.V., Dispenzieri A, et al., Improved survival in multiple myeloma and the impact of novel therapies Blood March 1, 2008 vol. 111 no. 5 2516-2520.

8 De Barberi, A., Peptichemio: A synthesis of pharmacological, morphological, biochemical and biomolecular investigations, in Symposium on Peptichemio. 1972: Milan, Italy. p. 1-46.

9 Hug, V., Hortobagyi, G.N., Buzdar A.U. et al., A phase II study of Peptichemio in advanced breast cancer. Cancer, 1980. 45: p. 2524.

10 Lawley, P.D. and P. Brookes, Further studies on the alkylation of nucleic acids and their constituent nucleotides. Biochem J, 1963. 89: p. 127-38.

11 Gullbo, J., et al., Structure-activity relationship for alkylating dipeptide nitrogen mustard derivatives. Oncol Res, 2003. 14(3): p. 113-32.

12 Gullbo, J., et al., Antitumor activity of the alkylating oligopeptides J1 (L-melphalanyl-p-L-fluorophenylalanine ethyl ester) and P2 (L-prolyl-m-L-sarcolysyl-p-L-fluorophenylalanine ethyl ester): comparison with melphalan. Anticancer Drugs, 2003. 14(8): p. 617-24.

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

14 Gullbo, J., et al., Activity of hydrolytic enzymes in tumour cells is a determinant for anti-tumour efficacy of the melphalan containing prodrug J1. J Drug Target, 2003. 11(6): p. 355-63.

15 Wickström M, The alkylating prodrug J1 can be activated by aminopeptidase N, leading to a possible target directed release of melphalan. Biochem Pharmacol, 2010. 79: p. 1281-1290.

16 Wickström M, J.J., Ponthan F, The novel melphalan prodrug J1 inhibits neuroblastoma growth in vitro and in vivo. Mol Cancer Ther, 2007. 6: p. 2409-2417.

17 Gullbo, J., Preclinical Development of New Alkylating Oligopeptides for Cancer Therapy., in Dept of Medical Sciences, Division of Clinical Pharmacology. Uppsala, Uppsala University 2003.

18 Chauhan D., Anderson K., Dana Farber Cancer Institute, Harvard Medical School, Boston. Unpublished data.

19 Furner, R.L. and R.K. Brown, L-phenylalanine mustard (L-PAM): the first 25 years. Cancer Treat Rep, 1980. 64(4-5): p. 559-74.

20 Teicher, B.A., Antitumor alkylating agents, in Cancer: Principles & Practise of Oncology (on CD-ROM), V.T. DeVita, S. Hellman, and S.A. Rosenberg, Editors. 1997, Lippincott-Raven Publishers: Philadelphia, Pennsylvania.

21 Durie et al. International uniform response criteria for multiple myeloma. Leukemia 2006;20:1467-73

22. Rajkumar SV, Harousseau JL, Durie B, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. Blood 2011; 117:4691.

23. Mohty B, El-Cheikh J, Yakoub-Agha I, et al. Treatment strategies in relapsed and refractory multiple myeloma: A focus on drug sequencing and 'retreatment' approaches in the era of novel agents. Leukemia, 2012; 26(1), 73–85