Protocol OP-109
Version 2.2, 10 March 2021

Protocol Title: A randomized, two-period, cross-over, Phase 2 study, comparing the pharmacokinetics, and assessing safety and tolerability of peripheral and central intravenous administration of melflufen in patients with relapsed and refractory multiple myeloma.

National Clinical Trial number: NCT04412707

Title Page

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Protocol Number:	OP-109
Compound Name:	Melflufen
Short Title:	A Phase 2 study comparing the pharmacokinetics and assessing safety and tolerability of peripheral and central i.v. administration of melflufen in patients with RRMM.
Sponsor Name:	Oncopeptides AB
Legal Registered Address:	Västra Trädgårdsgatan 15 SE-111 53 Stockholm, Sweden
Clinical Research Organization (CRO):	PSI CRO AG Baarerstrasse 113a 6300 Zug, Switzerland

Regulatory Agency Identifying Number(s):

IND: 116362

EudraCT: 2019-004127-21

Approval Date:	**Version 1.0: 02 December 2019** **Amendment 1 Version 2.0: 30 April 2020** **Amendment 2 Version 2.1: 23 December 2020** **Amendment 3 Version 2.2: 10 March 2021**

Signature Page – Sponsor and Lead Investigator

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Protocol Number: OP-109

Sponsor:

_____ _____

[redacted] Date

Clinical Study Physician
Oncopeptides AB
Luntmakargatan 46
111 37 Stockholm, Sweden
Phone: [redacted]

_____ _____

[redacted] Date

Clinical Operations Director

Protocol Agreement Page - Principal Investigator

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Protocol Number: OP-109

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

_____

Name of study center

_____

Principal Investigator Name (Printed)

_____ _____

Principal Investigator (Signature) Date

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

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

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment 3	*10-Mar-2021*
Amendment 2	*23-Dec-2020*
Amendment 1	*30-Apr-2020*
Original Protocol	*02-Dec-2019*

Amendment 3 (10-March-2021)

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment:

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

Section # and Name	Description of Change	Brief Rationale
Section 8.4.1 Time Period and Frequency for Collecting AE and SAE Information	All SAEs will be recorded and reported to the assigned Pharmacovigilance CRO, TFS ~~PSI pharmacovigilance (PVG) unit~~, within 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to ~~the~~ TFS ~~PVG unit~~ within 24 hours after becoming aware of the updated SAE data. Investigators are not obligated to actively seek AE or SAE after EoT visit and conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a patient has been discontinued from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify TFS ~~the PVG unit~~.	Safety CRO changed for the study from PSI to TFS

Section # and Name	Description of Change	Brief Rationale
Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting Several sections within the appendix	• It is not acceptable for the investigator to send photocopies of the patient's medical records to the assigned Pharmacovigilance CRO (TFS ~~PSI Safety Desk~~) in lieu of completion of the SAE form and AE/SAE eCRF page. • There may be instances when copies of medical records for certain cases are requested by assigned Pharmacovigilance CRO (TFS ~~PSI Safety Desk).~~ In this case, all patient identifiers, with the exception of the patient number, will be redacted on the copies of the medical records before submission to assigned Pharmacovigilance CRO (TFS ~~PSI Safety Desk~~). • There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to assigned Pharmacovigilance CRO (TFS ~~PSI Safety Desk~~). However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to assigned Pharmacovigilance CRO (TFS ~~PSI Safety Desk~~). • The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by assigned Pharmacovigilance CRO (TFS ~~PSI Safety Desk~~) to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include	Safety CRO changed for the study from PSI to TFS

Section # and Name	Description of Change	Brief Rationale
	additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. **SAE Reporting to safety.report@oncopeptides.com ~~SafetyDesk@psi-cro.com~~ via Paper CRF** • SAE reports are completed on paper and transferred to ~~PSI PVG unit~~ TFS , ~~either~~ via email to safety.report@oncopeptides.com ~~safetydesk@psi-cro.com~~ , or facsimile can be used as back-up only if emailing reports is not possible (~~local~~ fax number~~s~~ is ~~are~~ provided in the Investigator Site File). • In ~~rare~~ exceptional circumstances and in the absence of facsimile equipment, notification to the CRA or Medical Monitor by telephone is acceptable ~~with a copy of the SAE data collection tool sent by overnight mail or courier service.~~ • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. ~~Contacts for SAE reporting:~~ ~~Nickolai Usachev, Senior Manager PVG Unit, PSI~~ ~~Email: nickolai.usachev@psi-cro.com~~ ~~Mobile phone: +79219445972~~	

Section # and Name	Description of Change	Brief Rationale
Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information	**Pregnancy Reporting to assigned Safety CRO, TFS ~~PSI~~; via Paper Pregnancy Reporting Form** • ~~Facsimile or~~ E~~e~~mail transmission of the Pregnancy paper Reporting Form is the preferred method to transmit this information to the assigned Safety CRO. If emailing the report is not possible facsimile can be used as a back-up method. (~~FAX: [country-specific] or~~ Email: safety.report@oncopeptides.com ~~safetydesk@psi-cro.com~~ or use the fax number provided in the Investigator Site file). • In ~~rare~~ exceptional circumstances and in the absence of email ~~facsimile~~ or ~~email~~ facismile equipment, notification to ~~of~~ the CRA or Medical Monitor by telephone is acceptable ~~with a copy of the Pregnancy data collection tool sent by overnight mail or courier service~~.	Safety CRO changed for the study from PSI to TFS
Protocol	Administrative updates and corrected typos.	Administrative update

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1. Protocol Summary

1.1. Synopsis

Protocol Title:

A randomized, two-period, cross-over, Phase 2 study, comparing the pharmacokinetics, and assessing safety and tolerability of peripheral and central intravenous administration of melflufen in patients with relapsed and refractory multiple myeloma.

Short Title:

A Phase 2 study comparing the pharmacokinetics and assessing safety and tolerability of peripheral and central i.v. administration of melflufen in patients with RRMM.

Rationale:

The outcome in relapsed and refractory multiple myeloma (RRMM) is still unsatisfactory despite recent improvements in treatment. Thus, new therapeutic options are needed. Melphalan flufenamide (hereinafter referred to as melflufen) is a peptide-drug conjugate that is rapidly taken up by multiple myeloma (MM) cells due to its high lipophilicity (Chauhan et al 2013, Wickström et al 2017). Once inside the myeloma cell, the activity of melflufen is determined by its immediate cleavage by peptidases into hydrophilic alkylator payloads that are entrapped (Wickström et al 2017, 2010, Gullbo et al 2003). Melflufen is 50-fold more potent than melphalan in myeloma cells in vitro due to the increase of intracellular alkylator activity (Chauhan et al 2013, Wickström et al 2017).

Melflufen has been evaluated in combination with low dose dexamethasone in patients with RRMM in a Phase 1/2 clinical trial (O-12-M1, NCT01897714). The trial established the recommended dose at 40 mg of melflufen every 28 days combined with 40 mg dexamethasone weekly. As of the database lock 9th November 2017, there were 45 patients treated with 40 mg melflufen every 28 days in combination with weekly dexamethasone. The Overall Response Rate (ORR) (Partial Response [PR] or better) was 31% and the Clinical Benefit Rate (CBR) (Minimal response [MR] or better) was 49%. The patients had a median of 4 prior lines of therapy, including Immunomodulatory Drugs (IMiDs), Proteasome Inhibitors (PIs) and alkylators. The median progression free survival (PFS) was 5.7 months based on 41 events, and the overall survival (OS) was 20.7 months based on 23 events in the 45 patients (Richardson et al 2020).

There are also ongoing clinical studies in RRMM patients, including a phase 2 study in patients refractory to pomalidomide and/or an anti-CD38 antibody (anti-CD38 mAbs) (OP-106 Horizon, NCT02963493), a phase 2 study in patients with impaired renal function (OP-107 Bridge, NCT03639610), a phase 1/2 study where melflufen and dexamethasone are combined with daratumumab or bortezomib (OP-104 Anchor, NCT03481556), and a randomized phase 3 study (OP-103 Ocean, NCT03151811) comparing melflufen and dexamethasone to pomalidomide and dexamethasone.

Current labeling of several other alkylating agents such as melphalan, bendamustine and cyclophosphamide, allows for peripheral vein administration but local reactions at the infusion site have been observed for several alkylating compounds. In addition, in trials with

Peptichemio, a mixture of six synthetic peptides containing m-L-phenyl alanine mustard, (which is the alkylating moiety of e.g. melphalan) phlebitis was very common leading to oedema and phlebosclerosis. (Paccagnella et al 1986). In guidelines for clinical management of extravasations, there are different opinions on the tissue damaging potential of melphalan, but in the European Society for Medical Oncology (ESMO) guidelines it is described as an irritant (Pérez-Fidalgo 2012). Nonclinical local tolerance testing by intradermal injection in mice showed no difference between melphalan and melflufen at clinically relevant concentrations. (data on file). In clinical studies to date, melflufen has only been administered via a central vein, but peripheral vein administration might be potentially preferable to some patients if the safety and tolerability profile is acceptable.

Objectives and endpoints:

Objectives	Endpoints
Primary	
• To evaluate and compare the pharmacokinetic (PK) variables C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ of melphalan after central and peripheral intravenous infusion of melflufen	• Maximum observed concentration C_{max} • Area under the concentration-time profile from 0 hours (start of infusion) to the last measurable concentration $AUC_{(0-t)}$ • Area under the concentration-time profile from 0 hours to infinity $AUC_{(0-\infty)}$
• To assess the local tolerability of peripheral intravenous administration of melflufen	• Frequency and severity of local reactions including phlebitis at infusion site after peripheral intravenous administration
Secondary	
• To evaluate and compare the PK variables C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ of melflufen and desethyl-melflufen, and to evaluate the elimination half-life ($t_{½}$) for melflufen, melphalan and desethyl-melflufen after central and peripheral intravenous infusion of melflufen	• Maximum observed concentration C_{max} • Area under the concentration-time profile from 0 hours to the last measurable concentration $AUC_{(0-t)}$ • Area under the concentration-time profile from 0 hours to infinity $AUC_{(0-\infty)}$ • Elimination half-life $t_{½}$
• To assess safety and general tolerability of melflufen	• Frequency and Grade of Treatment Emergent Adverse Events (TEAEs)
To evaluate efficacy: • Best response during the study • Overall response rate (ORR) • Clinical benefit rate (CBR) • Duration of response (DOR)	• Best Response (stringent complete response (sCR), complete response (CR), very good partial response (VGPR), partial response (PR), minimal response (MR), stable disease (SD) or progressive disease (PD)
	• ORR (including CR/sCR, VGPR and PR)

• Duration of Clinical Benefit (DOCB) • Time to response (TTR) • Time to progression (TTP) • Time to next treatment (TTNT) • Progression Free Survival (PFS)	• CBR proportion of patients with ≥ MR as best response
	• DOR (time from the first confirmed response of sCR, CR, VGPR or PR to first confirmed disease progression, or death due to any cause).
	• DOCB (time from first evidence of confirmed assessment of sCR, CR, VGPR, PR, or MR to first confirmed disease progression, or to death due to any cause.)
	• TTR (time from randomization to the date of the first documented confirmed response in a patient that has responded with ≥ PR (sCR, CR, VCPR or PR))
	• TTP (time from the date of randomization to the date of the first documented confirmed PD)
	• TTNT (time from randomization to the date of next anti-myeloma treatment)
	• PFS (time from the date of randomization to the date of first documentation of confirmed PD or death due to any cause)
Exploratory:	
• To assess translational biomarkers that might predict effects of the treatment, aid in monitoring of disease progression as well as improve understanding of mechanism of action	• Deoxyribonucleic Acid (DNA), Ribonucleic Acid (RNA) and protein based drug response biomarkers including but not limited to aminopeptidases and esterases
• To assess and compare patient satisfaction and preference, nurse convenience and preference after central and peripheral intravenous administration of melflufen	• Value in each scale assessed by patients • Value in each scale assessed by nurses
• To assess Quality of Life (QoL) based on Patient Reported Outcome (PRO)	EQ-5D-5L • Value and changes from baseline in VAS and EQ-index • Number of subjects by category and dimension
• To assess Use of health services and days of hospitalization	• Number of health services • Number and days of hospitalization

Overall Design:

This is a randomized, two-period, cross-over Phase 2 study, comparing PK, and assessing safety and tolerability and efficacy of peripheral and central intravenous administration of melflufen in patients with RRMM, see Appendix 10. It is an international study, enrolling patients in US and Europe. The study will enroll patients following at least 2 lines of prior therapy.

Patients will be randomized (1:1) to Arm A or Arm B, see 1.2 Schema. For each arm, treatment will be given in 28-day cycles and may be given in an outpatient treatment setting. PK samples will be collected at Day 1 of Cycles 1 and 2.

Number of Patients:

Approximately 25 participants will be randomly assigned to study treatment, the main PK and local tolerability analysis will take place when there are 20 PK evaluable patients given at least two doses of melflufen with PK sampling, sufficient to evaluate all PK parameters, one PK sampling series following peripheral administration and one PK sampling series following central administration. If a patient is not able to receive two doses of 40 mg melflufen, including an observation period of 28 days after the second dose, with sufficient PK samples taken, they will be replaced, if necessary to achieve 20 PK evaluable patients.

Intervention Groups and Duration:

Arm A:

- In Cycle 1, melflufen 40 mg will be administered as a 30-minute infusion via a peripheral venous catheter (PVC). From cycle 2 and onwards melflufen will be administered as a 30-minute infusion via a central catheter*.
- Dexamethasone will be given p.o. at the standard dose of 40 mg weekly, at day 1, 8, 15 and 22. Patients ≥ 75 years of age should receive a dose of dexamethasone p.o. of 20 mg weekly.

Arm B:

- In Cycle 1, melflufen 40 mg will be given as a 30-minute infusion via a central catheter. At Cycle 2, melflufen will be administered as a 30-minute infusion via a PVC. From Cycle 3 and onwards melflufen will be administered as a 30-minute infusion via a central catheter*.
- Dexamethasone will be given p.o. at the standard dose of 40 mg weekly, at day 1, 8, 15 and 22. Patients ≥ 75 years of age should receive a dose of dexamethasone p.o. of 20 mg weekly.

Dose modifications and delays in therapy may be implemented based on patient tolerability. In the event of a cycle delay unrelated to dexamethasone toxicity, it is recommended to continue dexamethasone weekly.

* After 6 patients have received peripheral infusion with adequate PK data, a data and safety monitoring committee (DSMC) will assess the safety and tolerability of received peripheral infusion. The DSMC may then allow continuation with peripheral infusion in Cycle 3 and

onwards (in both Arm A and B). The investigator in agreement with the patient will determine whether continued treatment will use peripheral or central administration.

Data and Safety Monitoring Committee:

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

The DSMC will assess the benefit/risk profile of the study. All reported Grade 3-4 treatment-related non-hematological adverse events (AEs), all local toxicities at the peripheral injection site as well as all serious adverse events (SAEs), and as well as efficacy and PK data will then be presented to the DSMC.

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

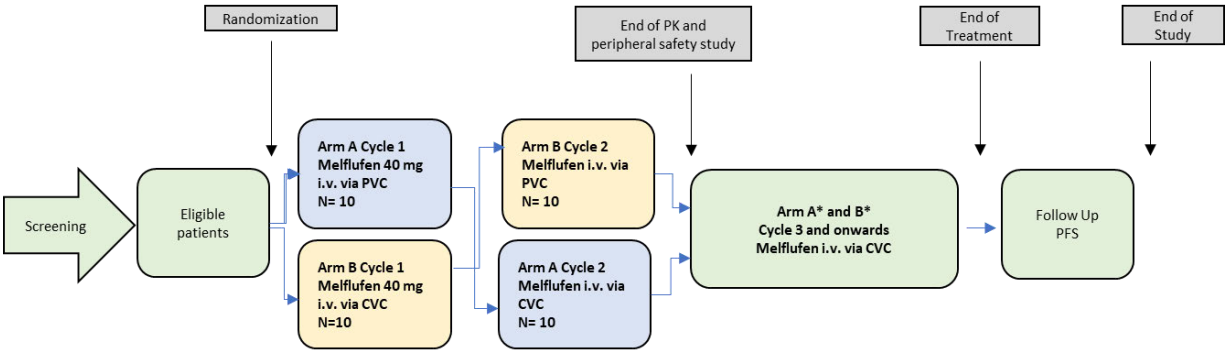
After 6 patients have received 2 cycles of 40 mg melflufen, one cycle via central and one cycle via peripheral infusion with adequate PK data and with an observation period of at least 28 days, a DSMC will assess the safety and tolerability of received infusions. The DSMC may then allow continuation with peripheral infusion in Cycle 3 onwards (in both Arm A and B). The investigator in agreement with the patient will determine whether continued treatment will use peripheral or central administration.

If no major safety signals have been reported, recruitment may continue during preparations for DSMC meeting.

Following a DSMC evaluation of data from at least 20 PK evaluable patients with an observation period of at least 28 days from the second dose of melflufen, the main PK and safety and tolerability study may be concluded.

A patient is considered to have completed the PK study when administered two 40 mg doses of melflufen with PK sampling, one PK sampling series following peripheral administration and one PK sampling series following central administration and that the sampling series are sufficient to evaluate all PK parameters. Patients in both arm A and B will receive treatment until there is documented PD according to IMWG-URC guidelines, unacceptable toxicity, the patient/treating physician determines it is not in the patient´s best interest to continue or patient´s withdrawal of consent.

1.2. Schema



1.3. Inclusion Criteria

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

1. Male or female, age 18 years or older;
2. Capable of giving signed informed consent as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol;
3. A prior diagnosis of MM with documented disease progression in need of treatment at time of screening;
4. Measurable disease defined as any of the following:
   - Serum monoclonal protein ≥ 0.5 g/dL by serum protein electrophoresis (SPEP)
   - ≥ 200 mg/24hr of monoclonal protein in the 24hour urine collection by electrophoresis (UPEP)
   - Serum free light chain (SFLC) ≥ 10 mg/dL AND abnormal serum kappa to lambda free light chain (FLC) ratio
5. Received at least 2 prior lines of therapy and is refractory to an IMiD and a PI. The definition of refractory includes intolerance to an IMiD/PI after at least two 28-day cycles of therapy, see Appendix 10 and Appendix 8.
6. Adequate peripheral arm veins for repeated intravenous infusions
7. Life expectancy of ≥ 6 months;
8. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2, see Appendix 6. Patients with ECOG performance status **> 2** solely based on bone pain secondary to MM may be eligible following consultation and approval of medical monitor;
9. 12-lead Electrocardiogram (ECG) with QT interval calculated by Fridericia Formula (QTcF) interval of ≤ 470 msec, see Appendix 11

10. Adequate organ function with the following laboratory results during screening (within 21 days) and immediately before study treatment administration on Cycle 1 Day 1:
    - Absolute neutrophil count (ANC) ≥ 1,000 cells/mm^3 (1.0 x 10^9/L) (Growth factors cannot be used within 10 days (14 days for pegfilgrastim) prior to initiation of study treatment)
    - Platelet count ≥ 75,000 cells/ mm^3 (75 x 10^9/L) (without transfusions during the 10 days prior to initiation of therapy)
    - Hemoglobin ≥ 8.0 g/dL (Red blood cell [RBC] transfusions are permitted)
    - Total Bilirubin ≤ 1.5 x upper limit of normal (ULN), except patients diagnosed with Gilbert's syndrome that have been reviewed and approved by the Medical Monitor
    - AST (SGOT) and ALT (SGPT) ≤ 3.0 x ULN
    - Renal function: Estimated glomerular filtration rate (eGFR) by CKD-EPI formula of ≥ 45 mL/min, see Appendix 12.
11. Must have or be willing to have an acceptable central catheter (Port a Cath, peripherally inserted central catheter [PICC] line, or central venous catheter [CVC]) and a PVC;
12. a) **Male patients:** A male patient is eligible if he agrees to use contraception as detailed in Appendix 4 of this protocol during the treatment period and for at least 3 months after the last dose of study treatment and refrains from donating sperm during this period

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

I. Not a woman of childbearing potential (WOCBP) as defined in Appendix 4

or

II. A WOCBP who agrees to follow the contraceptive guidance in Appendix 4 during the treatment period and for at least 28 days after the last dose of study treatment

1.4. Exclusion Criteria

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

1. Primary refractory disease (i.e. never responded with at least MR to any prior therapy);
2. Evidence of mucosal and/or internal bleeding or platelet transfusion refractory (platelet count fails to increase by > 10,000 cells/mm^3 after a transfusion of an appropriate dose of platelets);
3. Any medical conditions that, in the Investigator's opinion, would impose excessive risk to the patient or would adversely affect his/her participating in this study. Examples of such conditions are: a significant history of cardiovascular disease (e.g., myocardial infarction, significant cardiac conduction system abnormalities, uncontrolled hypertension, ≥ Grade 3 thromboembolic event in the last 6 months);

4. Known active infection that is uncontrolled or has required intravenous systemic therapy within 14 days of randomization. Patients that have required oral anti-infective treatment within 14 days of randomization should be discussed with the Medical Monitor;
5. Other malignancy diagnosed or requiring treatment within the past 3 years with the exception of adequately treated basal cell carcinoma, squamous cell skin cancer, carcinoma in-situ of the cervix or breast or very low and low risk prostate cancer in active surveillance;
6. Pregnant or breast-feeding females;
7. Serious psychiatric illness, active alcoholism, or drug addiction that may hinder or confuse compliance or follow-up evaluation;
8. Human immunodeficiency virus (HIV) or active hepatitis B or C viral infection;
9. Concurrent known or suspected amyloidosis or plasma cell leukemia;
10. POEMS syndrome (plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein and skin changes);
11. Known central nervous system (CNS) or meningeal involvement of myeloma
12. Any of the following treatments, within the specified timeframe
    - Previous cytotoxic therapies, including cytotoxic investigational agents, for MM within 3 weeks (6 weeks for nitrosoureas) prior to initiation of therapy.
    - The use of live vaccines within 30 days before initiation of therapy.
    - IMiDs, PIs and or corticosteroids within 2 weeks prior to initiation of therapy.
    - Other investigational therapies and monoclonal antibodies within 4 weeks of initiation of therapy.
    - Prednisone up to but no more than 10 mg orally q.d. or its equivalent for symptom management of comorbid conditions is permitted but dose should be stable for at least 7 days prior to initiation of therapy.

    Other washout times may be considered following consultation with the medical monitor.
13. Residual side effects to previous therapy > Grade 1 prior to initiation of therapy (Alopecia any grade and/or neuropathy Grade 1 without pain are permitted);
14. Prior stem cell transplant (autologous and/or allogenic) within 6 months of initiation of therapy;
15. Prior allogeneic stem cell transplantation with active graft-versus-host-disease;
16. Prior major surgical procedure or radiation therapy within 4 weeks of the initiation of therapy (this does not include limited course of radiation used for management of bone pain within 7 days of initiation of therapy);
17. Known intolerance to the required dose and schedule of steroid therapy, as determined by the investigator;
18. Known hypersensitivity reaction to melphalan, melflufen or its excipients
19. Prior treatment with melflufen

1.5. Schedule of Activities (SoA)

Assessment	**Screening Days -21 to -1**	**Regimen A and B, All Cycles** (except where specified)				**End of Treatment** [y]	**PFS -FU** [z]	**End of Study**
		Day 1	Day 8	Day 15	Day 22			
		Visit window: ±3days (except for cycle 1 day 1)				±3days	±7days	
Informed consent [a]	X							
Inclusion/exclusion criteria	X	X						
Medical history [b]	X							
Myeloma history including characteristics [c]	X							
Physical examination and symptom assessment [d]	X	X	(X)	(X)	(X)	X		
Vital signs [e]	X	X	(X)	(X)	(X)	X		
ECOG performance status	X	X				X		
Pregnancy test, WOCBP [f]	X	X				X		
12- lead Electrocardiogram [g]	X					X		
Chest X-ray [h]	(X)							
Hematology [i]	X	X	(X)	X	(X)	X		
Chemistry [j]	X	X				X	(X)	
Biomarker blood samples [k]		X [C1]				X		

Assessment	**Screening Days -21 to -1**	**Regimen A and B, All Cycles** (except where specified)				**End of Treatment** [y]	**PFS -FU** [z]	**End of Study**
		Day 1	Day 8	Day 15	Day 22			
		Visit window: ±3days (except for cycle 1 day 1)				±3days	±7days	
β2-microglobulin	X							
Hepatitis B, C and HIV screen	X							
Urinalysis	X							
Bone marrow aspiration [l]	X	(X)				(X)	(X)	
M protein assessment [m]	X	X				X	X	
Myeloma response assessment		X[C2→]				X	X	
Extramedullary myeloma (plasmacytoma) assessment [n]	X	(X)				(X)	(X)	
Lytic bone lesions assessment: Skeletal X-ray or low-dose CT [o]	X	(X)				(X)	(X)	
Randomization [p]	X							
Criteria for initiation of therapy/ new cycle [q]		X						
Dexamethasone administration and review of patient compliance [r]		X	X	X	X			
Melflufen administration		X						
Pharmacokinetic samples [s]		X [C1,C2]						
Concomitant medications [t]	X	→	→	→	→	X →		
AE monitoring [u]		→	→	→	→	X →		

Inspection of peripheral infusion site [v]		(X)	(X)					
Patient treatment satisfaction and preference scales[w]		X[C1,C2,C3]						
QoL questionnaire EQ-5D-5L [x]		X				X	X	
Nurse convenience and preference scales [aa]		X[C1,C2]						
Use of health services and hospitalization [bb]	X	X				X	X	
Subsequent therapy							(X)	
End of study information								X

(X) Only if indicated

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

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

c) MM history including characteristics include date of initial diagnosis, ISS, R-ISS stage and cytogenetics at diagnosis (if previously evaluated). ISS and R-ISS stage at time of study entry, see Appendix 9. Prior surgery and/or radiation and anticancer therapy, including start and stop dates, documentation of best response, date of progressive disease and relapsed or refractory status, see Appendix 10.

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

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

f) All WOCBP must have a medically supervised negative serum or urine pregnancy test prior to the initiation of therapy at each cycle.

g) A 12-lead ECG will be performed at screening and End of Treatment visit and as clinically indicated. QTc interval to be assessed by Fridericia formula, see Appendix 11.

h) Chest X-ray is optional if low-dose CT is performed for skeletal assessment.

i) Hematology: CBC with differential, and platelet count should be taken at screening and at day 1, 8, 15 and 22 of all cycles, prior to initiation of therapy, and at the end of treatment (EOT) visit. If patient tolerability is good, i.e. no dose modifications, dose delays or need of supportive therapy (Granulocyte colony stimulating factor (G-CSF), blood or platelet transfusion) in the two preceding cycles, then CBC assessments may be excluded on Day 8 and Day 22. If needed due to logistic reasons, the blood sampling may be done up to 23 hours prior to the scheduled dosing on Day 1 after consultation with medical monitor.

j) Chemistry should be taken at screening, at day 1 of all cycles, prior to initiation of therapy and at End of Treatment visit. eGFR will be evaluated using CKD-EPI formula, see Appendix 12. During Progression free survival follow-up (PFS-FU) Serum calcium and albumin (corrected calcium) required if evidence of PD.

k) Blood samples for biomarkers should be collected before dosing at Cycle 1 Day 1 and at EOT visit.

l) Bone marrow aspirate (BMA) to be collected at screening for % plasma cells, morphology, cytogenetics by Interphase Fluorescence In Situ Hybridization (iFISH), and for exploratory biomarker analysis. A repeat sample is required in patients with suspect CR to confirm response and may be needed to confirm progression, if taken, samples will also be used for biomarker analysis.

m) SPEP and UPEP and serum and urine IFE (if SPEP or UPEP are not detectable and to confirm a CR), quantitative immunoglobulins per routine lab practice and SFLC assay (only required if SPEP and UPEP are not measurable [UPEP is < 200 mg/24 hours and SPEP is < 0.5 g/dL]) are to be conducted at screening, Cycle 1 Day 1. prior to each cycle even if treatment is delayed and at End of Treatment visit. Quantitative immunoglobulins need to be repeated for patients with IgA or IgD myeloma. In the event treatment is delayed, ≥ 2 weeks, response assessments are required to be repeated on the day the new cycle starts. If treatment is discontinued at or beyond 6 weeks the response assessments should then be repeated on the day of the decision (or as soon as possible ≥ 30 days after last dose of study drug) as part of the EOT visit.

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

o) Assessment of lytic bone lesions can be done either by skeletal survey, or low dose CT scan. Required ≤ 6 weeks prior to initiation of treatment. Additional imaging assessments may be performed at the investigator's discretion and should be documented in the electronic Case Report Form (eCRF). Repeat imaging assessments (same technique as used at screening) at any time when clinically indicated or to confirm PD. Limited X-rays or scans may be performed as clinically indicated if able to confirm PD.

p) Treatment cannot begin prior to randomization and must begin ≤ 5 days after randomization.

q) Evaluate if the melflufen dose should be given, delayed or reduced

r) Evaluate if the dexamethasone dose should be given, held, reduced, delayed or permanently discontinued.

s) PK Samples will be drawn in connection to the first two melflufen infusions, Cycle 1 and Cycle 2.

t) Concomitant medications and procedures: All blood products and medications within 21 days prior to first dose until the EOT Visit.

u) Special attention to patient evaluation of pain and other symptoms from the peripheral infusion site, see Appendix 13. SAEs will be collected from signing of the ICF until 30 days after last dose of study treatment or initiation of subsequent therapy whichever occurs first. AEs will be collected from the start of study treatment until 30 days after the last dose of any study drug (melflufen or dexamethasone) or initiation of subsequent therapy whichever occurs first. Any SAE that occurs after this timepoint and is considered related to melflufen or study participation in the opinion of the investigator will be collected.

v) When administered melflufen via PVC the peripheral infusion site should be inspected pre and post infusion on Day 1, and on Day 8, including assessment of any local reaction such as redness, swelling, signs of phlebitis or extravasation using the common terminology criteria for adverse events (CTCAE) version 5.0, see Appendix 5 and Visual infusion Phlebitis (VIP) scale, see Appendix 13. All signs of extravasations or phlebitis should be photo documented at least daily until resolution, see section 6.1.2 for detailed instructions.

w) Treatment satisfaction scale will be completed after received administration of melflufen on Day 1 of Cycle 1 and Cycle 2. Treatment preference scale will be completed prior to any procedures on Day 1 of Cycle 3 only, and prior to being told anything related to health, see appendix 15.

x) The questionnaire should be completed on Day 1, prior to any procedures on the day of the visit and prior to being told anything related to health, it should be administered even if the treatment is not given, at the time of EOT visit, and at PFS-FU visits until time of progression or starting a new treatment. See Section 8.1 and Appendix 14.

y) End of Treatment visit should be scheduled 30 days after last dose of study treatment (melflufen or dexamethasone) or as soon as possible if the decision to remove patient from therapy occurs later than 30 days after last dose (such as in the case of a prolonged cycle). If a new treatment for MM is to be introduced sooner than 30 days after last dose of study drug the EOT visit should occur as close as possible before the first dose of the new drug. Ongoing neutropenia and thrombocytopenia Grade 3-4 at the EOT visit are to be followed until resolution (≤ Grade 2) or initiation of subsequent therapy. SAEs should be followed until resolution or stabilization with no expected resolution.

z) Patients who discontinue therapy for reasons other than disease progression should continue to have monthly disease assessments done until documented progression or initiation of subsequent therapy, second primary malignancy should also be followed and documented. Confirmed progression requires 2 consecutive M protein assessments at any time (including the same day for SPEP/FLC). The second assessment must be a separate serum and urine sample. If the second consecutive M protein sample can only be obtained after the start of subsequent therapy, it may still be used as confirmation of PD. Documentation of the date and regimen of the first subsequent anti-cancer treatment should be completed if it occurs during PFS-FU

aa) Nurse convenience and preference scales will be completed after the patient was given the administration of melflufen on Day 1 of Cycle 1 and Cycle 2, see Appendix 15.

bb) Use of health services and days of hospitalization will be completed by the patient at screening, on Day 1 of each cycle, at time of EOT visit, and PFS-FU prior to any procedures on the day of the visit and prior to being told anything related to health, see Appendix 16.

2. Introduction

Melflufen is a first in class anti-cancer peptide-drug conjugate designed for targeted enrichment of alkylating moieties in tumor cells and belongs to a novel class of drugs called peptide-drug conjugates. Once monthly intravenous (i.v.) melflufen, in combination with weekly dexamethasone, has shown encouraging clinical results in relapsed and RRMM patients (see current Investigator's Brochure [IB] for details). In clinical studies to date, melflufen has only been administered via a central vein, but peripheral vein administration might be potentially preferable to some patients if the safety and tolerability profile is acceptable.

2.1. Study Rationale

The outcome in RRMM is still unsatisfactory despite recent improvements in treatment. Thus, new therapeutic options are needed. Melflufen is a peptide-drug conjugate that is rapidly taken up by MM cells due to its high lipophilicity (Chauhan et al 2013, Wickström et al 2017). Once inside the myeloma cell, the activity of melflufen is determined by its immediate cleavage by peptidases into hydrophilic alkylator payloads that are entrapped (Wickström et al 2017, 2010, Gullbo et al 2003). Melflufen is 50-fold more potent than melphalan in myeloma cells in vitro due to the increase of intracellular alkylator concentration (Chauhan et al 2013, Wickström et al 2017).

Melflufen has been evaluated in combination with low dose dexamethasone in patients with RRMM in a Phase 1/2 clinical trial (O-12-M1, NCT01897714). The trial established the recommended dose at 40 mg of melflufen every 28 days combined with 40 mg dexamethasone weekly. As of the database lock 9th November 2017, there were 45 patients treated with 40 mg melflufen every 28 days in combination with weekly dexamethasone. The Overall Response Rate (ORR) (PR or better) was 31% and the CBR (MR or better) was 49%. The patients had a median of 4 prior lines of therapy, including IMiD, PIs and alkylators. The median progression free survival (PFS) was 5.7 months based on 41 events, and the overall survival (OS) was 20.7 months based on 23 events in the 45 patients (Richardson et al 2020).

There are also ongoing clinical studies in RRMM patients, including a phase 2 study in patients refractory to pomalidomide and/or an anti-CD38 mAbs (OP-106 Horizon, NCT02963493), a phase 2 study in patients with impaired renal function (OP-107 Bridge, NCT03639610), a phase 1/2 study where melflufen and dexamethasone are combined with daratumumab or bortezomib (OP-104 Anchor, NCT03481556), and a randomized phase 3 study (OP-103 Ocean, NCT03151811) comparing melflufen and dexamethasone to pomalidomide and dexamethasone.

Current labeling of several other alkylating agents such as melphalan, bendamustine and cyclophosphamide, allows for peripheral vein administration but local reactions at the infusion site have been observed for several alkylating compounds. In trials with Peptichemio, a mixture of six synthetic peptides containing m-L-phenyl alanine mustard, (which is the alkylating moiety of e.g. melphalan), phlebitis was very common leading to oedema and phlebosclerosis. (Paccagnella et al 1986). In guidelines for clinical management of extravasations, opinions differ on the tissue damaging potential of melphalan, but in the ESMO guidelines it is described as an irritant (Pérez-Fidalgo 2012). Nonclinical local tolerance testing by intradermal injection in mice showed no difference between melphalan and melflufen at clinically relevant concentrations (data on file). In clinical studies to date, melflufen has only been administered via a central vein,

but peripheral vein administration might be potentially preferable to some patients if the safety and tolerability profile is acceptable.

2.2. Background

2.2.1. Multiple Myeloma

MM is a malignancy of the differentiated plasma cells that affects the older patient with a median age at onset of 65 to 70 years and a slight male predominance. MM is the second most common hematologic malignancy and 32,110 patients were estimated to be diagnosed with myeloma in the United States in 2019 with a median 5-year survival of 52.2% (SEER 2019).

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

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

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

2.2.2. Melflufen

Melflufen, a first-in-class anti-cancer peptide-drug conjugate, is rapidly taken up by MM cells due to its high lipophilicity (Wickström 2017). Once inside the myeloma cell, melflufen is

immediately cleaved by peptidases, leading to entrapment of the hydrophilic alkylator payloads. (Wickström et al 2017, 2010, Gullbo et al 2003).

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

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

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

Melflufen has been evaluated in combination with low dose dexamethasone in patients with RRMM in a Phase 1/2 clinical trial (O-12-M1, NCT01897714). The trial established the recommended dose at 40 mg of melflufen every 28 days combined with 40 mg dexamethasone weekly. As of the database lock 9th November 2017, there were 45 patients treated with 40 mg melflufen every 28 days in combination with weekly dexamethasone. The Overall Response Rate (ORR) (PR or better) was 31% and the CBR (MR or better) was 49%. The patients had a median of 4 prior lines of therapy, including IMiD, PIs and alkylators. The median progression free survival (PFS) was 5.7 months based on 41 events, and the overall survival (OS) was 20.7 months based on 23 events in the 45 patients (Richardson et al 2020).

There are also ongoing clinical studies in RRMM patients, including a phase 2 study in patients refractory to pomalidomide and/or daratumumab (OP-106 Horizon, NCT02963493), a phase 2 study in patients with impaired renal function (OP-107 Bridge, NCT03639610)), a phase 1/2 study where melflufen and dexamethasone are combined with daratumumab or bortezomib (OP-104 Anchor, NCT03481556), and a randomized phase 3 study (OP-103 Ocean, NCT03151811) comparing melflufen and dexamethasone to pomalidomide and dexamethasone.

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

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

The most common treatment emergent adverse events (TEAE) in the trials O-12-M1 OP-104 (Anchor) and OP-106 (Horizon) were hematological events, such as thrombocytopenia, neutropenia and anemia. This is not unexpected since hematological events are common both as a consequence of MM disease and of treatment with alkylators. These events were assessed to be dose-related, reversible and monitorable.

Treatment related Grade 3 and 4 Adverse Events (AE)s were reported in 37 patients out of 45 patients (82%) in the O-12-M1 trial. Those related to melflufen and occurring in ≥ 5% of the

patients are presented in Table 2-1. No non-hematological grade 3/4 AEs were reported in >5% of the patients.

Table 2-1 Summary of Melflufen Treatment related Grade 3 or 4 AE

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

Taken together, clinical and preclinical data support that melflufen provides alkylating peptides to tumor cells such as MM cells and thereby exerts a higher anti-tumor activity compared with equimolar administration of the alkylator melphalan but with a similar safety profile.

In clinical studies to date, melflufen has only been administered via a central vein, but peripheral vein administration might be potentially preferable to some patients if the safety and tolerability profile is acceptable.

In non-clinial trials melflufen has been administered in the tail vein in rodents and in the cephalic vein in dogs. In mice, tissue damage has been demonstrated at high concentrations, but not in rats at lower concentrations. In dogs, melflufen was somewhat more potent than melphalan on a molar basis in causing acute inflammatory effects around the infusion site when given peripherally in the cephalic vein but when tissues were examined 28 days after the infusion, no difference between the two alkylators was observed. It is to be noted that the concentrations used in the dog study were the recommended clinical infusion solution concentration of melflufen whereas the melphalan concentration was at the low end of the recommended clinical infusion solution concentration for this alkylator. These data on local tolerance with melflufen suggest that the compound, like many cytotoxic agents, has a propensity to cause damage to the vascular endothelium and surrounding tissue particularly when there is extravasation. However, when comparing the damage to the tissue after direct intradermal injection in mice with clinically recommended infusion solution concentrations, melflufen appears no worse than either melphalan or bendamustine, two alkylators routinely administered peripherally in the clinical setting.

These data support performance of a small crossover clinical study to compare PK of peripheral versus central infusion of melflufen and to verify local tolerance of the peripheral infusion in humans since this administration route could be feasible for some patients that would not prefer or are not suitable for placement of a central venous catheter.

Please see the Investigators' Brochure (IB) for further information.

2.3. Benefit/Risk Assessment

Although the incorporation of novel agents such as PIs, IMiDs and anti CD38 mAbs has significantly improved outcomes of patients suffering from MM, myeloma is not yet curable and new treatment options are needed. Ongoing trials in RRMM with melflufen and dexamethasone have shown promising efficacy. The safety profile has been consistent and manageable throughout the trials, with thrombocytopenia and other hematologic toxicities being most prominent, and severe non-hematologic toxicities uncommon. It is therefore reasonable to evaluate if melflufen can be administered in a peripheral vein with acceptable side effects.

More detailed information about the known and expected benefits and risks of melflufen may be found in the Investigators Brochure (IB).

3. Objectives and Endpoints

Table 3-1 summarizes all primary, secondary and exploratory objectives and endpoints for this study.

Table 3-1 Objectives and Endpoints

Objectives [a]	Endpoints [a]
Primary:	
• To evaluate and compare the pharmacokinetic (PK) variables C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ of melphalan after central and peripheral intravenous infusion of melflufen.	• Maximum observed concentration C_{max} • Area under the concentration-time profile from 0 hours (start of infusion) to the last measurable concentration $AUC_{(0-t)}$ • Area under the concentration-time profile from 0 hours to infinity $AUC_{(0-\infty)}$
• To assess the local tolerability of peripheral intravenous administration of melflufen	• Frequency and severity of local reactions including phlebitis at infusion site after peripheral intravenous administration
Secondary:	
• To evaluate and compare the PK variables C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ of melflufen and desethyl-melflufen, and to evaluate the elimination half-life ($t_{½}$) for melflufen, melphalan and desethyl-melflufen after central and peripheral intravenous infusion of melflufen.	• Maximum observed concentration C_{max} • Area under the concentration-time profile from 0 hours to end of drug infusion $AUC_{(0-t)}$ • Area under the concentration-time profile from 0 hours to infinity $AUC_{(0-\infty)}$ • Elimination half-life $t_{½}$
• To assess safety and general tolerability of melflufen	• Frequency and Grade of Treatment emergent Adverse Events (TEAEs)
To evaluate efficacy: • Best response during the study	Best Response (stringent complete response (sCR), complete response (CR), very good partial response (VGPR), partial response

• Overall response rate (ORR) • Clinical benefit rate (CBR) • Duration of response (DOR) • Duration of Clinical Benefit (DOCB) • Time to response (TTR) • Time to progression (TTP) • Time to next treatment (TTNT) • Progression Free Survival (PFS)	(PR), minimal response (MR), stable disease (SD) or progressive disease (PD))
	ORR (including CR/sCR, VGPR and PR)
	CBR proportion of patients with ≥ MR as best response
	DOR (time from the first confirmed response of sCR, CR, VGPR or PR to first confirmed disease progression, or death due to any cause.
	DOCB (time from first evidence of confirmed assessment of sCR, CR, VGPR, PR, or MR to first confirmed disease progression, or to death due to any cause.)
	TTR (time form randomization to the date of the first documented confirmed response in a patient that has responded with ≥ PR (sCR, CR, VCPR or PR))
	TTP (time from the date of randomization to the date of the first documented confirmed PD)
	TTNT (time from randomization to the date of next anti-myeloma treatment)
	PFS (time from the date of randomization to the date of first documentation of confirmed PD or death due to any cause)
Exploratory:	
• To assess translational biomarkers that might predict effects of treatment, aid in monitoring of disease progression as well as improve understanding of mechanism of action.	• DNA, RNA and protein-based drug response biomarkers including but not limited to aminopeptidases and esterases
• To assess and compare patient satisfaction and preference, nurse convenience and preference after central and peripheral intravenous administration of melflufen	• Value in each scale assessed by patients • Value in each scale assessed by nurses

• To assess Quality of Life (QoL) based on Patient Reported Outcome (PRO)	EQ-5D-5L • Value and changes from baseline in VAS and EQ-index • Number of patients by category and dimension
• To assess Use of health services and days of hospitalization	• Number of health services • Number and days of hospitalization

a) All tumor response and progression-dependent endpoints are as assessed by investigators according to the IMWG-URC (Kumar et al. 2016), see Appendix 7.

4. Study Design

4.1. Overall Design

This is a randomized, two-period, cross-over Phase 2 study, comparing PK, and assessing safety and tolerability, and efficacy of peripheral and central intravenous administration of melflufen in patients with RRMM, see Appendix 10. It is an international study, enrolling patients in US and Europe. The study will enroll patients following at least 2 lines of prior therapy and is refractory to an IMiD and a PI.

Patients will be randomized (1:1) to Arm A or Arm B, see Table 4-1. For each arm, treatment will be given in 28-day cycles and may be given in an outpatient treatment setting. PK samples will be collected at Day 1 of Cycles 1 and 2.

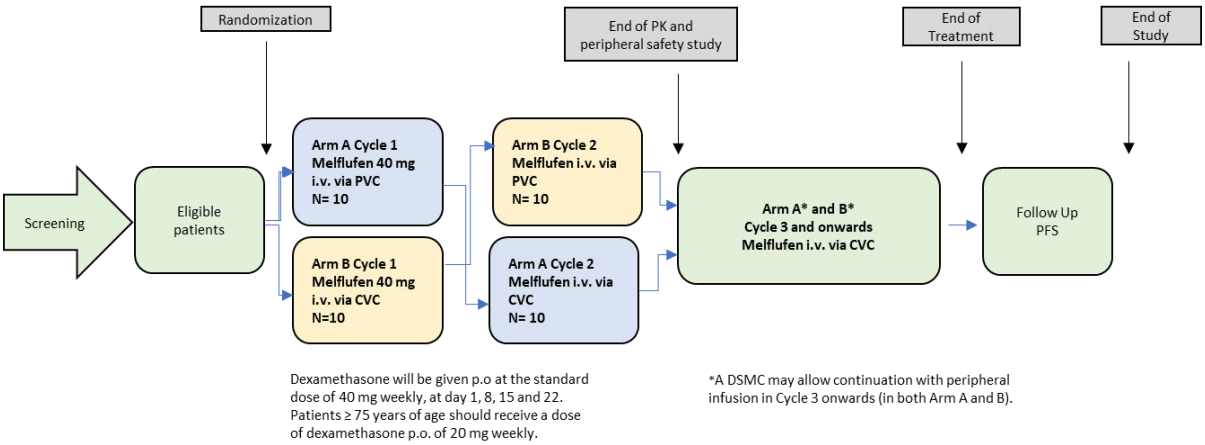
Arm A:

- At Cycle 1, melflufen 40 mg will be administered as a 30-minute infusion via a peripheral venous catheter (PVC). From cycle 2 and onwards melflufen will be administered as a 30-minute infusion via a central catheter*.
- Dexamethasone will be given p.o. at the standard dose of 40 mg weekly, at day 1, 8, 15 and 22. Patients ≥ 75 years of age should receive a dose of dexamethasone p.o. of 20 mg weekly.

Arm B:

- At Cycle 1, melflufen 40 mg will be given as a 30-minute infusion via a central catheter. At Cycle 2, melflufen will be administered as a 30-minute infusion via a PVC. From Cycle 3 and onwards melflufen will be administered as a 30-minute infusion via a CVC*.
- Dexamethasone will be given p.o. at the standard dose of 40 mg weekly, at day 1, 8, 15 and 22. Patients ≥ 75 years of age should receive a dose of dexamethasone p.o. of 20 mg weekly.

Table 4-1 Study Design



Dose modifications and delays in therapy may be implemented based on patient tolerability. In the event of a cycle delay unrelated to dexamethasone toxicity, it is recommended to continue dexamethasone weekly.

* After 6 patients have received peripheral infusion with adequate PK sampling, a DSMC will assess the safety and tolerability of received infusions. The DSMC may then allow continuation with peripheral infusion in Cycle 3 and onwards (in both Arm A and B) to further study local tolerability with repeat peripheral infusions. The investigator in agreement with the patient will determine whether continued treatment will use peripheral or central administration.

4.1.1. Treatment duration

Patients in both arm A and B will receive treatment until any of the following events is reached:

- there is documented PD according to the IMWG-URC guidelines (Kumar et al.2016) to be confirmed on two consecutive assessments, and verified by the Medical Monitor prior to treatment discontinuation, see Appendix 7.
- unacceptable toxicity.
- the patient/treating physician determines it is not in the patient's best interest to continue
- patient's withdrawal of consent.

4.2. Scientific Rationale for Study Design

The study will enroll patients with RRMM that have received at least 2 lines of prior therapy and are refractory to an IMiD and a PI. This population is expected to be similar to what was studied in the O12-M1 study in which ORR was 31%, PFS was 5.7 months and median overall survival (OS) was 20.7 months (Richardson et al, 2020) and is therefore reasonable to include in this trial.

Current labeling of several other alkylating agents such as melphalan, bendamustine and cyclophosphamide, allows for peripheral vein administration but local reactions at the infusion site has been observed for several alkylating compounds. However, in trials with Peptichemio, a mixture of six synthetic peptides containing m-L-phenyl alanine mustard (which is the alkylating

moiety of e.g. melphalan), phlebitis was very common leading to oedema and phlebosclerosis. (Paccagnella et al 1986). In clinical studies to date, melflufen has only been administered via a central vein, but peripheral vein administration might be potentially preferable to some patients if the safety and tolerability profile is acceptable.

The data on local tolerance in non-clinical trials with melflufen suggest that the compound, like many cytotoxic agents, has a propensity to cause damage to the vascular endothelium and surrounding tissue particularly when there is extravasation. However, when comparing the damage to the tissue after direct intradermal injection in mice with clinically recommended infusion solution concentrations, melflufen appears no worse than either melphalan or bendamustine, two alkylators routinely administered peripherally in the clinical setting.

PK assessments for melflufen and the metabolites desethyl-melflufen and melphalan after central administration of melflufen in previous clinical studies demonstrate a very rapid disappearance of melflufen from plasma with an elimination half-life of less than 5 minutes. The peak concentration of melphalan is observed with a delay after end of melflufen infusion indicating formation of melphalan in tissues followed by a slow out-transport from tissues to plasma (data on file). The pattern and rate constants for these events are expected to be similar after peripheral and central administration but should be verified in a clinical study.

These data support performance of a small crossover clinical study to compare PK of peripheral versus central infusion of melflufen and to verify local tolerance of the peripheral infusion in humans since this administration route could be feasible for some patients that would not prefer or are not suitable for placement of a CVC.

4.3. Justification for Dose

The dose and schedule of melflufen was established in the Phase 1/2 trial (O-12-M1) with melflufen in combination with weekly dexamethasone in RRMM patients as 40 mg on Day 1 of a 28-day cycle. The same dosing schedule has been used in the ongoing trials OP-106, OP-103 and OP-107. Hematologic toxicity is the most common AE reported, with thrombocytopenia being the most clinically important AE.

4.4. End of Treatment Definition

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

4.5. End of Study Definition

4.5.1. End of PK and Peripheral Safety Study

A patient is considered to have completed the PK study when administered two 40 mg doses of melflufen with PK sampling, one PK sampling series following peripheral administration and one PK sampling series following central administration and that the sampling series are sufficient to evaluate all PK parameters. If a patient is not able to receive two doses of 40 mg, including an observation period of 28 days after the second dose, with sufficient PK samples taken, they will be replaced.

The main PK analysis will take place when there are 20 PK evaluable patients.

4.5.2. End of Study

A patient is considered to have completed the study if he/she has completed all phases of the study including follow up visits for time to next anti-myeloma treatment.

A patient is considered to end the study when he/she complete the study or withdraw from the study for any reason prior to completion.

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

5. Study Population

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

5.1. Inclusion Criteria

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

1. Male or female, age 18 years or older;
2. Capable of giving signed informed consent as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol;
3. A prior diagnosis of MM with documented disease progression in need of treatment at time of screening;
4. Measurable disease defined as any of the following:
    - Serum monoclonal protein ≥ 0.5 g/dL by serum protein electrophoresis (SPEP)
    - ≥ 200 mg/24hr of monoclonal protein in the 24hour urine collection by electrophoresis (UPEP)
    - Serum free light chain (SFLC) ≥ 10 mg/dL AND abnormal serum kappa to lambda free light chain (FLC) ratio
5. Received at least 2 prior lines of therapy and is refractory to an IMiD and a PI. The definition of refractory includes intolerance to an IMiD/PI after at least two 28-day cycles of therapy, see Appendix 10 and Appendix 8;
6. Adequate peripheral arm veins for repeated intravenous infusions
7. Life expectancy of ≥ 6 months;
8. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2, see Appendix 6; Patients with ECOG performance status **> 2** solely based on bone pain secondary to MM may be eligible following consultation and approval of medical monitor;
9. 12-lead Electrocardiogram (ECG) with QT interval calculated by Fridericia Formula (QTcF) interval of ≤ 470 msec, see Appendix 11;
10. Adequate organ function with the following laboratory results during screening (within 21 days) and immediately before study treatment administration on Cycle 1 Day 1:

- Absolute neutrophil count (ANC) ≥ 1,000 cells/mm^3 (1.0 x 10^9/L) (Growth factors cannot be used within 10 days (14 days for pegfilgrastim) prior to initiation of study treatment)
- Platelet count ≥ 75,000 cells/ mm^3 (75 x 10^9/L) (without transfusions during the 10 days prior to initiation of therapy)
- Hemoglobin ≥ 8.0 g/dL (Red blood cell [RBC] transfusions are permitted)
- Total Bilirubin ≤ 1.5 x upper limit of normal (ULN), except patients diagnosed with Gilbert's syndrome that have been reviewed and approved by the Medical Monitor
- AST (SGOT) and ALT (SGPT) ≤ 3.0 x ULN
- Renal function: Estimated glomerular filtration rate (eGFR) by CKD-EPI formula of ≥ 45 mL/min, see Appendix 12.

11. Must have or be willing to have an acceptable central catheter (Port a Cath, peripherally inserted central catheter [PICC] line, or central venous catheter [CVC]) and a PVC;
12. a) **Male patients:** A male patient is eligible if he agrees to use contraception as detailed in Appendix 4 of this protocol during the treatment period and for at least 3 months after the last dose of study treatment and refrain from donating sperm during this period
    b) **Female patients**: A female patient is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies:
        i. Not a woman of childbearing potential (WOCBP) as defined in Appendix 4 **or**
        ii. A WOCBP who agrees to follow the contraceptive guidance in Appendix 4 during the treatment period and for at least 28 days after the last dose of study treatment

5.2. Exclusion Criteria

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

1. Primary refractory disease (i.e. never responded with at least MR to any prior therapy);
2. Evidence of mucosal and/or internal bleeding or platelet transfusion refractory (platelet count fails to increase by > 10,000 cells/mm^3 after a transfusion of an appropriate dose of platelets);
3. Any medical conditions that, in the Investigator's opinion, would impose excessive risk to the patient or would adversely affect his/her participating in this study. Examples of such conditions are: a significant history of cardiovascular disease (e.g., myocardial infarction, significant cardiac conduction system abnormalities, uncontrolled hypertension, ≥ Grade 3 thromboembolic event in the last 6 months);
4. Known active infection that is uncontrolled or has required intravenous systemic therapy within 14 days of randomization. Patients that have required oral anti-infective treatment within 14 days of randomization should be discussed with the Medical Monitor;
5. Other malignancy diagnosed or requiring treatment within the past 3 years with the exception of adequately treated basal cell carcinoma, squamous cell skin cancer,

carcinoma in-situ of the cervix or breast or very low and low risk prostate cancer in active surveillance;

6. Pregnant or breast-feeding females;
7. Serious psychiatric illness, active alcoholism, or drug addiction that may hinder or confuse compliance or follow-up evaluation;
8. Human immunodeficiency virus (HIV) or active hepatitis B or C viral infection;
9. Concurrent known or suspected amyloidosis or plasma cell leukemia;
10. POEMS syndrome (plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein and skin changes);
11. Known central nervous system (CNS) or meningeal involvement of myeloma;
12. Any of the following treatments, within the specified timeframe
    - Previous cytotoxic therapies, including cytotoxic investigational agents, for MM within 3 weeks (6 weeks for nitrosoureas) prior to initiation of therapy.
    - The use of live vaccines within 30 days before initiation of therapy.
    - IMiDs, PIs and or corticosteroids within 2 weeks prior to initiation of therapy.
    - Other investigational therapies and monoclonal antibodies within 4 weeks of initiation of therapy.
    - Prednisone up to but no more than 10 mg orally q.d. or its equivalent for symptom management of comorbid conditions is permitted but dose should be stable for at least 7 days prior to initiation of therapy.

Other washout times may be considered following consultation with the medical monitor.

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

5.3. Lifestyle Considerations

No restrictions are required.

5.4. Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently eligible to be enrolled. A minimal set of screen failure information is required to

ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

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

5.5. Population Diversity

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

6. Study Intervention

Study intervention is defined as treatment with melflufen and dexamethasone administered to a study patient according to the protocol.

Treatment will be given in cycles, in an outpatient treatment setting. Each cycle is 28 days. Melflufen will be administered as a 30-minute i.v. infusion, every 28 days, via central or peripheral line. Dexamethasone will be administered orally on days 1, 8, 15 and 22.

6.1. Study Treatment (s) Administered

Table 6-1 Study Drugs

Study Drug:	**Melflufen**	**Dexamethasone**
Dosage formulation:	Powder for solution for infusion	Tablet
Unit dose strength:	20 mg	4 mg
Dosage levels:	40 mg	40 mg (20 mg for patients ≥ 75 years)
Route of administration:	Intravenous (i.v.)	Oral
Dosing instructions:	Intravenous infusion at Day 1 of each 28-day cycle.	Oral at Day 1, 8, 15 and 22of each 28-day cycle.

Study Drug:	Melflufen	Dexamethasone
Packaging and labeling:	Melflufen powder for solution for infusion is filled in 50 mL glass vials with grey rubber stoppers and flip-off seals. Each vial contains 20 mg of melflufen. The vials will be delivered in boxes containing enough vials for several administrations. Each vial and box will be labeled as required per country requirement.	Dexamethasone will be supplied by Oncopeptides to countries other than the USA. Where supplied, it will be labeled as required per country requirement.
Storage conditions:	Cold/Refrigerated (2-8°C or 36-46 °F)	Ambient (15-25°C or 59-77°F)
Further information:	Investigators Brochure (IB) and the study Pharmacy Manual	Summary of Product Characteristics (SmPC) or Prescribing Information, as well as study Pharmacy Manual

6.1.1. Study Regimens and Administration

Patients will be randomized (1:1) to Arm A or Arm B, both arms will receive melflufen and dexamethasone.

Arm A:

- At Cycle 1, melflufen 40 mg will be given as a 30-minutes infusion via a **PVC.** Cycles from cycle 2 and onwards will be administered via a **central catheter.**
- Dexamethasone will be given p.o. at day 1, 8, 15 and 22 in each cycle.

Arm B:

- At Cycle 1, melflufen 40 mg will be given as a 30-minutes infusion via a **central catheter.** Cycle 2 will be administered via a **PVC.** From cycle 3 and onwards melflufen will be administered via a **central catheter.**
- Dexamethasone will be given p.o, at day 1, 8, 15 and 22 in each cycle.

6.1.2. Melflufen Preparation and Administration

Prior to melflufen administration, prophylactic treatment with anti-emetic drug(s) is recommended, see Section 6.5.2. Subsequent anti-emetic drugs against delayed emesis should be administered at the discretion of the investigator.

Note: Please refer to the Pharmacy Manual for complete instructions on preparation and administration of melflufen

- Melflufen is administered i.v. either via a peripheral catheter or through a central catheter, which should be inserted according to standard local practice. All patients must have an acceptable catheter for infusion (PVC, Port A Cath, PICC line or CVC).
- Melflufen degrades in solution. It is very important to adhere to the timelines for preparation that are outlined in the Pharmacy Manual. This requires very good coordination between staff at the pharmacy and the patient treatment area.
- Melflufen is reconstituted in 40 mL glucose 5% infusion solution per 20mg vial of melflufen. The reconstituted melflufen is diluted to 250 mL in cold 0.9% saline infusion solution and should be refrigerated as recommended in the Pharmacy Manual.

Before infusion:

- Document vital signs prior to start of infusion.
- Prepare the central/peripheral catheter by flushing with approximately 20 mL of 0.9% saline.
- Inspect infusion site.
- Take a photo of PVC infusion site after cannulation but before administration at each cycle when using PVC.

Infusion:

- The melflufen should be administered as a 30-minute intravenous infusion. Following DSMC meeting and general approval for peripheral administration in later cycles (>=C3), and if peripheral venous administration is chosen, consider alternating between right and left arm, if good veins in both arms.
- Record start and stop time for infusion.
- Inspect infusion site for any signs of extravasation.

After infusion:

- First flush the central/peripheral catheter with approximately 20 mL of 0.9% saline. Then follow with additional flushing as per institutional guidelines if necessary.
- Document vital signs after stop of the infusion.
- When applicable, the peripheral infusion site should be inspected, including assessment of any local reaction such as redness, swelling, signs of phlebitis or extravasation using CTCAE 5.0, see Appendix 5 and VIP, see Appendix 13.
- When applicable, take a photo of PVC infusions site 15 minutes and 4 hours after removal of cannula. When a peripheral infusion is given at a later stage, following approval of DSMC, only a 15-minute post-removal photo is applicable.
- All signs of extravasations or phlebitis should be photo documented at least on the day of infusion and the day following infusion. If VIP grading is above 1 it should be continued to be documented daily until grade 1 or resolution.

The planned and actual administered dose as well as the start and stop time for the infusion, should be documented in the source documents and on the appropriate eCRF page.

See Section 6.2 for melflufen supply, storage and accountability. Refer to the Pharmacy Manual for details on melflufen preparation and administration.

6.1.2.1. Documentation of Phlebitis and/or Extravasation

Each incident of extravasation and/or Phlebitis must be correctly documented.

- Date and time
- Signs and symptoms
- Area for Extravasation or Phlebitis
- Approximate amount of drug extravasated, if applicable
- Actions taken with time and date
- Photographic documentation using a digital camera
- Use a pen to mark the area to be photographed
- Place a tape measure with millimeter measure aside the marked area
- Measure the longest possible axis of the area and the longest axis perpendicular to this axis in mm.
- Place the photo in the patient's medical records/patient's binder as source data
- Outcome
- Report extravasation, phlebitis, or other infusion site reactions as AEs, according to procedure described in Appendix 3
- Continue to monitor the infusion site until all signs and symptoms of extravasation, phlebitis or other infusion site reactions have resolved.

6.1.2.2. Handling of Phlebitis and/or Extravasation

Extravasation

Any definite or suspected extravasation should be managed according to the ESMO-EONS guidelines (Pérez-Fidalgo 2012).

In case of a suspected extravasation:

- the administration of melflufen should immediately be stopped.
- the cannula should be left in place and gentle aspiration be performed to remove as much extravasated solution as possible.
- the removed volume should be documented.
- then remove the cannula.
- mark the outline of the extravasated area, apply local dry compresses and elevate the limb.

Please refer to the ESMO-EONS practice guidelines, see appendix 17.

Phlebitis

If phlebitis ≥ grade 2 according to the VIP scale occurs during melflufen infusion (see Appendix 13) the infusion should be aborted and the remaining amount should be administered via a central catheter. Topical treatment may be administered as clinically indicated.

6.1.3. Dexamethasone Administration

Dexamethasone should be administered orally on Day 1, 8, 15 and 22. Dexamethasone is best administered prior to melflufen when both drugs are given on the same day (Day 1 of each cycle). For Day 1 administrations of dexamethasone, actual time will be collected in the eCRF.

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

On Day 1 of each Cycle the patient will be provided dexamethasone for one full cycle. Review of compliance will be done on Day, 8, 15 and 22 of each cycle and during unscheduled visits if melflufen is being delayed.

6.2. Preparation/Handling/Storage/Accountability

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

6.3. Measures to Minimize Bias: Randomization and Blinding

This open label trial will accrue approximately 25 patients in a 1:1 ratio in order to have 20 evaluable patients.

All patients meeting the required eligibility criteria, to be verified by the Medical Monitor, will be randomized to Arm A or Arm B using Medidata RAVE system for randomization. When the patient has been approved for randomization by the Medical Monitor, prior to the start of study treatment, the site will enter data in RAVE to obtain what arm the patient is randomized to. Treatment cannot begin prior to randomization and must begin ≤ 5 days after randomization. However, pretreatment tests/procedures must remain within the screening timelines specified in the SoA.

6.4. Study Treatment Compliance

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

Drug accountability will be reviewed by the CRO monitor during site visits and at the completion of the study. At study close-out, and as appropriate during the study, all unused study drug packaging and any associated supplies should be discarded according to the site drug destruction policy following review and approval of the site CRO monitor

6.5. Concomitant Therapy

Any blood products, medications and vaccines (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the patient is receiving within 28 days prior to the initiation of therapy or receives during the study must be recorded along with:

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

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

6.5.1. Required Concomitant Therapy

Males and females of child-bearing potential shall be required to use effective contraceptive methods (or abstinence) prior to initiation of study treatment while on therapy and for 28 days after last dose of study treatment for women and 3 months for men. The best method should be determined in consultation with the Investigator, see Appendix 4.

6.5.2. Recommended Concomitant Therapy

- Pneumocystis prophylaxis

  All patients are recommended to receive pneumocystis prophylaxis concomitant treatment according to the NCCN Guidelines, Prevention and Treatment of Cancer-

related Iinfection (NCCN 2019) or institutional guidelines.
http://www.nccn.org/professionals/physician_gls/pdf/infections.pdf

  - Trimethoprim/sulfamethoxazole – Prophylaxis: single or double strength daily or double strength 3 x per week. May require adjustment for renal insufficiency.
  - Patients who are found to be intolerant of pneumocystis prophylaxis while on study may continue on study at the discretion of the investigator
- Antimicrobial prophylaxis:
  - For patients with history of cytomegalovirus (CMV) infection that required treatment, prophylactic treatment per NCCN Guidelines, Prevention and Treatment of Cancer-related Infections (NCCN 2019) or institutional guidelines is recommended.
  - Patients with neutropenia are strongly recommended to receive antimicrobial prophylaxis throughout the treatment period per NCCN Guidelines, Prevention and Treatment of Cancer-related Infections (NCCN 2019) or institutional guidelines.
- Thrombocytopenia and neutropenia are known consequences of MM but also the most common expected AEs associated with melflufen. Careful attention is to be paid to the monitoring of blood counts. General supportive measures, together with appropriate blood and platelet transfusions and hematopoietic growth factors should be administered if necessary. It is recommended, at the investigator's discretion, that platelet transfusion should be avoided within ≤ 5 days of the next dose in order to assess endogenous platelet recovery and avoid the possibility of excessive myelosuppression (Excluding Cycle 1, Day 1 which adheres to the guidelines in Section 6.6.1 for use of growth factors and platelet transfusions prior to the first dose of therapy).
- Prophylactic treatment with anti-emetic(s) prior to melflufen administration is recommended. Subsequent anti-emetic drugs against emesis should be administered at the discretion of the investigator.
- Patients should receive full supportive care while on study at the investigator's discretion, including red blood cell transfusions, anti-diarrheals, analgesics, etc.
- Bisphosphonate therapy i.v. or p.o. should be administered if indicated in accordance with institutional guidelines.
- Other prophylactic treatment for patient related concomitant conditions or risks may be considered.

6.5.3. Prohibited Concomitant Therapy

- Concurrent therapy with any approved or investigative anticancer therapeutic drug with activity against MM, including alpha interferon and/or chronic use of clarithromycin, is not allowed
- Corticosteroids for non-malignant conditions (e.g., asthma, inflammatory bowel disease) prednisone > 10 mg/day (or its equivalent) are not permitted.

- Other investigative agents should not be used during the study
- Radiation therapy to a limited area for bone pain to a pre-existing lesion may be considered in consultation with the medical monitor and approval of the sponsor
- The use of live vaccines is prohibited during the study and for 90 days after last dose of study treatment.
- The prophylactic use of G-CSF and platelet transfusions are not permitted to render the patient eligible for trial participation except as described within the inclusion criteria section 5.1
- Thrombopoietin receptor agonists are not permitted

6.6. Dose Modifications

Dose modifications are permitted according to guidelines described in this section.

- Toxicity should be assessed using CTCAE version 5.0, see Appendix 5.
- All dose modifications should be based on the worst preceding toxicity.
- Each suspected adverse drug reaction (ADR) should be attributed to a specific drug (melflufen and/or dexamethasone), if possible, so that the dose modifications can be made accordingly.
- No dose escalations are permitted in any given patient once a dose level has been reduced.
- Dose modifications different from those stated in the protocol should only be made in consultation with the medical monitor or Sponsor; unless required for immediate patient safety.
- All interruptions or changes to study treatment administration must be recorded in the eCRF.
- In case of dose reduction of any study therapy due to an AE, the dose should not be re-escalated to the higher dose once the AE resolves.

6.6.1. Criteria for initiation of therapy Cycle 1 Day 1

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

- ANC ≥ 1,000 cells/ mm^3 (1.0 x 10^9/L) (Growth factors cannot be used within 10 days [14 days for pegfilgrastim] prior to initiation of therapy)
- Platelet count ≥ 75,000 cells/ mm^3 (75 x 10^9/L) (without transfusion during the previous 10 days prior to initiation of therapy)
- Hemoglobin ≥ 8.0 g/dl (RBC transfusions are permitted)
- eGFR by CKD-EPI formula of ≥ 45 mL/min

See Section 6.5 for required, recommended and prohibited concomitant medications.

6.6.2. Criteria for Initiation of a New Cycle of Treatment

The following guidelines apply to all cycles following Cycle 1. Patients should be assessed at the beginning of each cycle according to the tests and evaluations outlined for Day 1 in the SoA. Refer to Section 6.6.4 below for dose modifications of melflufen related to toxicity.

To begin a new cycle of treatment the following hematologic and non-hematologic criteria must be met:

Hematologic:

- ANC must be ≥ 1,000 cell/mm^3 (1.0 x10^9/L)
- Platelet count must be ≥ 50,000 cell/mm^3 (50.0 x 10^9/L) (platelet transfusions not recommended within ≤ 5 days of dosing, see Section 6.5.2)

Non-hematologic:

- All non-hematologic toxicities must be ≤ Grade 1 or returned to baseline (except peripheral neuropathy Grade 2 without pain, alopecia any grade and fatigue ≤ Grade 2.

If these criteria are not met on the scheduled Day 1, the new cycle should be delayed, and patients should be re-evaluated weekly. Refer to Section 6.6.4 for guidelines on dose modification of melflufen due to drug related toxicity.

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

Refer to Section 6.6.5 for guidelines on dose modification of dexamethasone due to drug related toxicity.

In the event of a cycle delay, unrelated to dexamethasone toxicity, dexamethasone may be continued weekly at the investigators' discretion.

6.6.3. Dose Reduction Steps

6.6.3.1. Dose Reduction Steps for Melflufen

Dose modifications of melflufen for drug related toxicity are permitted. Multiple dose reductions are permitted, however, the lowest dose permitted is 20 mg. If a patient is unable to tolerate the lowest dose of melflufen due to drug related toxicity the patient must be withdrawn from treatment and enter PFS-FU. However, if, in the opinion of the investigator, it is in the patient's best interest to continue treatment on a lower dose (15 mg or 10 mg), this may be considered after review and approval of the medical monitor, and after resolution of the AE. Prior to each cycle of melflufen the criteria for initiation of therapy must be met (See Section 6.6.2). Table 6-2 describes the dose reduction steps for melflufen.

Table 6-2 Dose reduction steps for melflufen

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

6.6.3.2. Dose Reduction Steps for Dexamethasone

Table 6-3 outlines the dose reduction steps for dexamethasone. Dose reductions of dexamethasone other than those listed in Table 6-3or discontinuation may be considered in consultation with the medical monitor.

Table 6-3 Dose reduction steps for dexamethasone

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

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

6.6.4. Dose Modification Guidelines for Melflufen, Based on Toxicity

6.6.4.1. Dose Modifications for Hematologic Toxicity

Melflufen is a potent myelosuppressive agent, therefore it is essential that careful attention be paid to the monitoring of blood counts. General supportive measures, together with appropriate RBC and platelet transfusions and hematological growth factors, should be instituted as necessary (See Section 6.5.2).

It is recommended that, at the investigator's discretion, platelet transfusion should be avoided ≤ 5 days of the next dose of melflufen in order to assess endogenous platelet recovery and avoid the possibility of excessive myelosuppression.

Please note: The guidelines in Table 6-4 are based on the laboratory values obtained at each cycle on Day 29 (scheduled Day 1) or subsequent weekly evaluations as noted below (not the blood counts during the cycle on Days 8, 15 or 22). Patients that experience a Grade 4 thrombocytopenia or neutropenia on Day 29 in **more than one sequential cycle** on the same dose level **will require a one level dose reduction when the criteria for initiation of a new cycle are met.**

Table 6-4 Dose modification guidelines for hematologic toxicity

Hematologic criteria for initiation of a new cycle	• **ANC ≥ 1,000 cell/mm^3 (1.0 x10^9/L)** • **Platelet count ≥ 50,000 cell/mm^3 (50.0 x 10^9/L)**	
Day	**Criteria <u>met</u> for new cycle**	**Criteria <u>not met</u> for new cycle**
Day 29	Continue at same dose level Investigator discretion: • Optional to hold one week (to Day 36)	Hold dose. Evaluate in one week (to Day 36)
Day 36	Continue at same dose level* Investigator discretion: • Optional one level dose reduction, from cycle 3 and onwards • Optional to hold one week (to Day 43)	Hold dose. Evaluate in one week (to Day 43)
Day 43	Continue at same dose level* Investigator discretion: (consultation with medical monitor is encouraged) • One level dose reduction • Optional to hold one week (to Day 50)	Hold dose. Evaluate in one week (to Day 50)
Day 50	Continue with required one level dose reduction	Hold dose. Evaluate in one week (to Day 57)
Day 57	Continue with required one level dose reduction	Discontinue from therapy**
*Second failure to recover from treatment related Grade 4 neutropenia or thrombocytopenia on Day 29 in a subsequent cycle within the same dose level will result in a one-step dose reduction once recovered. Optional dose delays are permitted as detailed in this table above. ** If the criteria for initiation of a new cycle of therapy **are not met** by Day 57 due to drug related toxicity, then the patient must be discontinued from therapy, unless in the investigators opinion the patient is benefitting from therapy. Continuation must be discussed with the Medical Monitor or Sponsor on a case by case basis.		

Alternate dose modifications (prolongations/reductions, such as directly to 20 mg) may be considered in discussion with the medical monitor or the Sponsor. Continued dosing with or without dose reduction may be considered after contact with the medical monitor in case of non-study treatment related cycle prolongations (for example: influenza).

Patients who discontinue treatment for a study related AE including abnormal laboratory value must be followed as described in Section 8.1.6.

6.6.4.2. Dose Modifications for Non-Hematologic Toxicity

In order to start a new cycle of therapy the resolution of all non-hematologic toxicity must be to ≤ Grade 1 or baseline except peripheral neuropathy Grade 2 without pain, alopecia any grade, fatigue ≤ Grade 2. (Also see section 6.6.2). The following guidelines should be followed:

- If the criteria for initiation of a new cycle of therapy are not met on Day 29 (the next scheduled Day 1 of any given cycle), dose should not be given, and the patient should be re-evaluated weekly.
- If cycle prolongation of more than 14 days is needed to meet the criteria for initiation of a new cycle, a one-step dose reduction is necessary.
- The option to "hold one week" for further resolution of toxicity is permitted at the investigator's discretion based on the timelines in Table 6-4 above.
- If cycle prolongation of more than 28 days (beyond Day 57) is needed, study treatment is to be discontinued unless in the investigator's opinion the patient is benefitting from therapy. Continuation must be discussed with the medical monitor or Sponsor on a case by case basis.
- Grade 3 or 4 treatment related non-hematologic toxicity that occurs or persists on Day 29 (scheduled Day 1) of any cycle requires a one-step dose reduction when the criteria for a new cycle are met with the following exceptions:
    - The toxicity can be managed with appropriate therapy or the risk of recurrence may be reduced by the use of appropriate prophylactic therapy (e.g. anti-emetics and anti-diarrheas for nausea, vomiting and diarrhea)

  AND/OR

    - The toxicity was transient and/or does not warrant a dose reduction in the opinion of the investigator in consultation with the medical monitor (headache, abnormal laboratory value, fatigue).

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

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

Patients who discontinue treatment for a study related AE including abnormal laboratory value must be followed as described in Section 8.1.6.

6.6.5. Dose Modifications for dexamethasone

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

discontinued following consultation with the medical monitor. In the event of a cycle delay, unrelated to dexamethasone toxicity, dexamethasone may be continued weekly at the investigators' discretion.

Table 6-5 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 proton pump inhibitors (PPI). If symptoms persist despite above measures, decrease dexamethasone dose by one dose level.
Gastrointestinal	≥ Grade 3 (requiring hospitalization or surgery)	Hold dexamethasone until symptoms adequately controlled. Restart and decrease one dose level of current dose along with concurrent therapy with H2 blockers, sucralfate, or PPI. If symptoms persist despite above measures, discontinue dexamethasone and do not resume.
Gastrointestinal	Acute pancreatitis	Discontinue dexamethasone and do not resume
Cardiovascular	Edema ≥ Grade 3 (limiting function and unresponsive to therapy or anasarca)	Diuretics as needed and decrease dexamethasone dose by one dose level; if edema persists despite above measures, decrease dose another dose level. Discontinue dexamethasone and do not resume if symptoms persist despite second reduction.
Neurology	Confusion or Mood alteration ≥ Grade 3 (interfering with function +/- interfering with activities of daily living)	Hold dexamethasone until symptoms resolve. Restart with one dose level reduction. If symptoms persist despite above measures, discontinue dexamethasone and do not resume.
Musculoskeletal	Muscle weakness ≥ Grade 3 (symptomatic and interfering with function +/- interfering with activities of daily living)	Decrease dexamethasone dose by one dose level. If weakness persists despite above measures, decrease dose by one additional dose level. Discontinue dexamethasone and do not resume if symptoms persist.

Body System	Symptom	Recommended Action
Metabolic	Hyperglycemia ≥ Grade 3 or higher	Treatment with insulin or oral hypoglycemics as needed. If uncontrolled despite above measures, decrease dose by one dose level until levels are satisfactory.

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

6.7. Intervention after the End of the Study

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

7. Discontinuation of Study Treatment and Patient Discontinuation/Withdrawal

7.1. Discontinuation of Study Treatment

- A patient may withdraw from the study treatment at any time at his/her own request.
- If the patient withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent, if allowed as per local regulations.

7.2. Patient Discontinuation/Withdrawal from the Study

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

- His/her own request at any time*.
- At the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.
- Any of the events outlined in Section 4.1.1, Treatment Duration.
- Requiring other anticancer therapeutic drug, corticosteroids for non-malignant conditions, other investigative agent, live vaccine, or dialysis, as further detailed in Section 6.5.3, Prohibited Concomitant Therapy.
- Confirmed pregnancy.
- Lost to follow-up.
- An incidence or a seriousness of SAEs in this study or other studies indicating a potential danger for the patient's health caused by the study treatment
    - The reason(s) for withdrawal of study treatment and the date at which the decision is made should be documented.
    - Safety monitoring and follow-up assessments should continue as appropriate according to the study schedule, unless the patient has withdrawn consent for study participation.

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

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

- If a patient withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- The reason(s) for withdrawal of study participation and the date at which the decision is made should be documented.

7.3. Lost to Follow Up

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

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

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

8. Study Assessments and Procedures

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

8.1. Study Procedures

8.1.1. Procedures during screening

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

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

The screening visit will occur within 21 days before dosing with any of the study drugs. The following assessments will be performed at the screening visit:

- Demographics
  - Date of birth, age, gender, race and ethnicity
- Medical history, including the following:
  - Prior and current medical illness and conditions
  - Prior surgical procedures
- Myeloma history including characteristics
  - Date of initial diagnosis
  - ISS and R-ISS stage and cytogenetics at diagnosis (if previously evaluated)
  - ISS and R-ISS stage at time of study entry, see Appendix 9
  - All prior myeloma treatment, also including surgery and/or radiation, documenting:
    - start and stop dates
    - assessment of best response
    - date of progressive disease and relapsed or refractory status, see Appendix 10
- Use of Health services and Hospitalization questionnaire, prior to any study visit activities (tests, examination or treatment), see Appendix 16.
- Physical examination, including height, weight and assessment for extramedullary myeloma. Baseline symptoms and residual toxicity from previous therapy, including neuropathy
- Vital signs including blood pressure, pulse, respiration rate and temperature
- ECOG performance status
- Pregnancy test, only for WOCBP
- 12- lead electrocardiogram (ECG); QTc interval to be assessed by Fridericia formula, see Appendix 11
- Blood tests;
  - Hematology: CBC with differential and platelet count
  - Chemistry: sodium, chloride, potassium, magnesium, calcium, phosphate, uric acid, blood urea nitrogen [BUN](or urea), creatinine, eGFR by CKD-EPI formula , glucose (fasting), ALT/AST (SGPT/SGOT), alkaline phosphatase, total protein, total bilirubin, albumin, and lactate dehydrogenase (LDH).
  - β2-microglobulin

- M protein assessments, see Section 8.2.1
- Hepatitis B screening: HBsAg, Anti-HBs, Anti-HBc
- Hepatitis C screening: Anti-HCV
- HIV screening: Anti-HIV1/2 and HIV1/2 antigen
- Urinalysis
- Bone marrow aspiration; A total of 10 mL should not be exceeded for all assessments included. Refer to Laboratory Manual for additional information.
    1. % plasma cells and morphology – may be analyzed locally
    2. One sample to be sent to central laboratory for
        a. Cytogenetics by iFISH in selected plasma cells. Mandatory probes include t(4;14), t(14;16), t(14;20), del(17/17p), 1q amp (1p32/1q21)
        b. Exploratory biomarkers. Remaining material in the sample.
- Chest X-ray (Optional if low-dose is CT performed for skeletal assessment)
- Assessment of known or suspected extramedullary myeloma. If imaging is used the method of assessment (e.g. CT, MRI or PET-CT) must provide bidimensional measurements with same method to be used throughout the study.
- Skeletal X-ray or low-dose CT scan; required if previous assessment is > 6 weeks from initiation of therapy.
- Review prior/concomitant medications
- Inclusion/Exclusions criteria review
- SAE monitoring

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

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

8.1.2. Procedures during study treatment phase, all cycles

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

8.1.3. Procedures Day 1, all cycles

- Inclusion/Exclusions criteria review on Cycle 1 day 1, for subsequent cycles criteria for initiation of treatment should be fulfilled, see Section 6.6.1 and Section 6.6.2.
- Use of Health services and Hospitalization and QoL questionnaire EQ-5D-5L, prior to any study visit activities (tests, examination or treatment), see Appendix 16 and Appendix 14. The questionnaires should be administered even if the treatment is not given.
- Patient preference scale, Cycle -3 only, prior to any study visit activities, see Appendix 15.
- Physical examination; including weight and assessment for extramedullary myeloma. Extramedullary myeloma that can be followed by physical exam should also be evaluated each cycle with measurements documented in the source documents.
- Assessment of known or suspected extramedullary myeloma as clinically indicated or to

confirm a response or progression. If imaging is used the method of assessment (e.g. CT, MRI or PET-CT) must provide bidimensional measurements with same method to be used throughout the study.

- Vital signs; including blood pressure, pulse, respiration rate, temperature, to be assessed pre and post dose on each dosing day.
- ECOG performance status
- Pregnancy test; only for WOCBP
- Blood tests:
  - Hematology: CBC with differential and platelet count
  - Chemistry: sodium, chloride, potassium, magnesium, calcium, phosphate, uric acid, blood urea nitrogen [BUN](or urea), serum creatinine, eGFR by CKD-EPI formula, glucose (non-fasting), ALT/AST (SGPT/SGOT), alkaline phosphatase, total protein, total bilirubin, albumin, and lactate dehydrogenase (LDH)
  - Biomarker assessment (before dosing at Cycle 1 Day 1)
- Bone marrow aspiration; A total of 5 mL should not be exceeded. Only applicable if to confirm a suspected CR or PD.
  - Remaining material in sample to be sent to central laboratory for analysis of exploratory biomarkers. Refer to Laboratory Manual for additional information
- Concomitant medications review
- M-protein assessments, see Section 8.2.1 on planned Day 1 of each cycle (day 29 of prior cycle).
  - If treatment is delayed an assessment should still be made at day 29 and should be repeated prior to next cycle if the delay is 2 weeks or longer, and to confirm any response or PD.
- Myeloma response assessment (from Cycle 2 Day 1 and onwards)
- Skeletal X-ray or low-dose CT scan; as clinically indicated
- Administration of dexamethasone, and provide patient with one cycle of Dexamethasone
- Administration of Melflufen; see Section 6.1.2
- Patient treatment satisfaction scale, Cycle 1 and 2 only, after received melflufen infusion, see Appendix 15.
- Nurse convenience and Nurse preference scale, following completion of melflufen administration, Cycle 1 and 2, see Appendix 15.
- Pharmacokinetic blood samples; For all patients, cycle 1 and 2 only, see Section 8.6.
- AE monitoring
- Inspection of peripheral infusion site, when indicated, see SoA

8.1.4. Procedures Day 8, 15 and 22

- Physical examination: symptom directed as needed during treatment.
- Hematology blood tests: CBC with differential and platelet count. If patient tolerability is good, i.e. no dose modifications, dose delays or need of supportive therapy (G-CSF, blood or platelet transfusion) in the two preceding cycles, then CBC assessments may be excluded Day 8 and Day 22.
- Concomitant medications review
- Dexamethasone review

- AE monitoring
- Inspection of peripheral infusion site, when indicated, see SoA

If patient tolerability is good, i.e. no dose modifications, dose delays or need of supportive therapy (Granulocyte colony stimulating factor [G-CSF], blood or platelet transfusion) in the two preceding cycles, then visit to site and CBC assessments may be excluded Day 8 and Day 22.

8.1.5. Procedures if melflufen or dexamethasone are discontinued

If melflufen or dexamethasone are discontinued but the other study drug is continued, the schedule of assessments should continue as per planned assessment according to Section 8.1.3, 8.1.4and SoA.

8.1.6. Procedures after active study treatment phase

Refer to Section 4.1.1 for treatment duration. An EOT visit will be scheduled within 30 days (accepted time window ±3 days) of the last dose of study treatment, or as soon as possible if the decision to remove patient from therapy occurs later than 30 days after last dose (such as in the case of a prolonged cycle). Patients that discontinue therapy for reasons other than disease progression will enter PFS follow-up.

Patients with Grade 3 or 4 thrombocytopenia or neutropenia should be followed until resolution to ≤ Grade 2 or start of subsequent therapy. SAEs should be followed until resolution or stabilization with no expected resolution.

Patients who withdraw consent for treatment will continue to be followed for disease progression unless they explicitly withdraw consent for these procedures.

8.1.7. Procedures at End of Treatment Visit

End of Treatment visit should be scheduled 30 days (accepted time window ±3 days) after last dose of study treatment or as soon as possible if the decision to remove patient from therapy occurs later than 30 days after last dose (such as in the case of a prolonged cycle). Patients with PD as the reason for EOT should have the PD confirmed with 2 consecutive assessments and verified by the Medical Monitor prior to discontinuation of therapy. If the investigator due to suspicion of rapid PD consider it necessary to urgently obtain result for M protein in order to assess the disease status, the M protein assessments may be performed at the local laboratory following consultation and approval of medical monitor. If M protein samples are sent for analysis at the local laboratory samples should also be sent to central laboratory. If a new treatment for MM is to be introduced sooner than 30 days after last dose of study drug the EOT visit should occur as close as possible before the first dose of the new drug. Patients progressing while on treatment, require 2 consecutive M protein assessments at any time (including the same day for SPEP/FLC) prior to discontinuation of treatment. The second assessment must be a separate serum and urine sample. (If the second consecutive M protein sample can only be obtained after the start of subsequent therapy, it may be used as confirmation of PD).

- Use of Health services and Hospitalization and QoL questionnaire EQ-5D-5L, prior to any study visit activities (tests, examination or treatment), see Appendix 16 and Appendix 14.
- Physical examination; including weight and assessment for extramedullary myeloma

- Vital signs; including blood pressure, pulse, respiration rate and temperature
- ECOG performance status
- Pregnancy test; only for WOCBP
- 12-lead ECG, QTc interval to be assessed by Fridericia formula
- Blood tests;
    - Hematology: CBC with differential and platelet count
    - Chemistry: sodium, chloride, potassium, magnesium, calcium, phosphate, uric acid, blood urea nitrogen [BUN](or urea), serum creatinine, eGFR by CKD-EPI formula, glucose (non-fasting), ALT/AST (SGPT/SGOT), alkaline phosphatase, total protein, total bilirubin, albumin, and lactate dehydrogenase (LDH).
    - Biomarker assessment
- M protein assessments see Section 8.2.1.
- Myeloma response assessment
- Known or suspected extramedullary myeloma assessment if clinically indicated and to confirm response or progression. If imaging is used the method of assessment (e.g. CT, MRI or PET-CT) must provide bidimensional measurements with same method to be used throughout the study.
- Skeletal X-ray or low dose CT scan; as clinically indicated
- Concomitant medications review
- Dexamethasone review
- AE monitoring; Ongoing neutropenia and thrombocytopenia Grade 3-4 at the EOT visit are to be followed until resolution (≤ Grade 2) or initiation of subsequent therapy. SAEs should be followed until resolution or stabilization with no expected resolution.

8.1.8. Procedures during Progression Free Survival Follow-up

Patients who discontinue therapy for reasons other than disease progression should continue to have monthly disease assessments done until documented progression or initiation of subsequent therapy.

- Use of Health services and Hospitalization and QoL questionnaire EQ-5D-5L, prior to any study visit activities (tests, examination or treatment), see Appendix 16 and Appendix 14.
- Known or suspected extramedullary myeloma should be assessed as clinically indicated until confirmed disease progression. If imaging is used the method of assessment (e.g. CT, MRI or PET-CT) must provide bidimensional measurements with same method to be used throughout the study.
- M protein response assessment 8.2.1;
    - monthly until confirmed disease progression or initiation of next anti-myeloma treatment, for patients who discontinue study treatment for reasons other than progression.
    - Confirmed progression requires 2 consecutive M protein assessments at any time (including the same day for SPEP/FLC). The second assessment must be a separate serum and urine sample. If the second consecutive M protein sample only can be obtained after the start of subsequent therapy, it may be used as confirmation of PD.
    - The first assessment should be performed 4 weeks after the EOT visit. Serum calcium, albumin (corrected calcium) required if this is the presenting symptom of progression.
    - When confirmed progression, the patient has reached end of study, see Section 4.5.2

- Myeloma response assessment
- Second primary malignancies follow-up

8.2. Efficacy Assessments

8.2.1. M protein Response assessment

Samples for M protein assessments should be sent to the central laboratory for analysis, except where specified, refer to Laboratory Manual for instructions. A local laboratory assessment for M protein analysis may only be used on certain occasions if approved by the medical monitor.

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

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

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

8.2.3. Extramedullary myeloma (plasmacytoma) assessment

- Known or suspected extramedullary myeloma are to be assessed at screening, as clinically indicated and to confirm response or progression.
- Method(s) of evaluation should be able to provide bidimensional measurements and must be defined at baseline (for lesions present at screening); methods may include, CT, PET-CT, MRI or physical examination. For skin lesions, only measurable lesions with a caliper should be reported
- Once the method is selected, extramedullary myeloma lesions should be evaluated with the same method throughout the trial.
- Lesions will be assessed according to IMWG-URC guidelines (Kumar et al 2016) see, Appendix 7.
- Lesions that are evaluable but not measurable (such as malignant ascites or pleural effusion) should be reported. These lesions should disappear completely in case of CR or increase in size in order to be reported as cause for progression.

8.3. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

8.3.1. Physical Examinations

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

The outcome of the assessments will be recorded as “normal” or “abnormal”. Abnormal findings will be assessed as “clinically significant” or “not clinically significant”. Clinically significant findings prior to first dose of study treatment will be documented as Medical History. Clinically significant findings after first dose will be documented as AEs.

8.3.2. Local tolerance assessments

The peripheral infusion site should be inspected pre and post infusion, including assessment of any local reaction such as but not limited to redness, swelling, signs of phlebitis or extravasation and graded using CTCAE 5.0, see Appendix 5 and VIP Score, see Appendix 13. All signs of extravasations or phlebitis should be photo documented at least daily until resolution.

8.3.3. Vital Signs

Vital signs will be measured, at the timepoint specified in the SoA, Sections 6.1.2 and 8.1.3and will include temperature, systolic and diastolic blood pressure, pulse and respiratory rate.

- Blood pressure and pulse measurements will be assessed preferable with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the patient.

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

8.3.4. Electrocardiograms

A 12-lead ECG will be obtained as outlined in the SoA using an ECG machine that automatically calculates the heart rate and measures PR, QRS and QT. QTc interval should be assessed by Fridericia formula, see Appendix 11.

The ECGs will be taken in supine position, after the patient has been lying down for at least three minutes.

The Investigator (or a qualified observer at the investigational site) will interpret the ECG using one of the following categories: "normal" or "abnormal". Abnormal findings will be assessed as "clinically significant" or "not clinically significant".

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

8.3.5. Clinical Safety Laboratory Assessments

- See Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- The investigator must review the laboratory report, add an assessment of clinical significance, and document this review. The laboratory reports must be filed with the source documents.
- The investigator must record any clinically relevant changes occurring during the study in the AE section of the eCRF. Clinically significant abnormal laboratory findings are those that:
    - Require concomitant therapy
    - Require medical intervention
    - Require change in study treatment
    - Investigator considers clinically significant for any reason
- Ongoing neutropenia and thrombocytopenia Grade 3-4 at the EoT visit are to be followed until resolution (≤ Grade 2) or initiation of subsequent therapy.

- All ANC and platelet counts collected during the protocol participation, i.e. both those collected at protocol specified time points and any additional time points (unscheduled assessments), must be reported in the eCRF and if applicable also in the SAE report;
- All ANC and platelet counts associated with a SAE regardless of the nature of the event, must be reported in the details of the SAE report.
- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in patient management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded in the eCRF.

8.3.6. Bone Marrow Aspiration (BMA)

- BMA sample is used
  - to quantify baseline percent plasma cell involvement, assess morphology and
  - for cytogenetics analysis, by use of iFISH.
  - to assess exploratory biomarkers of response.
- Repeat BMA at time of suspected hematologic CR (optional for PD) for % plasma cells and exploratory biomarkers.

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

8.4. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.

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

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or study procedures, or that caused the patient to discontinue the study. (see Section 7)

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

All SAEs will be collected from signing of the informed consent form until 30 days after last dose of any study drug or initiation of subsequent therapy whichever occurs first.

All AEs will be collected from the start of any study drug until 30 days after the last dose of any study drug or initiation of subsequent therapy whichever occurs first.

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

All SAEs will be recorded and reported to the assigned Pharmacovigilance CRO, TFS, within 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to TFS within 24 hours after becoming aware of the updated SAE data.

Investigators are not obligated to actively seek AE or SAE after EoT visit and conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a patient has been discontinued from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify TFS.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

8.4.2. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each patient at subsequent visits/contacts. All SAEs, will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures of AEs and SAEs is given in Appendix 3.

8.4.3. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.4. Pregnancy

- Details of all pregnancies in female patients and, if indicated, female partners of male patients, occurring after the start of any study drug and until 30 days after the last dose of any study drug for female patient, and 90 days after the last dose of any study drug for female partners of male patients will be collected.
- If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.4.5. Fatal Events

- Death is an outcome of a SAE and is not a SAE in itself. When death is an outcome, the event(s) resulting in death should be reported (e.g., "pulmonary embolism" with a fatal outcome). The appropriate diagnosis or term should be recorded and assigned severity Grade 5;
- In instances of death due to "Disease Progression" the cause of death should be indicated as the event or condition resulting in death to the extent possible (e.g., "respiratory failure" due to progressive MM);
- Deaths that occur later than 30 days after the last study drug administration should be reported as SAEs only if assessed as related to the study treatment.

8.4.6. Laboratory Test Abnormalities

Laboratory abnormalities are usually not recorded as AEs; however clinically significant laboratory abnormalities must be recorded as AEs (or serious AEs) if they meet the definition of an AE (or serious AE) as described in Appendix 3.

Clinically significant laboratory abnormalities are those that:

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

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

8.4.7. Additional Laboratory Reporting Guidelines

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

- Collected and reported during the study period and the EOT visit;
- Ongoing Grade 3 and 4 platelet and ANC values at the time of the EOT visit are to be followed until resolution (≤ Grade 2), or stabilization, or initiation of a subsequent therapy;
- All ANC and platelet counts collected during the treatment period and until the EOT visit, i.e. both those collected at protocol specified time points and any additional time points (unscheduled assessments), must be reported in the eCRF and if applicable also as an AE/SAE;
- All ANC and platelet counts associated with a SAE regardless of the nature of the event, must be reported in the details of the SAE report;
- Supportive care such as platelet transfusions and G-CSF given for an AE or prophylactic reason must be reported in the eCRF and if applicable also in the SAE report.

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

8.5. Treatment of Overdose

For this study, any dose of melflufen greater than 40 mg per cycle (including 40 mg administered < 28 days [+/-3day window]) will be considered an overdose.

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

In the event of an overdose, the investigator should:

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

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

8.6. Pharmacokinetics

Thirteen plasma samples (3 mL each) for determination of melflufen and the metabolites desethyl-melflufen and melphalan will be drawn in connection to the first two melflufen treatment cycles (Cycle 1 and 2), see Table 8-1 for time points.

All PK samples must be drawn peripherally, from a catheter where melflufen has not been given, preferably from the other arm and not from the central catheter.
A blood volume of approximately 39 mL/cycle will be collected for PK evaluations at Cycle 1 and at Cycle 2.

Table 8-1 PK sampling timepoints

	Cycle 1 and Cycle 2
During melflufen infusion	Sample 1: 5 minutes Sample 2: 10 minutes Sample 3: 15 minutes Sample 4: 20 minutes Sample 5: 25 minutes Sample 6: 30 minutes -immediately before end of infusion
After end of melflufen infusion	Sample 7: 5 minutes

	Sample 8: 10 minutes Sample 9: 15 minutes Sample 10: 30 minutes Sample 11: 60 minutes Sample 12: 120 minutes Sample 13: 240 minutes

All timepoints for PK sampling need to be documented. Refer to the Laboratory Manual for details on specimen collection and processing.

8.7. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.8. Genetics

At screening Cytogenetics characterization of MM will be conducted. DNA and RNA sequencing will be conducted as a part of exploratory analysis with aim to identify novel biomarkers that can predict response and resistance to treatment.

8.9. Biomarkers

Collection of samples for biomarker research is also part of this study and following samples are required and will be collected from all patients in this study as specified in the SoA and in Table 8-2. Samples will be tested to identify biomarkers that predict the treatment outcome and detect patient subgroups that are likely to respond to the study drug(s).

Table 8-2 Summary of biomarker assessments

Marker	Tissue	Timepoints	Method	Purpose of analysis
Novel biomarkers including but not limited to expression of aminopeptidases/esterases	Bone Marrow	• Screening • At the time of response (CR) and PD	DNA/RNA sequencing	Identifying novel biomarkers that may predict response/resistance
	Blood	• Pretreatment Cycle1 Day 1 • EoT visit	Circulating tumour cells, Single cell DNA/RNA sequencing	
	Plasma (back-up	• Cycle 1 Day 1 (first three	In a case of remaining	

	PK samples if available)	timepoint samples)	back up samples from the PK analysis, samples will be used for protein profiling	

8.10. Health outcome and Quality of Life measures

8.10.1. Patient Reported Outcome Assessments

EQ-5D-5L will be used to evaluate functional status and well-being in the study. A paper version of the form will be used. The questionnaire should be submitted to patients by site personnel familiar with these procedures and/or preferably a QoL dedicated person in the team. The patient should complete the questionnaires prior to any procedures on the day of the visit and prior to being told anything related to health; the questionnaire should be administered even if the treatment is not given. If the patient wishes to have the questions read aloud and then answer orally and the study personnel write the answer on the questionnaires, this is acceptable. QoL questionnaires will be submitted to patients at Cycle1 Day 1, each subsequent cycle on day 1, at the time of EOT visit and at PFS-FU visits until time of progression or starting a new treatment. If PD/EOT and next treatment occur at the same time, only one assessment is required, if the EOT visit is for a reason other than PD, continue QOL assessments each month until PD and at time new treatment begins.

8.10.2. Patient treatment satisfaction, nurse convenience and nurse preference of administration

An 11-point numerical rating scale (NRS) will be used to measure patient treatment satisfaction. The scale ranges from 0-10, where “0” represents no satisfaction, and “10” represents very satisfied. The patient should complete the treatment satisfaction NRS after received administration of melflufen on Day 1 of Cycle 1 and 2. Treatment preference scale will be completed prior to any procedures on Day 1 of Cycle 3 only, and prior to being told anything related to health. If the patient wishes to have the questions read aloud and then answer orally and the study personnel write the answer on the questionnaires, this is acceptable.

An 11-point NRS will be used to measure nurse convenience to administer treatment. The scale ranges from 0-10, where “0” represents not convenient at all, and “10” represents very convenient. The nurse should complete the convenience NRS after the patient was given the treatment on the day of the visit. Nurse convenience should be captured at Cycle 1 Day 1 and Cycle 2 Day 1.

Nurse preference to administration will be measured by asking a question on which type of administration the nurse would prefer in treating this patient, this time. The administration options indicated are peripheral venous catheter (venflon) and central catheter (= a PICC-line, a venous port (“Port-Cath”) or a CVC). The nurse preference to administration should be captured after the patient was given the treatment on the day of the visit, at Cycle 1 Day 1 and Cycle 2 Day 1.

8.10.3. Use of health services and hospitalization

Use of health services and days of hospitalization will be captured at screening visit, Day 1 of each cycle, at time of EOT visit, and PFS-FU prior to any procedure on the day of the visit and prior being told anything related to health.

8.10.4. Eastern Cooperative Group Oncology Performance Status

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

9. Statistical Considerations

9.1. Sample Size Determination

Evaluation of combined data for the melflufen studies O-12-M1, OP-103, OP-104 and OP-107 on patients with MM has demonstrated a relationship between melphalan systemic exposure and the lowest (nadir) levels of neutrophils and thrombocytes in treatment cycle 1. The incidence of grade 3 and grade 4 events increased in parallel with the melphalan AUC values. For melflufen and desethyl-melflufen no corresponding relationship has been found. Melphalan AUC has therefore been selected as the main PK parameter for which similarity between central and peripheral melflufen administration should be assessed.

The within-patient variability in melphalan PK parameters after melflufen administration has been evaluated in study OP-103 from data for the first two treatment cycles in 59 patients. The within-patient standard deviations in log scale were Cmax: 0.251, AUC: 0.248 and AUCinf: 0.217. Based on a geometric mean ratio peripheral vs. central of 0.95, a 90% CI for the ratio of geometric means within bioequivalence limits of 0.8 and 1.25, and 80% power, a sample size of 20 patients (10 per sequence) is required assuming a within-patient variability for period differences (in log scale) of 0.29.

Approximately 25 patients will be enrolled to achieve 20 PK- and local tolerance-evaluable patients.

9.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
PK	All patients that have received at least two melflufen doses of 40 mg and have sufficient PK samples taken at Cycle 1 and 2 for determination of all PK variables. One PK sampling series following peripheral administration and one PK sampling series following central administration. Patients with a dose reduction in cycle 2 are not evaluable for PK.
Safety	All patients randomly assigned to study treatment that receive at least a partial dose of study treatment (melflufen and/or dexamethasone). Patients will be analyzed according to the treatment/administration route (peripheral or central) they actually received. All safety endpoints will be performed using the safety analysis set.

Full analysis set (FAS)	All patients who are randomized. Patients will be analyzed according to the treatment assigned at randomization. All efficacy endpoints will be performed using the Full analysis set.

9.3. Statistical Analyses

The statistical analysis plan will describe the patient populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.3.1. General Considerations for the Statistical Analysis

The statistical analyses as outlined in this section will be further described in the statistical analysis plan (SAP). Statistical analyses will be reported using summary tables, inferential analyses, figures, and data listings. For continuous variables, the number of patients with non-missing data (n), mean, standard deviation (sd), median, minimum, and maximum will be summarized. For discrete data, the frequency and percent distribution will be summarized. Graphical methods will be used, as appropriate, to illustrate study endpoints. Individual patient data recorded on the eCRFs and any derived data will be presented by in data listings.

9.3.1.1. Handling of drop-outs and missing data

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

9.3.2. Efficacy Analyses

Endpoint	Statistical Analysis Methods
Secondary	
Best response during the study	Best response during the study (sCR, CR, VGPR, PR, MR, SD or PD) assessed by the investigator according to IMWG-URC (Kumar et al.2016), will be described as absolute (n) and relative (%) frequencies.
ORR (including CR/sCR, VGPR and PR)	The overall response rate (ORR) will be estimated as the proportion of patients who achieve a confirmed response of sCR, CR, VGPR, or PR as their best response, as assessed by the investigator. At the end of the trial an exact two-sided 95% confidence interval for ORR will be determined.

CBR proportion of patients with ≥ MR as best response	Clinical benefit rate (CBR) i.e. proportion of patients that achieve a confirmed minimal response or better (sCR, CR, VGPR, PR and MR). CBR will be summarized using the same method as for ORR.
DOR (time from the first confirmed response of sCR, CR, VGPR or PR to first confirmed disease progression, or death due to any cause.	Duration of response (DOR) is defined as the time from the first evidence of confirmed assessment of sCR, CR, VGPR, or PR to first confirmed disease progression according to the IMWG-URC or to death due to any cause. DOR is defined only for patients with a confirmed PR or better. The distribution of DOR will be summarized using the Kaplan Meier (K-M) method (Kaplan et al. 1958). The median DOR will be estimated from the 50th percentile of the corresponding K-M estimates. The 95% CI for median DOR will be constructed using the method of Brookmeyer (Brookmeyer et al. 1982)
DOCB (time from first evidence of confirmed assessment of sCR, CR, VGPR, PR, or MR to first confirmed disease progression, or to death due to any cause.)	Duration of clinical benefit (DOCB) will be calculated from the first evidence of confirmed assessment of sCR, CR, VGPR, PR or MR to first confirmed disease progression, or to death due to any cause. Duration of clinical benefit is defined only for patients with a confirmed MR or better. DOCB will be summarized using the same method as for DOR
TTR (time form randomization to the date of the first documented confirmed response in a patient that has responded with ≥ PR (sCR, CR, VCPR or PR))	Time to response (TTR) will be calculated as time from randomization to first documented confirmed response in a patient that has responded with PR or better. TTR will be presented descriptively for patients with a response.
TTP (time from the date of randomization to the date of the first documented confirmed PD)	The time to progression (TTP) is defined as the time in months from randomization to the date of the first documented confirmed progression. TTP will be summarized using the same method as for DOR.
TTNT (time from randomization to the date of next anti-myeloma treatment)	Time to next treatment (TTNT) will be calculated from the date of initiation of therapy to start of next line of therapy. TTNT will be summarized using the same method as for DOR.
PFS (time from the date of randomization to the date of first documentation of confirmed PD or death due to any cause)	Progression free survival (PFS) will be measured from time from the date of randomization to the date of first documentation of confirmed disease progression (PD) or death due to any cause, whichever occurs first.

	PFS will be summarized using the same method as for DOR.

All efficacy analyses will be performed on FAS and safety analysis set by total group.

9.3.3. Safety Analyses

All safety analyses will be performed on the Safety Population and presented by administration group.

Endpoint	Statistical Analysis Methods
Primary	
Frequency and Grade of local reactions including phlebitis at infusion site after peripheral intravenous administration	The frequency and grade (according to using CTCAE 5.0 and VIP Score) of local reactions including phlebitis at infusion site during Cycle 1 and Cycle 2 will be summarized for peripheral intravenous administration
Secondary	
Frequency and Grade of Treatment emergent Adverse Events (TEAEs)	The number of patients experiencing treatment emergent adverse events (TEAEs) will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT). The maximum grade (according to CTCAE 5.0) for each type of adverse event will be recorded for each patient, and frequency tables will be presented and reviewed to determine patterns. Additionally, the relationship of the adverse event(s) to the study treatment will be taken into consideration.

Analysis of safety data

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

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

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

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

A patient reporting the same AE more than once will be counted only once when

calculating incidence 1) within a given SOC, and 2) within a given SOC and PT combination. For such cases, the maximum CTCAE toxicity grade and strongest causal relationship to study treatment for the event will be used in the incidence calculations. Treatment-related AEs, defined as AEs with a relationship of possibly or probably related will be summarized in the same way.

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

Actual value for all hematology and serum chemistry, will be summarized at each scheduled visit. Selected laboratory test results will be assigned toxicity grades using CTCAE 5.0. Shift tables assessing the toxicity grade at baseline versus worst toxicity recorded on study will be presented. Actual value and change from baseline for weight and vital sign results, including blood pressure, pulse, and temperature, will be summarized at each scheduled visit. Any clinically significant values will be reported by the investigator as AEs.

9.3.4. Statistical evaluation of PK parameters

Descriptive statistics for drug concentrations by time point and PK variables will be provided for melflufen, melphalan and desethyl-melflufen by route of administration.

Formal statistical analysis will for each compound be performed on the PK parameters $AUC_{(0\text{-}last)}$ which is referred to as $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}inf)}$ and C_{max} to assess relative plasma exposure. The PK parameters will undergo a logarithmic transformation and will be analyzed using a linear mixed effects model which will include terms for period, sequence and treatment as fixed effects and subject nested within sequence as a random effect. Adjusted geometric mean ratios (GMRs) and 90% confidence intervals (CIs) for the adjusted GMRs for the comparisons between central and peripheral administration will be provided.

The main parameter for evaluation of similarity between routes of administration is melphalan AUCinf. Similarity is confirmed when the 90% confidence interval for the GMR is within the bioequivalence limits of 0.8 and 1.25.

9.3.5. Exploratory analyses

Biomarker Analyses Set

DNA, RNA and protein-based drug response biomarkers including but not limited to aminopeptidases and esterases. The population will be presented separately from the main clinical study report (CSR).

Treatment satisfaction and QoL

Endpoint	Statistical methods
• Value in each scale assessed by patients • Value in each scale assessed by nurses	Value in each scale will be presented with descriptive statistics
• Value and changes from baseline in EQ-5D-5L	The observed value and change from baseline in VAS and EQ-index will be summarized with descriptive statistics at each visit. Also, number of subjects in each category by dimension will be summarized by visit.
• Number of health services • Number and days of hospitalization	Will be presented with descriptive statistics.

9.4. Interim Analyses

When the PK and peripheral safety study is completed an interim CSR will be performed. The interim analyses will include at least 20 patients that have received two melflufen doses of 40 mg, have an observation period of 28 days after the second dose and at least one peripheral i.v. infusion. The objective of the interim CSR will be to evaluate if peripheral i.v. infusion of melflufen can be introduced in other trials, as an alternative to central i.v. infusion. An evaluation will be performed by comparing treatment arms with respect to PK and evaluate safety e.g. frequency and grade of local reactions including phlebitis and extravasation at infusion site for patients receiving peripheral infusion. Due to the short duration of treatment, efficacy endpoints will not be included in the interim CSR. Details of the interim analysis will be described in the SAP.

9.4.1. Data Safety Monitoring Committee (DSMC)

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

A DSMC will assess the benefit/risk profile of the study. All reported Grade 3-4 treatment-related non-hematological AEs, all local toxicities at the peripheral injection site as well as all SAEs, and any treatment-related deaths due to hematologic or non-hematologic AEs as well as efficacy and PK data will then be presented to the DSMC.

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

After 6 patients have received 2 cycles of 40 mg melflufen, one cycle via peripheral infusion and one cycle via central infusion with adequate PK data, a DSMC will assess the safety and tolerability of received infusions. The DSMC may then allow continuation with peripheral infusion in Cycle 3 onwards (in both Arm A and B) to further study local toxicity

with repeat peripheral infusions. The investigator in agreement with the patient will determine whether continued treatment will use peripheral or central administration.

If no major safety signals have been reported, recruitment may continue during preparations for DSMC meeting.

Following a DSMC evaluation of data from at least 20 PK evaluable patients with an observation period of at least 28 days from the second dose of melflufen, the main PK and safety and tolerability study may be concluded.

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

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

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the patient or his/her legally authorized representative and answer all questions regarding the study.
- Patients must be informed that their participation is voluntary. Patients or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health

Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Patients must be re-consented to the most current version of the ICF(s) during their participation in the study if the update is relevant to the patient.
- A copy of the ICF(s) must be provided to the patient or the patient's legally authorized representative.

10.1.4. Data Protection

- Patients will be assigned a unique identifier by the sponsor. Any patient records or datasets that are transferred to the sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.
- The patient must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient.
- The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Dissemination of Clinical Study Data

- Oncopeptides AB assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report, the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results (the study results will be posted in clinicaltrials.gov). Any publication will be a joint publication between the sponsor and the investigators and authorship will be determined by mutual agreement.
- The completed original eCRF is the sole property of the sponsor and should not be made available in any form to third parties (except to authorized representatives of appropriate regulatory authorities) without written permission from the sponsor.

10.1.6. Data Quality Assurance

- All patient data relating to the study will be recorded on eCRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The data collection tool for the study will be a validated, internet based, electronic data capture (EDC) software system called RAVE.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 25 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.
- During protocol development, processes and data that are critical to ensure human subject protection and the reliability of trial results have been identified and documented in Sponsor Oversight document(s).
- Risk identification and evaluation will be conducted on an ongoing basis by the sponsor and CRO, as these are key to managing and mitigating risks.

10.1.7. Source Documents

- Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in Source Data Location List developed for each site.

10.1.8. Study and Site Closure

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

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

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

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

10.1.9. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies in their entirety.
- Any publication will be a joint publication between Oncopeptides AB and the investigators and authorship will be determined by mutual agreement.

10.1.10. Compensation for health damage of subjects/insurance

The sponsor maintains clinical trial insurance coverage for this study in accordance with the laws and regulations of the country in which the study is performed.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 10-1 will be performed by the local laboratory at each site.
- The tests detailed in Table 10-2 will be performed by central labs, names and addresses to the central labs used in this study is found in the Laboratory manual.
- Protocol-specific requirements for inclusion or exclusion of patients are detailed in Section 5 of the protocol.
- PK 8.6 and Multiple Myeloma lab assessments 8.2.1 will be performed at central laboratories – please refer to the Laboratory Manual for details on sample collection and processing.
- Blood and bone marrow volumes collected in this study is estimated in Table 10-3.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 10-1 Protocol-Required Laboratory Assessments at Local Lab

Laboratory Assessments	Minimal Required Parameters	
Hematology	Platelet Count Red blood cell (RBC) Count • Hemoglobin (Hb) • Hematocrit RBC Indices (optional): • Mean corpuscular volume (MCV) • Mean corpuscular hemoglobin (MCH) • % Reticulocyte count	White blood cell (WBC) count with Differential: • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils • Calculation of ANC
Clinical Chemistry	Alanine Aminotransferase (ALT) (Serum Glutamic-Pyruvic Transaminase (SGPT)) Albumin Alkaline phosphatase (ALP) Aspartate Aminotransferase (AST) (Serum Glutamic-Oxaloacetic Transaminase (SGOT)) Blood urea nitrogen (BUN) or urea	Calcium Chloride Creatinine (serum) eGFR by CKD-EPI formula Glucose (fasting as baseline) Lactate dehydrogenase (LDH) Magnesium Phosphate Potassium (K) Sodium Total Bilirubin Total Protein Uric Acid
Bone marrow	% plasma cells Morphology (screening only)	

Laboratory Assessments	Minimal Required Parameters
Routine analysis, urine	pH, glucose, protein, blood, ketones by dipstick Microscopic examination (if blood or protein is abnormal)
Other Screening Tests	Serum or urine human chorionic gonadotropin (hCG) pregnancy test, for example urine dipstick, (as needed for women of childbearing potential)

The results of each test must be entered into the eCRF. Investigators must document their review of each laboratory safety report and an assessment of clinical significance.

Table 10-2 Protocol-Required Laboratory Assessments at Central Lab

Laboratory Assessments	Minimal Required Parameters
Hepatitis B/C and HIV screen	Hepatitis B serum Antigen Anti - Hepatitis B core Antigen Anti - Hepatitis B serum Antigen Anti-HCV antibody Anti-HIV1/2 antibody/antigen
Urinalysis of 24 hr urine sample*	Total Protein Urine Protein Electrophoresis (UPEP) Urine Immunofixation (U-IFE) - At screening and if UPEP are not detectable and to confirm CR
Serum Myeloma Tests*	Protein Electrophoresis (SPEP) Immunofixation (S-IFE) - At screening and if SPEP are not detectable and to confirm CR Free Light Chain (SFLC) • Kappa • Lambda • Ratio Quantitative Immunoglobulins • IgA • IgD • IgE • IgG • IgM
Bone marrow	Cytogenetics by iFISH (screening only) Exploratory biomarkers, screening and if sample to confirm CR or progression is taken
Blood samples	Exploratory biomarkers, Cycle 1 Day 1 and EoT
Other Screening Tests	Beta-2 microglobulin

* M protein assessment may be performed at the local laboratory on certain occasions if approved by medical monitor as stated in section 8.1.7.

Table 10-3 Blood and Bone Marrow Volumes

Assessment	**Screening Days -21 to -1**	**Regimen A and B, All Cycles (except where specified)**				**EoT**	**PFS - FU**
		Day 1	Day 8	Day 15	Day 22		
Pregnancy test, WOCBP 5 mL	(X)	(X)				(X)	
Hematology 5-10 mL	X	X	(X)	X	(X)	X	
Biomarker blood sample 10 mL		X				X	
Chemistry 5-10 mL	X	X				X	(X)
Hepatitis B, C and HIV screen 5-10 mL	X						
Bone marrow aspiration 2-10 mL	X	(X)				(X)	(X)
M protein assessment 8.5 mL	X[a]	X				X	(X)
Pharmacokinetic samples, Cycle 1 and 2 only (3 mL per collection)		(X)					
Approximate Blood Volume per visit (mL)	40	40 + (40 when PK)	5-10	5-10	5-10	40	20
Approximate Bone Marrow Volume per visit (mL)	2-10	(2-10)				(2-10)	(2-10)

a) Including B2 Microglobulin

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

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

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

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

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

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

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

e. Is a congenital anomaly/birth defect

f. Other situations:

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

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

Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

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

Assessment of Severity

The investigator will make an assessment of severity/intensity for each AE and SAE reported during the study. Whenever possible, the CTCAE version 5.0 should be used to describe the event and for assessing the severity of AEs. Any events representing a change in the CTCAE Grade need to be reported on the AE eCRF. This includes any abnormal laboratory values that the investigator considers clinically significant see Section 8.3.5

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

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

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

Assessment of Causality

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

- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- Causality should be assessed using the following categories:

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

- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to assigned Pharmacovigilance CRO (TFS). However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** assigned Pharmacovigilance CRO (TFS)**.**
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by assigned Pharmacovigilance CRO (TFS) to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally completed eCRF.

- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

Reporting of SAEs

SAE Reporting to safety.report@oncopeptides.com via Paper CRF
• SAE reports are completed on paper and transferred to TFS via email to safety.report@oncopeptides.com, or facsimile can be used as back-up only if emailing reports is not possible (fax number is provided in the Investigator Site File). • In exceptional circumstances and in the absence of facsimile equipment, notification to the CRA or Medical Monitor by telephone is acceptable. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

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

Women in the following categories are not considered WOCBP

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

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

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

Contraception Guidance:

Male patients

From the start of the first dose of study drug until 3 months after the last dose of study drug, male study patients must agree to remain abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis), or use a male condom during each episode of penile penetration for the duration of the treatment and for 3 months after last dose of melflufen.

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

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

Female patients

Female patients of childbearing potential are eligible to participate if they, from the start of the first dose of study drug until 28 days after the last dose of study drug, agree to use a highly effective method of contraception consistently and correctly as described in Table 10-4.

Table 10-4 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*

Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[b] • Oral • Intravaginal • Transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Methods That Are User Independent [a]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion
Vasectomized partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the patient.
NOTES: a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for patients participating in clinical studies. b) Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive methods for patients participating in clinical studies. In this case, two highly effective methods of contraception should be utilized during the treatment period and for at least 3 months after the last dose of study treatment.

Pregnancy Testing:

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

Collection of Pregnancy Information:

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported on the study specific Pregnancy reporting

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

Male patients with partners who become pregnant

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

Female Patients who become pregnant

- The investigator will collect pregnancy information on any female patient who becomes pregnant after start of study drug and until 3 months after last dose of study drug. Information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a patient's pregnancy. The patient will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the patient and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- Any female patient who becomes pregnant while on study drug will discontinue study treatment.

Pregnancy Reporting to assigned Safety CRO, TFS; via Paper Pregnancy Reporting Form
• Email transmission of the Pregnancy paper Reporting Form is the preferred method to transmit this information to the assigned Safety CRO. If emailing the report is not possible facsimile can be used as a back-up method. (Email: safety.report@oncopeptides.com or use the fax number provided in the Investigator Site file). • In exceptional circumstances and in the absence of email or facismile equipment, notification to the CRA or Medical Monitor by telephone is acceptable.

- Initial notification via telephone does not replace the need for the investigator to complete and sign the Pregnancy CRF pages within the designated reporting time frames.
- Contacts for Pregnancy reporting can be found in Pregnancy report completion instruction.

10.5. Appendix 5: NCI CTCAE Version 5.0

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

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

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

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

10.7. Appendix 7: IMWG Uniform Response Criteria

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

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

All response categories require two consecutive assessments made at any time before the institution of any new therapy; all response categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable in serum, urine both or either. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not to be confirmed. For progressive disease, serum M-protein increases of ≥ 1 g/dL are sufficient to define relapse if starting M-protein is ≥ 0.5 g/dL.

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

10.8. Appendix 8: Line of Therapy Definition

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

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

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

New line of therapy

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

10.9. Appendix 9: ISS and R-ISS Score

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

(Palumbo et al. 2015)

10.10. Appendix 10: Definition of Relapsed Disease per IMWG definitions

Refractory Myeloma:

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

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

Relapsed Myeloma:

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

10.11. Appendix 11: Assessment of Q-Tc interval:

Q-Tc Fridericia Formula:

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

10.12. Appendix 12: Estimated Glomerular Filtration Rate (eGFR) by CKD-EPI equation

CKD-EPI equation calculator:

An online calculator for estimating eGFR may be accessed at the following link:

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

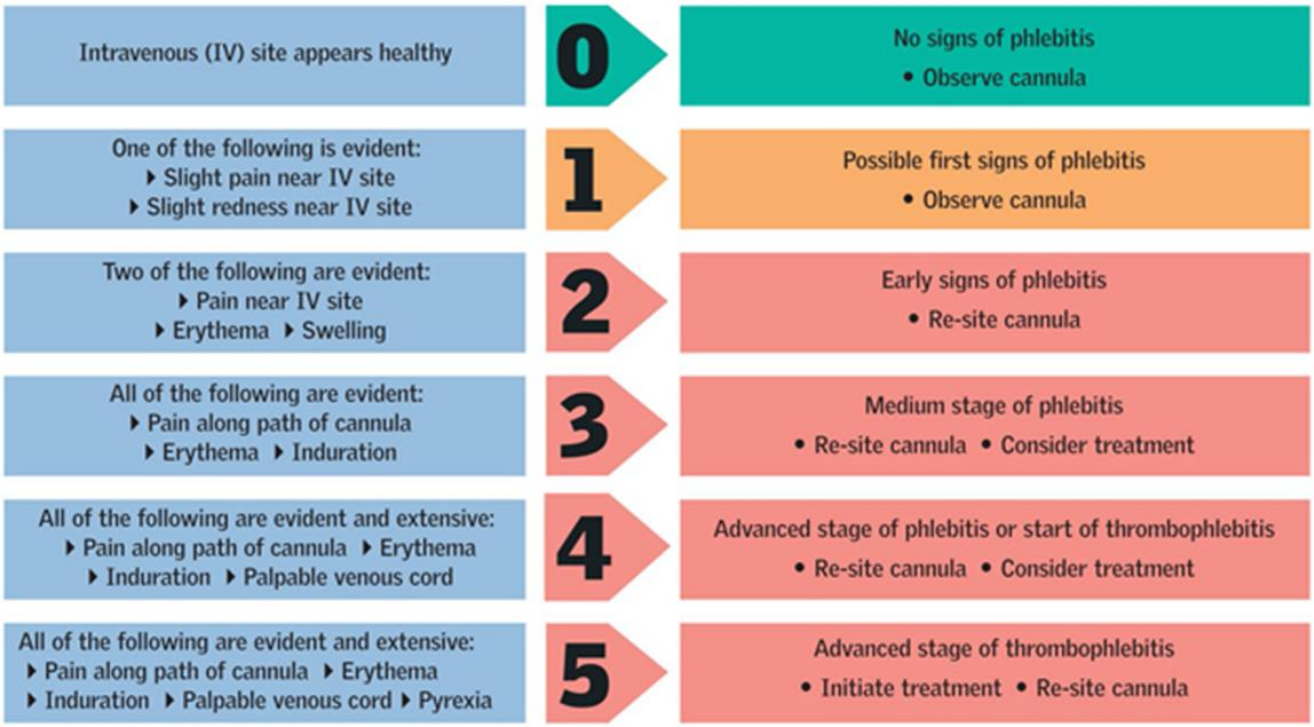
CKD-EPI equation:

GFR = 141 * min(Scr/κ,1)α * max(Scr/κ, 1)-1.209 * 0.993Age * 1.018 [if female] * 1.159 [if black]

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

(Levey A, Inker L 2017)

10.13. Appendix 13: Visual infusion Phlebitis Score



Permission to use the VIP score in this clinical study has been obtained from IV-team

The VIP score is a tool recommended by the RCN (Royal college of Nursing) for monitoring infusion sites, and have been evaluated, and deemed a reliable tool (Gallant 2006).

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

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

10.15. Appendix 15: Treatment satisfaction, nurse convenience and nurse preference

To the patient (with a *peripheral* catheter) Cycle 1 Day 1, Cycle 2 Day 1:

1. In total, how **satisfied** are you with receiving treatment via a peripheral venous catheter?

Please indicate the number that best describes your satisfaction:

□ □ □ □ □ □ □ □ □ □ □

0 1 2 3 4 5 6 7 8 9 10

Not satisfied at all *Very satisfied*

To the patient (with a *central* catheter) Cycle 1 Day 1, Cycle 2 Day 1:

2 In total, how **satisfied** are you with receiving treatment via a central catheter *(= a PICC-line, a venous port ("Port-a-Cath") or a central venous catheter*)?

Please indicate the number that best describes your satisfaction:

□ □ □ □ □ □ □ □ □ □ □

0 1 2 3 4 5 6 7 8 9 10

Not satisfied at all *Very satisfied*

To the Patient Cycle 3 Day 1:

3. Which type of administration did you prefer?

Please indicate the type of administration that best describes your preference:

□ Peripheral venous catheter (venflon)

□ Central catheter (= *a PICC-line, a venous port ("Port-a-Cath") or a central venous catheter*)

□ No preference

To the nurse Cycle 1 Day 1

For patients with a peripheral catheter

4 In total, how **convenient** was it to administer the treatment via a peripheral venous catheter?

Please indicate the number that best describes your convenience:

□ □ □ □ □ □ □ □ □ □ □

0 1 2 3 4 5 6 7 8 9 10

Not convenient at all *Very convenient*

To the nurse Cycle 1 Day 1

For patients with a central catheter

5. In total, how **convenient** was it to administer the treatment via central catheter *(= a PICC-line, a venous port ("Port-a-Cath") or a central venous catheter*)?

Please indicate the number that best describes your convenience:

□ □ □ □ □ □ □ □ □ □ □

0 1 2 3 4 5 6 7 8 9 10

Not convenient at all *Very convenient*

To the nurse Cycle 2 Day 1

6 In total, how **convenient** was it to administer the treatment via a peripheral venous catheter instead of via a central catheter *(= a PICC-line, a venous port ("Port-a-Cath") or a central venous catheter*)?

Please indicate the number that best describes your convenience:

□ □ □ □ □ □ □ □ □ □ □

0 1 2 3 4 5 6 7 8 9 10

Not convenient at all *Very convenient*

To the nurse Cycle 2 Day 1:

7. Which type of administration would you have preferred in treating this patient, this time?

Please indicate the type of administration that best describes your preference:

□ Peripheral venous catheter (venflon)

□ Central catheter (= *a PICC-line, a venous port ("Port-a-Cath") or a central venous catheter*)

□ No preference

10.16. Appendix 16: Use of health services and hospitalization

YOUR USE OF HEALTH SERVICES OVER THE LAST MONTH

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

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

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

YES [ ] NO [ ]

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

Oncopeptides questionnaire, modified from Health-care resource use questionnaire version 002, dated 11/07/2008.

10.17. Appendix 17: Management of chemotherapy extravasation: ESMO-EONS Clinical Practice Guidelines

https://www.esmo.org/Guidelines/Supportive-and-Palliative-Care/Management-of-Chemotherapy-Extravasation

10.18. Appendix 18: Abbreviations

Abbreviation	Description
AE	Adverse Event
ALT	Alanine transaminase/Alanine aminotransferase/glutamic pyruvic transaminase (SGPT)
ANC	Absolute Neutrophil Count
anti-CD38 mAbs	Anti CD38 monoclonal antibody
Anti-HBc	Anti-hepatitis B core antibody
Anti-HBs	Anti-hepatitis B surface antibody
ASCT	Autologous Stem-Cell Transplantation
AST	Aspartate transaminase/Aspartate aminotransferase/glutamic oxaloacetic transaminase (SGOT)
AUC	Area Under the Curve
BMA	Bone Marrow Aspirate
CA	Chromosomal Abnormalities
CBC	Complete Blood Count
CBR	Clinical Benefit Rate
CI	Confidence Interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CRF/eCRF	Case Report Form/electronic Case Report Form
CRO	Contract Research Organization
CR	Complete Response
CSR	Clinical Study Report
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events

CVC	Central Venous Catheter
DNA	Deoxyribonucleic Acid
DOCB	Duration of Clinical Benefit
DOR	Duration of Response
DSMC	Data Safety Monitoring Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
EOT	End of Treatment
ESMO	European Society for Medical Oncology
FLC	Free Light Chain
GCP	Good Clinical Practice
G-CSF	Granulocyte colony stimulating factor
H2	Histamine 2 receptor
HBV	Hepatitis B virus
HbsAg	Hepatitis B surface antigen
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent From
ICH	International Conference of Harmonization
IEC	Independent Ethics Committee
iFISH	interphase Fluorescence In Situ Hybridization
IFE	Immunofixation

Ig	Immunoglobulin
IMiD	Immunomodulatory Drug
IMWG	International Myeloma Working Group
IMWG-URC	International Myeloma Working Group Uniform Response Criteria
IND	Investigational New Drug
IRB	Institutional Review Board
ISS	International Staging System
IUD	Intra Uterine Device
i.v.	Intravenously
K-M	Kaplan-Meier
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MM	Multiple Myeloma
MR	Minimal Response
MRI	Magnetic Resonance Imaging
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NRS	Numeric Rating Scale
ORR	Overall Response Rate
PD	Progressive Disease
PET-CT	Positron Emission Tomography Computerized Tomography
PFS	Progression Free Survival
PFS-FU	Progression Free Survival Follow Up
PI	Proteasome Inhibitor

PICC	Peripherally Inserted Central Catheter
PK	Pharmacokinetics
p.o.	Per os/by mouth/orally
PPI	Proton pump inhibitor
PR	Partial Response
PT	Preferred Term
PVC	Peripheral venous catheter
PVG	Pharmacovigilance group
q.d.	Quaque die/ one a day
QoL	Quality of life
RNA	Ribonucleic Acid
RBC	Red Blood Cell
REB	Regional Ethics Board
R-ISS	Revised International Staging System
RRMM	Relapsed and Refractory Multiple Myeloma
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
sCR	Stringent Complete Response
SD	Stable Disease
SFLC	Serum Free Light Chain
SoA	Schedule of Activities
SOC	System Organ Class

SPEP	Serum Protein Electrophoresis
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Adverse Event
TTNT	Time to Next Treatment
TTP	Time to Progression
TTR	Time to Response
ULN	Upper Limit of Normal
UPEP	Urine Protein Electrophoresis
VGPR	Very Good Partial Response
VIP	Visual infusion Phlebitis
WOCBP	Woman of Childbearing Potential

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