Clinical Development Protocol

OP-103 OCEAN Trial

A Randomized, Controlled, Open-Label, Phase 3 Study of Melflufen/Dexamethasone Compared with Pomalidomide/ Dexamethasone for Patients with Relapsed Refractory Multiple Myeloma who are Refractory to Lenalidomide

Investigational Product	Melflufen
Study Sponsor	Oncopeptides AB Västra Trädgårdsgatan 15 SE-111 53 Stockholm, Sweden
Protocol Number	OP-103
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Clinical Research Organization (CRO)	Precision Oncology and PSI CRO 200 Route 31 North Suite 102 Flemington, NJ 08822 USA
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Signature Page

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Date of Original Protocol: **Version 1.1: December 7, 2016**
Version 2.0: June 29, 2017
Version 3.0: May 30, 2018

Approved By:

Johan Harmenberg, MD
Chief Medical Officer — 1 June 2018
Date

Pieter Sonneveld, MD
Global Lead Investigator — 4 June 2018
Date

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Protocol Acceptance Page

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

PSonneveld
Principal Investigator Name (Printed)

Principal Investigator Signature

4/June/2018
Date

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

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

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

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Protocol Synopsis

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Chemical Name	4-[Bis-(2-chloroethyl)amino]-L-phenylalanine-4-fluoro-L-phenylalanine ethyl ester hydrochloride
Study Protocol Title	A Randomized, Controlled, Open-Label, Phase 3 Study of Melflufen/Dexamethasone Compared with Pomalidomide/Dexamethasone for Patients with Relapsed Refractory Multiple Myeloma who are Refractory to Lenalidomide
Study Sponsor	Oncopeptides AB
Global Lead Investigator	Pieter Sonneveld, MD
Site(s)	Approximately 100 sites in Europe, North America and Asia/Pacific
Study Period	FPI 1Q2017
Background and Rational	Melflufen is a peptidase-potentiated therapy designed for targeted delivery of alkylating moieties to tumor cells. In contrast to other alkylating agents that are hydrophilic, the lipophilicity of melflufen leads to rapid and extensive distribution into tissues and cells. Inside cells, melflufen may directly bind deoxyribonucleic acid (DNA) or is readily metabolized by intracellular peptidases into the well-known antitumor compound melphalan, or by esterases into desethyl-melflufen, which also has alkylating properties. Due to the high activity of peptidases and esterases in human tumor cells, the formation of melflufen's metabolites is rapid in these cells with subsequent inflow of more melflufen (Gullbo et al. 2003c, Wickström et al. 2010). Since des-ethylmelflufen and melphalan are relatively hydrophilic, there is a possibility for intracellular trapping of these alkylators. This can be explained by a more efficient transport of melflufen into these cells, an efficient conversion into other alkylating molecules (i.e. melphalan and desethyl-melflufen) inside the cells and a less rapid disappearance of these molecules from the cells. The addition of melflufen to panels of primary cultures of human tumor cells, including multiple myeloma (MM), results in a similar pattern of activity as that of melphalan, but with 50 to 100-fold higher efficacy (Wickström et al. 2008), which is explained by the 50-fold higher intracellular exposure in MM cells of alkylating agents compared to that observed after an equimolar dose of melphalan (Chauhan et al. 2013). Mechanistically oriented studies have shown that melflufen-induced apoptosis is associated with (i) activation of caspases and poly ADP ribose polymerase cleavage; (ii) reactive oxygen species generation; (iii) mitochondrial dysfunction and release of cytochrome c; and (iv) induction of DNA damage (Chauhan et al. 2013). Moreover, melflufen inhibits MM cell migration and tumor associated angiogenesis and DNA repair. Importantly, in vitro studies in MM cell lines resistant to dexamethasone, bortezomib and melphalan have shown

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	cytotoxic activities of melflufen at concentrations similar to those observed in the parental, non-resistant cell lines. In efficacy studies conducted in mice and rats carrying different human tumors, including MM, superior antitumor activity of melflufen over equimolar dosage of melphalan was observed at seemingly comparable toxicity (Gullbo et al. 2004, Wickström et al. 2007, Chauhan et al. 2013). Melflufen is currently being evaluated in combination with low dose dexamethasone and as single agent in a Phase 1/2a clinical trial (O-12-M1) in relapsed/refractory MM (RRMM). The Phase 1 part of the clinical trial, completed in September 2014, established the maximum tolerated dose (MTD) at 40 mg of melflufen every 21 days combined with 40 mg dexamethasone weekly (Paba-Prada et al. ASH 2014). The cycle length was later changed to 28 days in a Phase 2 protocol amendment. The dose limiting toxicities consisted of dose-dependent neutropenia and thrombocytopenia manageable with dose delays and appropriate treatment, including dose reductions in subsequent cycles. A preliminary assessment of data from clinical trial O-12-M1 was performed on patients who were evaluable for efficacy by April 25, 2016. Of the 30 efficacy evaluable patients treated with at least 2 doses of 40 mg melflufen in combination with weekly dexamethasone, 19 patients (63%) have reported a best response of minimal response (MR) or better and 12 patients (40%) have reported partial response (PR) or better. These 30 patients had a median of 4 prior lines of therapy, including immunomodulatory drugs (IMiD)s, proteasome inhibitors (PI)s and alkylators. The median progression free survival (PFS) was 4.3 months at the time of data-cut based on 37 events in 40 patients with ≥ 1 cycle. Median number of cycles initiated is 3.5 (range 1 – 14). The safety profile of melflufen suggested by preclinical studies is supported by clinical data from 45 patients with solid tumors and from a total of 57 patients with RRMM in the ongoing Phase 1/2a clinical trial O-12-M1 (40 patients dosed at the MTD of 40 mg of melflufen and 17 patients dosed at other doses in Phase 1 part of the trial). Taken together, clinical and preclinical data support that melflufen provides peptidase potentiated alkylating metabolites to tumor cells such as MM and thereby exerts a higher anti-tumor activity compared with equimolar administration of melphalan but with a similar safety profile. Pomalidomide is indicated for patients with MM who have received at least two prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on or within 60 days of completion of the last therapy. Although the incorporation of novel agents such as PIs and IMiDs, including retreatment, sequential and combination therapy approaches, has significantly improved outcomes in addition to autologous stem-cell transplant (ASCT), for those that are eligible, myeloma is not yet curable and additional treatment options are needed.
Study Design	This is a randomized, controlled, open-label, Phase 3 multicenter study which will enroll patients with RRMM following 2-4 lines of prior therapy (Appendix D) and who are refractory to both the last line of

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	therapy and to lenalidomide (≥10 mg) administered within 18 months prior to randomization as demonstrated by disease progression on or within 60 days of completion of the last dose of lenalidomide. Patients will be randomized to either one of two arms. Arm A is the experimental Arm and Arm B is the control Arm. **Arm A:** Melflufen 40 mg on Day 1 and dexamethasone 40 mg on Days 1, 8, 15 and 22 of each 28-day cycle. **Arm B:** Pomalidomide 4 mg daily on Days 1 to 21 and dexamethasone 40 mg on Days 1, 8, 15 and 22 of each 28-day cycle. Patients ≥ 75 years of age will have a reduced dose of dexamethasone of 20 mg on Days 1, 8, 15 and 22 for both **Arm A** and **Arm B.** Patients may receive treatment until there is documented disease progression, unacceptable toxicity or the patient/treating physician determines it is not in the patient's best interest to continue. Dose modifications and delays in therapy may be implemented based on patient tolerability as detailed in the protocol Section 7.8. In the event of a cycle delay, unrelated to dexamethasone toxicity, it is recommended to continue dexamethasone weekly. A Schedule of Events for the study is outlined in Section 8.1.
Objectives	**Primary Objective*** • To compare the PFS of melflufen plus dexamethasone (**Arm A**) versus pomalidomide plus dexamethasone (**Arm B**) as assessed by the Independent Review Committee (IRC) according to the International Myeloma Working Group Uniform Response Criteria (IMWG-URC) (Rajkumar et al. 2011, Appendix C). **Key Secondary Objectives*** • To assess and compare the overall response rate (ORR), i.e., proportion of patients with ≥ PR (stringent complete response [sCR], complete response [CR], very good partial response [VGPR] and partial response [PR]) as best response in Arm A versus Arm B. • To assess and compare duration of response (DOR) in patients with ≥ PR (sCR, CR, VGPR, PR) as best response in Arm A versus Arm B • To assess and compare overall survival (OS) in Arm A versus Arm B • To assess and compare the safety and tolerability in Arm A and Arm B **Other Secondary Objectives*** • To assess and compare clinical benefit rate (CBR) (i.e., proportion of patients with, ≥ MR) as best response in Arm A versus Arm B • To assess and compare time to response (TTR) in patients with a PR or better in Arm A versus Arm B

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	• To assess and compare time to progression (TTP) in Arm A versus Arm B • To assess and compare the duration of clinical benefit (i.e., ≥ MR) in Arm A versus Arm B. • To assess and compare best response during the study in Arm A versus Arm B. • To assess and compare investigator assessment of primary and secondary endpoints in Arm A versus Arm B. • To assess and compare the primary and secondary endpoints in various subgroups of Arm A and Arm B. • To evaluate the melphalan pharmacokinetic (PK) parameters during treatment with melflufen, the impact of covariates on this relationship and the inter-occasion variability in melphalan exposure (Arm A) * All tumor response and progression-depended objectives are as assessed by the IRC according to the IMWG-URC (Rajkumar et al. 2011, Appendix C) unless otherwise specified. **Exploratory Objective** • To evaluate the relationship between melphalan exposure and effect on safety and efficacy variables (Arm A) • To assess minimal residual disease (MRD) in patients that achieve a CR (Arm A and Arm B).
Endpoints	**Primary Endpoint*** • PFS **Key Secondary endpoints*** • ORR • DOR • OS • Frequency and grade of Adverse Events (AE). **Other Secondary Endpoints*** • CBR • TTR • TTP • Duration of clinical benefit • Best response during the study (sCR, CR, VGPR, PR, MR, stable disease [SD] or PD) • Primary and secondary endpoints as assessed by investigators • PK parameters of melphalan * All tumor response and progression-dependent endpoints are as assessed by the IRC according to the IMWG-URC (Rajkumar et al. 2011, Appendix C) unless otherwise specified. **Exploratory endpoints** • PK parameters of melphalan, safety and efficacy variables specified in key secondary and other secondary endpoints

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	• MRD in patients that achieve a CR
Inclusion Criteria	**Patients will be considered for inclusion in this study if they meet all of the following criteria:** 1. Male or female, age 18 years or older 2. A prior diagnosis of multiple myeloma with documented disease progression requiring further treatment at time of screening 3. Measurable disease defined as any of the following: • Serum monoclonal protein ≥ 0.5 g/dL by protein electrophoresis. • ≥ 200 mg/24 hours of monoclonal protein in the urine on 24-hour electrophoresis • Serum free light chain ≥ 10 mg/dL AND abnormal serum kappa to lambda free light chain ratio 4. Received 2-4 prior lines of therapy (Appendix D), including lenalidomide and a PI, either sequential or in the same line, and is refractory (relapsed and refractory or refractory) to both the last line of therapy and to lenalidomide (≥ 10 mg) administered within 18 months prior to randomization. Refractory to lenalidomide is defined as progression while on lenalidomide therapy or within 60 days of last dose, following at least 2 cycles of lenalidomide with at least 14 doses of lenalidomide per cycle. 5. Life expectancy of ≥ 6 months 6. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2. (Patients with lower performance status based solely on bone pain secondary to multiple myeloma may be eligible following consultation and approval of the medical monitor) (Appendix A) 7. Females of child bearing potential (FCBP)* must have a medically supervised negative serum or urine pregnancy test with a sensitivity according to local Risk Evaluation and Mitigation Strategy™ (REMS) or pomalidomide pregnancy prevention plan (PPP) completed within 10 to 14 days prior to planned start of treatment. All FCBP must agree to either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before she starts taking treatment and as appropriate based on the treatment assignment (See Section 7.7.1). FCBP must also agree to ongoing pregnancy testing. Men must agree to use a condom during sexual contact with a FCBP even if they have had a vasectomy from the time of starting study treatment through 3 months after the last dose of melflufen (Arm A) or 28 days after the last dose of pomalidomide (Arm B). All patients enrolled in Canada and the USA must be willing to comply with all requirements of the Canadian or USA pomalidomide REMS program. All patients enrolled outside of Canada and the USA must be willing to comply with all the requirements of the PPP (Appendix J). (Willingness, to comply with the REMS or PPP, must be documented prior to knowledge of randomization but is only required if randomized to Arm B). 8. Ability to understand the purpose and risks of the study and provide

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	signed and dated informed consent. 9. 12-lead Electrocardiogram (ECG) with QT interval calculated by Fridericia Formula (QTcF) interval of ≤ 470 msec (Appendix H). 10. The following laboratory results must be met during screening and also immediately before study drug administration on Cycle 1 Day 1: • Absolute neutrophil count (ANC) ≥ 1,000 cells/mm^3 (1.0×10^9/L) (Growth factors cannot be used within 10 days prior to first drug administration) • Platelet count ≥ 75,000 cells/mm^3 (75×10^9/L) (without transfusions during the 10 days prior to first drug administration) • Hemoglobin ≥ 8.0 g/dl (red blood cell (RBC) transfusions are permitted) • Total Bilirubin ≤ 1.5 x upper limit of normal (ULN), or patients diagnosed with Gilberts syndrome that have been reviewed and approved by the medical monitor. • Aspartate transaminase (AST/SGOT) and alanine transaminase (ALT/SGPT) ≤ 3.0 x ULN. • Renal function: Estimated creatinine clearance by Cockcroft-Gault formula ≥ 45 mL/min. (Appendix G). 11. Must be able to take antithrombotic prophylaxis (see Section 7.7.1). 12. Must have or be willing to have an acceptable central catheter. (Port a cath, peripherally inserted central catheter [PICC] line, or central venous catheter) (Willingness must be documented prior to randomization but insertion only required if randomized to Arm A). *(FCBP) is any sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally postmenopausal (not having menstrual cycles due to cancer therapy does not rule out childbearing potential) for at least 24 consecutive months.
Exclusion Criteria	**Patients will be ineligible for this study if they meet any one of the following criteria:** 1. Primary refractory disease (i.e. never responded (≥ MR) to any prior therapy) 2. Evidence of mucosal or internal bleeding or platelet transfusion refractory (platelet count fails to increase by > 10,000 after a transfusion of an appropriate dose of platelets) 3. Any medical conditions that, in the Investigator's opinion, would impose excessive risk to the patient or would adversely affect his/her participating in this study. Examples of such conditions are: a significant history of cardiovascular disease (e.g., myocardial infarction, significant conduction system abnormalities, uncontrolled hypertension, ≥ grade 3 thromboembolic event in the last 6 months), 4. Prior exposure to pomalidomide 5. Known intolerance to IMiDs. (≥ Grade 3 hypersensitivity reaction or at the investigators discretion) 6. Known active infection requiring parenteral or oral anti-infective treatment within 14 days of randomization. 7. Other malignancy diagnosed or requiring treatment within the past

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	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. 8. Pregnant or breast-feeding females 9. Serious psychiatric illness, active alcoholism, or drug addiction that may hinder or confuse compliance or follow-up evaluation 10. Known human immunodeficiency virus or active hepatitis C viral infection 11. Active hepatitis B viral infection (defined as HBsAg+). • Patients with prior hepatitis B vaccine are permitted (defined as HBsAg-, Anti-HBs+, Anti-HBc-). • Non-active hepatitis B (HBsAg-, Anti-HBs+, Anti-HBc+) may be enrolled at the discretion of the investigator after consideration of risk of reactivation. 12. Concurrent symptomatic amyloidosis or plasma cell leukemia 13. POEMS syndrome (plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein and skin changes) 14. Previous cytotoxic therapies, including cytotoxic investigational agents, for multiple myeloma within 3 weeks (6 weeks for nitrosoureas) prior to randomization. The use of live vaccines within 30 days before randomization. IMiDs, PIs or corticosteroids within 2 weeks prior to randomization. Other investigational therapies and monoclonal antibodies within 4 weeks of randomization. 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 randomization 15. Residual side effects to previous therapy > grade 1 prior to randomization (Alopecia any grade and/or neuropathy grade 2 without pain are permitted) 16. Prior peripheral stem cell transplant within 12 weeks of randomization 17. Prior allogeneic stem cell transplantation with active graft-versus-host-disease). 18. Prior major surgical procedure or radiation therapy within 4 weeks of the randomization (this does not include limited course of radiation used for management of bone pain within 7 days of randomization). 19. Known intolerance to steroid therapy
Study Treatment(s)	Treatment will be given in an outpatient treatment setting in cycles. Each cycle is 28 days. **Arm A**: Melflufen 40 mg will be administered as a 30-minutes intravenous infusion on Day 1 of every 28-day cycle via acceptable central catheter **Arm B**: Pomalidomide capsules 4 mg administered orally Days 1 to 21 in each 28-day cycle.

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	Arm A and B: Dexamethasone tablets for 40 mg administered orally on Days 1, 8, 15 and 22 of each 28-day cycle for patient < 75 years of age. **OR** Dexamethasone tablets for 20 mg administered orally on Days 1, 8, 15 and 22 of each 28-day cycle for patient ≥ 75 years of age. Oral dexamethasone may be substituted with intravenous dexamethasone at the investigators discretion (USA only). In the event of cycle delays, it is recommended that dexamethasone continue weekly. Dose modifications and delays may be implemented based on patient tolerance as detailed in the protocol.
Duration of treatment	Patients will receive treatment until there is documented disease progression (to be confirmed on two consecutive assessments), unacceptable toxicity or the patient/treating physician determines it is not in the patient's best interest to continue.
Duration of follow-up	Patients who discontinue treatment for reasons other than disease progression will continue to be followed for disease response monthly until progression (PD to be confirmed on two consecutive assessments) or initiation of subsequent therapy. Patients with grade 3 or 4 neutropenia or thrombocytopenia at the end of treatment visit will continue to be followed until resolution (≤ grade 2) or initiation of subsequent therapy. Following PD or initiation of subsequent therapy patients will be followed every three months, for a minimum of 24 months, for overall survival including recordings of first subsequent therapy and secondary malignancies.
Concomitant Drug/Therapy	All blood products and concomitant medications received within 21 days of the initiation of therapy until the end of study visit should be recorded. Refer to Section 7.7 for a complete list of required, recommended and prohibited concomitant medications and therapies. Antibacterial, antifungal and antiviral prophylaxis should be given according to National Comprehensive Cancer Network (NCCN 2016) or institutional guidelines (See Section 7.7.2).
Number of Patients	It is anticipated that a total of 450 patients will be randomized over 24 months in order to reach 339 PFS events 6 months after the enrollment of the last patient.
Disease, safety and PK related assessments	**Screening Disease Assessments** • M-protein determination using the following procedures: – Serum protein electrophoresis (SPEP) and serum protein immunofixation (IFE) with quantitative immunoglobulins; and – Urine protein electrophoresis (UPEP) and urine protein IFE (all using the same 24-hour urine collection) – Serum free light chains (SFLC) and SFLC ratio. • Bone marrow to quantify percent myeloma cell involvement • Extramedullary plasmacytoma evaluation (by physical examination [PE] or imaging technique)

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	• Skeletal survey and/or low dose computerized tomography (CT) scan • Beta2 microglobulin • Cytogenetics/ Fluorescence In Situ Hybridization (FISH) • Lactate dehydrogenase (LDH) • International staging system (ISS) Staging Score and Revised ISS (R-ISS) **Efficacy Assessments** • M-protein determination using the following procedures: – SPEP and IFE with quantitative immunoglobulins (Ig) (quantitative Ig required only for patients with IgA or IgD myeloma); and – UPEP and urine protein immunofixation (all using the same 24-hour urine collection); and – SFLC and SFLC ratio • Bone marrow to quantify percent myeloma cell involvement • Extramedullary plasmacytoma evaluation (by PE or imaging technique) • Skeletal X-rays and/or low dose CT scan (same technique used at screening and each evaluation) • Serum calcium Disease status (assessed by M-protein quantitation, IFE and FLC from serum and 24-hour urine collection for UPEP and IFE) should be assessed at screening and Cycle 1 Day 1. Starting with Cycle 2, M-protein response to treatment should be assessed every cycle. Disease status, including skeletal x-rays and/or low dose CT of bones and imaging of known or suspected extramedullary plasmacytomas should be performed at screening and if indicated according to IMWG-URC (Rajkumar et al. 2011, Appendix C). Bone marrow aspirate should be performed at screening and to confirm suspected CR and MRD in patients who have achieved a negative IFE. Additional skeletal x-rays and/or imaging assessments may be performed if the patient has symptoms suggestive of progression of lesion(s) documented at screening or new lesions. If extramedullary plasmacytomas are present and measurable on physical examination, they should be assessed at every cycle. Extramedullary plasmacytomas documented and measurable only by imaging assessments should be assessed by the same relevant modality to confirm response or progression according to IMWG-URC. **Safety Assessments:** • Assessment and grading of AEs • Physical examinations with vital signs, neurologic assessment and assessment of performance status • Routine safety laboratory tests, (complete blood count (CBC) with differential and platelets; clinical chemistry, coagulation tests) with calculation of creatinine clearance by Cockcroft-Gault formula (Appendix G) • Pregnancy testing • Hepatitis B screening (HBsAg, Anti-HBs, Anti-HBc) • Electrocardiograms

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	• Chest X-ray AEs, including clinical laboratory and vital sign abnormalities, will be graded using the National Cancer Institute (NCI)'s Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (Appendix B). **Pharmacokinetic Assessments** The PK samples will be collected only in patients randomized to melflufen + dexamethasone treatment (Arm A). Three plasma samples for determination of melphalan concentrations will be drawn in connection to the first and second melflufen treatment cycles, 10 – 15 minutes after the end of infusion, 1 hour after the end of infusion and 2 to 4 hours after the end of infusion (as late as possible within the time frame).
Analysis Sets & Statistical methods	**Statistical Methods:** Patients will be randomized with an allocation ratio of 1:1 and randomization will be stratified by: • Age (Patients ≥ 75 years of age versus < 75 years of age) • Number of previous lines of treatment (2 prior lines versus 3-4 prior lines) • ISS Score (1 versus ≥ 2) **Analysis of Primary Endpoint:** The primary statistical analysis of PFS will be performed using a two-sided, 0.05 level stratified Cox proportional hazards regression model based on the Full analysis set, stratified by the stratification factors. **Key Secondary Endpoints:** The overall response rate (ORR) will be estimated as the proportion of subjects in each treatment group who achieve a confirmed sCR, CR, VGPR, or PR as their best response. The treatment groups will be compared using the Cochran Mantel Haenszel chi square test. The approximate 95% confidence interval (CI) for ORR will be calculated for each treatment arm. DOR and OS will be analyzed using the same methods as described for the primary analysis of PFS. No formal statistical analysis will be performed for the safety endpoints. **Definition of Analysis Sets** **Safety Analysis Set** All patients that receive at least one or partial dose of melflufen, pomalidomide or dexamethasone. This is the analysis set used for the safety analyses. Patients will be analyzed by the treatment received. **Full Analysis Set** The Full analysis set is defined as all subjects who are randomized. Subjects will be analyzed according to the treatment assigned at randomization. The primary analysis (PFS) will be performed using the Full analysis set.

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	Per Protocol Analysis Set All patients who receive at least one dose of study drug, have a baseline disease assessment, and have at least one post-baseline disease assessment and have no major protocol deviations. This is the analysis set used for the supportive analysis of the primary endpoint, PFS, and the secondary efficacy endpoints of the study. Patients will be analyzed by the actual treatment received. See Section 11 of the protocol for further details of the statistical analysis.
Sample size	The sample size calculation is based on comparing the melflufen + dexamethasone arm and the pomalidomide + dexamethasone arm in terms of PFS. Assuming a HR of 0.7 (melflufen and dexamethasone versus pomalidomide and dexamethasone), 90 % power and a significance level of 0.05, it is estimated that the final analysis will take place when 339 patients have experienced a PFS event. Based on the assumptions, it is anticipated that a total of 450 patients will be randomized over 24 months in order to reach 339 events, 6 months after the randomization of the last patient.
Study Conduct	The study is open-label and individual investigators will be unblinded to what treatment their individual patients are assigned to. Investigators will not have access to aggregated data. The following procedures are proposed to ensure the appropriate integrity of this open label trial: 1. An Independent Review Committee (IRC) will assess all tumor responses and progressions during the study. The IRC members will be blinded to all treatment data and will perform their reviews in closed-meeting sessions. All activities and processes surrounding the IRC will be outlined in the IRC Charter 2. An independent data monitoring committee (DMC) will perform surveillance of efficacy/safety balance at regular intervals during the study, using unblinded treatment-aggregated data. All activities and processes surrounding the DMC will be outlined in the DMC Charter. • The Clinical Research Organizations (CROs) and the Sponsor will be unblinded to individual patient data during the study but will not have access to the unblinded, aggregate data listings used by the DMC for their review. • The CROs' medical monitors and the Sponsor's safety officer may have access to aggregate safety data and treatment assignment as needed to fulfill the obligation of safety oversight of the study.
ICH and Ethics	This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki. The

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	study protocol will be reviewed and approved by local ethics committees or IRBs and patients will sign Informed Consent Forms before enrolling to the trial.

List of Abbreviations

AE	Adverse Event
ALT	Alanine transaminase/Alanine aminotransferase/glutamic pyruvic transaminase(SGPT)
ANC	Absolute neutrophil count
ASCT	Autologous stem-cell transplantation
AST	Aspartate transaminase/Aspartate aminotransferase/glutamic oxaloacetic transaminase(SGOT)
AUC	Area under the curve
BUN	Blood urea nitrogen
CA	Chromosomal abnormalities
CBC	Complete blood count
CBR	Clinical benefit rate
CI	Confidence interval
CMV	Cytomegalovirus
CRF/eCRF	Case Report Form/electronic Case Report Form
CRO	Contract Research Organization
CR	Complete Response
CT	Computerized tomography
CTCAE	Common terminology criteria for adverse events
DNA	Deoxyribonucleic acid
DOR	Duration of response
DSMC	Data Safety Monitoring Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
FCBP	Female of child bearing potential
FDA	Food and Drug Administration
FISH	Fluorescence In Situ Hybridization
FLC	Free light chain
GCP	Good Clinical Practice
IB	Investigator's brochure
ICH	International Conference of Harmonization
IEC	Independent Ethics Committee
IFE	Immunofixation
Ig	Immunoglobulin
IMiD	Immunomodulatory drug
IMWG	International Myeloma Working Group
IMWG-URC	International Myeloma Working Group Uniform Response Criteria
IND	Investigational new drug
IRC	Independent Review Committee
IRB	Institutional Review Board
ISS	International Staging System
K-M	Kaplan-Meier
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MM	Multiple Myeloma
MR	Minimal response

MRD	Minimal residual disease
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression free survival
PI	Proteasome Inhibitor
PICC	Peripherally inserted central catheter
PK	Pharmacokinetics
p.o.	Per os/by mouth/orally
POEMS	Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein
PPP	Pregnancy Prevention Plan
PR	Partial response
q.d.	Quaque die/ one a day
RBC	Red blood count
REMS	Risk Evaluation and Mitigation Strategy
RRMM	Relapsed Refractory Multiple Myeloma
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
sCR	Stringent complete response
SD	Stable disease
SFLC	Serum free light chain
SmPC	Summary of product characteristics
SOC	System organ class
SPEP	Serum protein electrophoresis
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment emergent adverse event
TTP	Time to Progression
TTR	Time to response
ULN	Upper limit of normal
UPEP	Urine protein electrophoresis
VGPR	Very good partial response

1 BACKGROUND

1.1 OVERVIEW OF MULTIPLE MYELOMA

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

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

There are currently 6 classes of approved drugs available for the treatment of MM, including steroids (prednisone and dexamethasone), immunomodulatory drugs (IMiDs) (thalidomide, lenalidomide and pomalidomide), proteasome inhibitors (PIs) (bortezomib, carfilzomib and ixazomib), histone deacetylase inhibitors (panobinostat), conventional chemotherapy (melphalan, cyclophosphamide, doxorubicin), including high dose melphalan with autologous stem-cell transplantation (ASCT) and the most recent addition of monoclonal antibodies (elotuzumab and daratumumab). The selection of treatment in relapsed/refractory multiple myeloma (RRMM) is challenging. The National Comprehensive Cancer Network (NCCN) guidelines (NCCN 2016) and a recent overview published in the Mayo Clinic Proceedings (Kumar et al. 2016) detail an array of single agent, doublet and triplet combination regimens that can be considered. In many cases, the same agents used as induction therapy may be reinstituted for relapsed disease if the disease recurred more than 6 to 12 months after the last therapy ended. However, if the time to relapse is of shorter duration, the patient is refractory to therapy, or the disease is associated with severe symptoms like renal failure or hypercalcemia, a regimen with different mechanism of action (class switch) is often selected. Patients for whom stem cells were cryopreserved early in the disease course, and who are transplant candidates, may benefit from ASCT as salvage therapy (Cavo et al. 2011). In general, MM patients will receive an average of 4 to 8 different treatment regimens during their lifespan.

Recent improvements in therapies have significantly increased both the expected life span and the quality of life for these patients. However, despite the availability of effective therapies, the optimal combinations and sequencing of these agents with other therapies and with one another is still unclear. Only 20 to 30% of the relapsed-refractory MM patients typically respond to any particular treatment and ultimately patients relapse from all available options. Given the inevitable relapses seen in these patients, new approaches to therapy are clearly still needed.

1.2 OVERVIEW OF MELFLUFEN

1.2.1 Melflufen Description

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

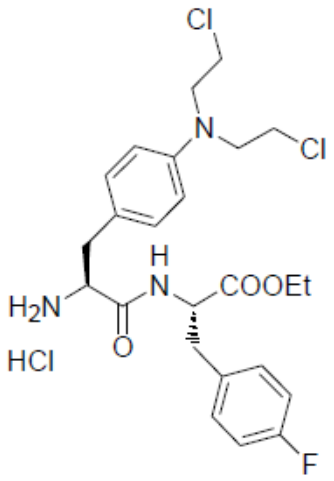

Figure 1-1: Structure of Melflufen

1.2.2 Melflufen Scientific Rational

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

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

considerably higher as discussed above. The metabolite des-ethylmelflufen reaches only very low concentrations in plasma with peak concentrations coinciding with end of melflufen infusion followed by a short elimination half-life.

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

A preliminary assessment of data from clinical trial O-12-M1 was performed on patients who were evaluable for efficacy by April 25, 2016. Of the 30 efficacy evaluable patients with late stage relapsed and relapsed-refractory MM treated with 40 mg melflufen in combination with dexamethasone, 19 patients (63%) have reported a best response of minimal response (MR) or better and 12 patients (40%) have reported partial response (PR) or better. These 30 patients had a median of 4 prior lines of therapy, including IMiDs, PIs and alkylators.

The safety profile of melflufen suggested by preclinical studies is supported by clinical data from 45 patients with solid tumors and from a total of 57 patients with RRMM in the ongoing Phase 1/2a clinical trial O-12-M1 (40 patients dosed at the maximum tolerated dose [MTD] of 40 mg of melflufen and 17 patients dosed at other doses in Phase 1 of the trial). Taken together, clinical and preclinical data support that melflufen provides peptidase-potentiated delivery of alkylating moieties to tumor cells (such as MM cells) and thereby exerts a higher anti-tumor activity compared with equimolar administration of melphalan but with a seemingly similar safety profile. The efficacy seems to be consistent across MM populations including patients who are double-refractory to IMiDs and PIs and refractory to alkylators.

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

1.3 CLINICAL EXPERIENCE

1.3.1 Clinical Experience in RRMM

Melflufen is currently being evaluated in combination with low dose dexamethasone, and as single agent, in a Phase 1/2a clinical trial O-12-M1 in RRMM. Adult patients with documented RRMM with at least 2 prior lines of therapy, including an IMiD and a

Proteasome Inhibitor (PI), and who demonstrated disease progression on or within 60 days of last therapy, Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2, life expectancy of ≥ 6 months and preserved organ function were eligible to enter the study. Phase I followed the standard 3 + 3 modified Fibonacci design with 3 to 6 patients per dose cohort, depending on dose limiting toxicity observed, at each dose level that was tested.

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

1.3.1.1 Clinical Safety

As of April 25, 2016, 40 patients had received 188 doses of melflufen 40 mg. The median number of initiated cycles is 3.5 (range 1 – 14).

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

Treatment related Grade 3 and 4 Adverse Events (AE)s were reported in 34 patients out of 40 patients (85%). Those related to melflufen and occurring in ≥ 5% of the patients are presented in

Table 1-1.

Table 1-1 Summary of Melflufen Treatment Related Grade 3 or 4 AE in ≥ 5% of 40 Patients Dosed with 40 mg Melflufen in Clinical Trial O-12-M1, as presented in Case Report Form (CRF)

System Organ Class (Preferred Term)	Patients with Grade 3 or 4 AEs n (%)	Patients with Grade 4 AEs n (%)
Any treatment-related event	34 (85)	20 (50)
Blood and lymphatic system disorders	33 (83)	20 (50)
Thrombocytopenia	27 (68)	17 (42)
Neutropenia	23 (58)	12 (30)
Anemia	17 (42)	0 (0)
Febrile neutropenia	2 (5)	0 (0)
General disorders and administration site conditions	7 (18)	0 (0)
Asthenia	2 (5)	0 (0)
Fatigue	2 (5)	0 (0)
Pyrexia	2 (5)	0 (0)

Investigations *Neutrophil count decreased* *White blood cell count decreased*	5 (12) 4 (10) 2 (5)	0 (0) 0 (0) 0 (0)
Infections and infestations *Pneumonia*	2 (5) 2 (5)	0 (0) 0 (0)

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

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

A total of 7 cases of pneumonia (2 associated with sepsis) and 2 additional cases of sepsis in various dose cohorts were reported as Serious Adverse Events (SAEs) (5 patients [12%] in the 40 mg cohort) in the 57 patients treated with any dose of melflufen. Four cases resulted in death, both cases of sepsis and 2 cases of pneumonia (1 associated with sepsis and one diagnosed as pneumocystis carinii). Three of the fatal events were in the 40 mg cohort.

Current data from the ongoing study were compared with the pomalidomide + dexamethasone arm in the pomalidomide Phase 3 study (Food and Drug Administration [FDA] US label). As of April 25, 2016, 58% (23 patients) of the 40 mg melflufen (+dexamethasone) treated patients had reported Grade 3 /4 neutropenia, 10% pneumonia, 0% upper respiratory infection and 0% sepsis regardless of relationship to study treatment. Whereas, the Phase 3 pomalidomide + dexamethasone study showed 48% neutropenia, 16% pneumonia, 3% upper respiratory infections and 1% neutropenic sepsis as grade 3/4 events. The Grade 3/4 AE rate with respect to neutropenia, pneumonia, upper respiratory infections and neutropenic sepsis were similar between the two studies.

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

The DSMC therefore recommended:

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

1.3.2 Evaluation of QTcF Intervals from Holter Recordings

Continuous 12-lead Holter recordings from before start of infusion to 120 minutes after start of the 30-minute infusion have been obtained on Day 1 of treatment cycles in a subset

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

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

1.3.3 Safety Summary

The clinical trials results, to date, indicate that the safety profile for melflufen is similar to that for other alkylators, where thrombocytopenia, anemia and neutropenia are the most common AEs, followed by pyrexia and asthenia. The DSMC investigated the 9 infectious SAEs in November 2015. The DSMC recommended that the international NCCN or institutional guidelines for infectious prophylaxis in MM should be followed. The incidences of Grade 3 and 4 neutropenia and thrombocytopenia after 40 mg doses of melflufen are comparable to the incidences observed in studies with low dose melphalan regimens in combination with high dose steroids (Richardson et al. 2010). There have been no reports of syncope, seizures, ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation, flutter, torsade de pointes, or sudden deaths in the clinical trials. The safety profile for melflufen is thus similar to that of other alkylators.

1.4 CLINICAL EFFICACY

As of April 25 2016, 30 patients were evaluable for efficacy (patients receiving at least two doses of 40 mg melflufen with appropriate follow-up). Of these 30 patients, 4 achieved very good partial response (VGPR), 8 achieved PR and 7 achieved MR. Ten patients maintained stable disease (SD) and one had progressive disease (PD). Median time from initial diagnosis to first dose of melflufen was 5.0 years (1-15). Median number of prior therapies was 4 (2-9). All patients but two had been exposed to IMiDs, PIs and alkylators. Of these 30 patients, 25 patients (83%) patients were IMiD-refractory, 20 (67%) were PI-refractory and 15 (50%) were alkylator refractory. Eighteen out of the 30 patients (60%) were double-refractory (IMiDs+PIs) and 9 (30%) were double- and alkylator-refractory. Twenty-four patients (80%) were refractory to last line of treatment.

The median progression free survival (PFS) in the trial has been evaluated both for the protocol defined efficacy evaluable patients, (i.e. treated with ≥ 2 doses of melflufen [n=30]) and all patients (those evaluable after ≥ 1 dose of melflufen [N=40]) with baseline and appropriate follow-up assessments. The median PFS for the efficacy evaluable population was at the time of data cut-off 7.9 months (95% confidence interval 4.1 to 11 months) based on 27 events in 30 patients with available data. Three patients were still alive, had not progressed and were therefore censored at the latest time of tumor assessment. For all treated patients, the median PFS was 4.3 months (95% confidence interval 3.7 to 8.5 months) based on 37 events in 40 patients with available data. These preliminary data suggest that the responses could be of considerable duration and that also the MR and SD patients may have a benefit of considerable duration until progression.

1.4.1 Clinical Pharmacokinetics

In humans, melflufen is metabolized to des-ethyl-melflufen, melphalan and the non-alkylating para-fluoro-phenylalanin ethyl ester. PK data for melflufen and melphalan are available from the completed clinical trial O-05-001 in patients with solid tumors and from six MM patients in the ongoing clinical trial O-12-M1. The elimination phase for melflufen could not be followed in clinical trial O-05-001 since the plasma concentrations were generally below the limit of quantitation during this phase. Subsequent improvements of the bioanalytical method and sampling schedule have allowed estimation of the melflufen elimination phase in clinical trial O-12-M1. Further, the metabolite des-ethyl-melflufen is quantified in clinical trial O-12-M1, while it was not measured in clinical trial O-05-001.

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

In the ongoing clinical trial O-12-M1 in MM patients, PK data from eight patients covering the dose range 15 mg to 55 mg were available as of 10 February 2015. Preliminary analysis showed that the melflufen plasma concentration reached a peak before end of infusion and is thereafter eliminated with a half-life of 3 to 5 minutes. Melphalan PK parameters were similar to those observed in clinical trial O-05-001. Des-ethyl-melflufen reached only very low concentrations in plasma and is eliminated with a half-life of approximately 15 minutes.

The combined results from the two clinical trials demonstrate that the PK of melflufen is characterized by low plasma concentrations and a very rapid disappearance from plasma after end of the intravenous infusion. The reasons for the decrease in melflufen concentrations during the ongoing infusion, frequently observed in both studies, are not known. The PK of melphalan after administration of melflufen is characterized by a rapid formation, where plasma concentrations exceed those of melflufen within 15 minutes after start of melflufen infusion, but where peak plasma concentrations are lower and AUC similar compared with equimolar infusions of melphalan at a similar rate (Mougenot et al. 2004, Nath et al. 2010). Peak plasma concentrations of melphalan appear with a delay by up to 10 minutes after the end of melflufen infusion. The elimination phase of melphalan is similar after melflufen and melphalan infusions, according to published data for melphalan administration (Mougenot et al. 2004, Nath et al. 2010).

Overall, the observations suggest a mechanism where melflufen is rapidly and widely distributed to tissues or blood components outside of the plasma compartment in which melphalan is predominantly formed. Melphalan is thereafter distributed back to the plasma.

1.5 OVERVIEW OF POMALIDOMIDE

Pomalidomide, an analogue of thalidomide, is an IMiD with antineoplastic activity. In in vitro cellular assays, pomalidomide inhibited proliferation and induced apoptosis of hematopoietic tumor cells. Additionally, pomalidomide inhibited the proliferation of

lenalidomide-resistant MM cell lines and synergized with dexamethasone in both lenalidomide-sensitive and lenalidomide-resistant cell lines to induce tumor cell apoptosis. Pomalidomide enhanced T cell- and natural killer (NK) cell-mediated immunity and inhibited production of pro-inflammatory cytokines (e.g., TNF-α and IL-6) by monocytes (Quach et al, 2009).

Pomalidomide is indicated for patients with MM who have received at least two prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on or within 60 days of completion of the last therapy.

The approval of pomalidomide was based on a phase 3 multi-center, randomized, open-label trial (MM-003) that compared pomalidomide + low-dose dexamethasone to high-dose dexamethasone in adult patients with RRMM (FDA Pomalyst prescribing information 2015, San Miguel et al. 2013). The trial enrolled patients who had received at least two prior treatment regimens, including lenalidomide and bortezomib, and demonstrated disease progression on or within 60 days of the last therapy. A total of 455 patients were enrolled in the trial: 302 in the pomalidomide + low-dose dexamethasone arm and 153 in the high-dose dexamethasone arm.

The trial demonstrated that treatment with pomalidomide in combination with low-dose dexamethasone was superior to high-dose dexamethasone in patients with primary refractory MM and RRMM. A statistically significant difference in favor of the experimental treatment was shown for the primary analysis of PFS based on IRAC assessed data (median 3.6 months versus 1.8 months, with a median follow-up of 4.2 months). The HR was 0.45 (95% CI: 0.35-0.59 $p < 0.001$) (FDA Pomalyst prescribing information 2015). The median PFS was subsequently reported to be 4.0 months versus. 1.9 months at a median of 10 months' follow-up, based on investigator assessed data (San Miguel et al. 2013). The ORR 23.5% of the pomalidomide + low-dose dexamethasone arm was higher than the 3.9% in the high-dose dexamethasone arm. In addition, median OS was significantly longer with pomalidomide + low-dose dexamethasone than high-dose dexamethasone: HR 0.70 (95% CI: 0.54-0.92 $p = 0.009$) (FDA Pomalyst prescribing information 2015).

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

2 RATIONALE

2.1 RATIONALE FOR THE SELECTED PATIENT POPULATION

The proposed pivotal trial will be conducted in MM patients who have received 2 to 4 prior lines of therapy, including lenalidomide and a PI, and who are refractory to both last line of therapy and to lenalidomide (≥ 10 mg) administered within 18 months prior to randomization (refractory defined as progression on or within 60 days of last dose, following at least 2 cycles of lenalidomide with at least 14 doses of lenalidomide per cycle). In this population, there are few remaining treatment alternatives. This population is within the approved pomalidomide indication (at least 2 prior therapies including lenalidomide and a PI and have demonstrated disease progression on or within 60 days of completion of the last therapy).

Important trial design features like pomalidomide plus dexamethasone treatment regimen (dose, schedule, treatment duration and dose reduction guidelines), patient visit frequency,

tumor evaluations and other features have been developed to resemble those in the pomalidomide Phase 3 trial (MM-003). Further, the inclusion/exclusion criteria have been developed in order to create an as comparable patient population as possible. In common with the pomalidomide indication, all patients should have received at least 2 prior lines of therapy. A maximum number of 4 prior lines have been specified in order to limit the number of end-stage patients in the trial since these patients may have limited bone-marrow reserves and therefore, could benefit more from patient-tailored treatment regimens. As in the pomalidomide label, patients should be refractory to last line of therapy but in the melflufen pivotal trial lenalidomide refractoriness is required in order to reflect the widespread use of this drug. It is anticipated that these patients may have an improved clinical benefit of melflufen plus dexamethasone treatment in comparison to pomalidomide plus dexamethasone.

Patients who have previously been exposed to pomalidomide will be excluded.

2.2 RATIONALE FOR DOSE SELECTION

Patients will be randomized to either one of two arms. Patients in **Arm A** (experimental arm) will be treated with melflufen 40 mg on Day 1 and dexamethasone 40 mg on Days 1, 8, 15 and 22 of each 28-day cycle. Patients in **Arm B** (control arm) will receive pomalidomide 4 mg daily on Days 1 to 21 and dexamethasone 40 mg on Days 1, 8, 15 and 22 of each 28-day cycle. The starting dexamethasone dose is planned to be reduced to 20 mg/day in all patients ≥ 75 years of age in line with the pomalidomide Phase 3 study (San Miguel et al. 2013).

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

The dose and schedule of pomalidomide in combination with dexamethasone are based on the FDA Pomalyst prescribing information (2015), where the recommended starting dose of pomalidomide is 4 mg once daily orally on Days 1 to 21 of repeated 28-day cycles until disease progression. Dose and schedule may be adjusted based on tolerability.

3 OBJECTIVES AND ENDPOINTS

3.1 PRIMARY OBJECTIVES

- To compare the PFS of melflufen plus dexamethasone (**Arm A**) versus pomalidomide plus dexamethasone (**Arm B**) as assessed by the Independent Review Committee (IRC) according to the International Myeloma Working Group Uniform Response Criteria (IMWG-URC) (Rajkumar et al. 2011, Appendix C).

3.2 SECONDARY OBJECTIVES

3.2.1 Key Secondary Objectives*

- To assess and compare the overall response rate (ORR), i.e., proportion of patients with ≥ PR (stringent complete response [sCR], complete response [CR], very good partial response [VGPR] and partial response [PR]) as best response in Arm A versus Arm B
- To assess and compare duration of response (DOR) in patients with ≥ PR (sCR, CR, VGPR, PR) as best response in Arm A versus Arm B
- To assess and compare overall survival (OS) in Arm A versus Arm B
- To assess and compare the safety and tolerability in Arm A and Arm B

3.2.2 Other Secondary Objectives*

- To assess and compare clinical benefit rate (CBR) (i.e. proportion of patients with ≥ MR) as best response in Arm A versus Arm B
- To assess and compare time to response (TTR) in patients with an PR or better in Arm A versus Arm B
- To assess and compare time to progression (TTP) in Arm A versus Arm B
- To assess and compare the duration of clinical benefit (i.e., ≥ MR) in Arm A versus Arm B
- To assess and compare best response during the study in Arm A versus Arm B.
- To assess and compare investigator assessment of primary and secondary endpoints in Arm A versus Arm B
- To assess and compare the primary and secondary endpoints in various subgroups of Arm A and Arm B
- To evaluate the melphalan pharmacokinetic (PK) parameters during treatment with melflufen, the impact of covariates on this relationship and the inter-occasion variability in melphalan exposure (Arm A)

* All tumor response and progression-dependent objectives are as assessed by the Independent Review Committee (IRC) according to the IMWG-URC (Rajkumar et al. 2011, Appendix C) unless otherwise specified.

3.3 EXPLORATIVE OBJECTIVES

- To assess the relationship between melphalan exposure and effect on safety and efficacy variables, including PFS and ORR, in **Arm A**
- To assess minimal residual disease (MRD) in patients that achieve a CR (Arm A and Arm B).

4 STUDY DESIGN

4.1 DESCRIPTION OF STUDY DESIGN

This is a randomized, controlled, open-label, Phase 3 multicenter study which will enroll patients with RRMM following 2-4 lines of prior therapy (Appendix D), who are refractory to both last line of therapy and to lenalidomide (≥ 10 mg) administered within 18 months prior to randomization as demonstrated by disease progression on or within 60 days of completion of the last dose of lenalidomide.

Patients will be randomized to either one of two arms.

Arm A:

Melflufen 40 mg on Day 1 and dexamethasone 40 mg on Days 1, 8, 15 and 22 of each 28-day cycle.

Arm B:

Pomalidomide 4 mg daily on Days 1 to 21 and dexamethasone 40 mg on Days 1, 8, 15 and 22 of each 28-day cycle.

Arm A and Arm B

Patients ≥ 75 years of age will have a reduced dose of dexamethasone of 20 mg on Days 1, 8, 15 and 22.

Oral dexamethasone may be substituted with intravenous dexamethasone at the investigators discretion (USA only). In the event of a cycle delay, unrelated to dexamethasone toxicity, it is recommended to continue dexamethasone weekly.

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

Dose modifications and delays in therapy may be implemented based on patient tolerability as detailed in the protocol (See Section 7.8).

A Schedule of Events for the study is outlined in Section 8.1.

5 PATIENT POPULATION

5.1 PATIENT SCREENING

Written informed consent must be obtained before any protocol-specific screening tests or procedures are performed. Patients must meet all the entry criteria detailed in Section 5.3 and Section 5.4. After informed consent is obtained, the screening assessments will be performed as detailed in Section 8 of the protocol. Table 8-1, Schedule of Event, lists all of the screening assessments including frequency and time lines of when assessments are to be performed.

Assessments performed as part of the patient's routine clinical evaluation and not specifically for this study need not be repeated after signed informed consent has been obtained provided the assessments fulfill the study requirements and are performed within the specified timeframe prior to enrollment. Laboratory results noted in the inclusion criteria must remain within the limits specified prior to first dose of study drug on Cycle 1 Day 1.

5.1.1 Screening Failures

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

5.2 PATIENT ELIGIBILITY

The Investigator must ensure that patients meet all the following inclusion and exclusion criteria. Confirmation of patient eligibility by the medical monitor is required prior to randomization.

5.3 INCLUSION CRITERIA

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

1. Male or female, age 18 years or older
2. A prior diagnosis of multiple myeloma with documented disease progression in need of treatment at time of screening.
3. Measurable disease defined as any of the following:
   - Serum monoclonal protein ≥ 0.5 g/dL by serum protein electrophoresis (SPEP)
   - ≥ 200 mg/24 hours of monoclonal protein in the urine on 24-hour urine electrophoresis (UPEP)
   - Serum free light chain (SFLC) ≥ 10 mg/dL AND abnormal serum kappa to lambda free light chain ratio
4. Received 2-4 prior lines of therapy (Appendix D), including lenalidomide and a proteasome inhibitor (PI), either sequential or in the same line, and is refractory (relapsed and refractory or refractory) to both the last line of therapy and to lenalidomide ($\geq$ 10 mg) administered within 18 months prior to randomization. Refractory to lenalidomide includes patients who relapsed while on lenalidomide therapy or within 60 days of last dose following at least 2 cycles of lenalidomide with at least 14 doses of lenalidomide per cycle.
5. Life expectancy of ≥ 6 months
6. ECOG performance status ≤ 2. (Patients with lower performance status based solely on bone pain secondary to multiple myeloma may be eligible following consultation and approval of the medical monitor) (Appendix A)
7. Females of child bearing potential (FCBP)* must have a medically supervised negative serum or urine pregnancy test with a sensitivity according to local Risk Evaluation and Mitigation Strategy™ (REMS) or pomalidomide pregnancy prevention plan (PPP) completed within 10 to 14 days prior to planned start of treatment. All FCBP must agree to either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before she starts taking treatment and as appropriate based on the treatment assignment (See Section 7.7.1). FCBP must also agree to ongoing pregnancy testing. Men must agree to use a condom during sexual contact with a FCBP even if they have had a vasectomy from the time of starting study treatment through 3 months after the last dose of melflufen (Arm A) or 28 days after the last dose of pomalidomide (Arm B). All patients enrolled in Canada and the USA must be willing to comply with all requirements of the Canadian or

USA pomalidomide REMS. All patients enrolled outside of Canada and the USA must be willing to comply with all requirements of the PPP (Appendix J). (Willingness, to comply with the REMS or PPP, must be documented prior to knowledge of randomization but is only required if randomized to Arm B).

8. Ability to understand the purpose and risks of the study and provide signed and dated informed consent.
9. 12-lead Electrocardiogram (ECG) with QT interval calculated by Fridericia Formula (QTcF) interval of ≤ 470 msec (Appendix H).
10. The following laboratory results must be met during screening (within 21 days) and also immediately before study drug administration on Cycle 1 Day 1:
    - Absolute neutrophil count (ANC) ≥ 1,000 cells/mm^3 (1.0 x 10^9/L) (Growth factors cannot be used within 10 days prior to first drug administration)
    - Platelet count ≥ 75,000 cells/mm^3 (75 x 10^9/L) (without required transfusions during the 10 days prior to first drug administration)
    - Hemoglobin ≥ 8.0 g/dl (red blood cell (RBC) transfusions are permitted)
    - Total Bilirubin ≤ 1.5 x upper limit of normal (ULN), or patients diagnosed with Gilberts syndrome, that have been reviewed and approved by the medical monitor.
    - Aspartate transaminase (AST/SGOT) and alanine transaminase (ALT/SGPT) ≤ 3.0 x ULN.
    - Renal function: Estimated creatinine clearance by Cockcroft-Gault formula ≥ 45 mL/min. (Appendix G).
11. Must be able to take antithrombotic prophylaxis (See Section 7.7.1).
12. Must have, or be willing to have an acceptable central catheter. (Port a cath, peripherally inserted central catheter [PICC] line, or central venous catheter) (Willingness must be documented prior to randomization but insertion only required if randomized to Arm A).

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

5.4 EXCLUSION CRITERIA

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

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

(e.g., myocardial infarction, significant conduction system abnormalities, uncontrolled hypertension, ≥ grade 3 thromboembolic event in the last 6 months)

4. Prior exposure to pomalidomide
5. Known intolerance to IMiDs. (≥ Grade 3 hypersensitivity reaction or at the investigators discretion)
6. Known active infection requiring parenteral or oral anti-infective treatment within 14 days of randomization
7. 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
8. Pregnant or breast-feeding females
9. Serious psychiatric illness, active alcoholism, or drug addiction that may hinder or confuse compliance or follow-up evaluation
10. Known human immunodeficiency virus or active hepatitis C viral infection.
11. Active hepatitis B viral infection (defined as HBsAg+) are excluded.
    - Patients with prior hepatitis B vaccine are permitted (defined as HBsAg-, Anti-HBs+, Anti-HBc-).
    - Non-active hepatitis B (HBsAg-, Anti-HBs+, Anti-HBc+) may be enrolled at the discretion of the investigator after consideration of risk of reactivation.
12. Concurrent symptomatic amyloidosis or plasma cell leukemia
13. POEMS syndrome [plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein (M-protein) and skin changes]
14. Previous cytotoxic therapies, including cytotoxic investigational agents, for multiple myeloma within 3 weeks (6 weeks for nitrosoureas) prior to randomization. The use of live vaccines within 30 days before randomization. IMiDs, PIs or corticosteroids within 2 weeks prior to randomization. Other investigational therapies and monoclonal antibodies within 4 weeks of randomization. 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 randomization.
15. Residual side effects to previous therapy > grade 1 prior to randomization (Alopecia any grade and/or neuropathy grade 2 without pain are permitted)
16. Prior peripheral stem cell transplant within 12 weeks of randomization
17. Prior allogeneic stem cell transplantation with active graft-versus-host- disease.
18. Prior major surgical procedure or radiation therapy within 4 weeks of randomization (this does not include limited course of radiation used for management of bone pain within 7 days of randomization).
19. Known intolerance to steroid therapy

Population diversity: This study will be available to all eligible patients, regardless of race, gender, or ethnic origin. There is no information currently available regarding differential effects of these regimens in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. The planned analysis will explore differences in treatment effect based on racial and gender groupings, but the sample size is not increased in order to provide additional power for such subset analyses. Investigators are encouraged to recruit a diverse population.

6 PATIENT ENROLLMENT

6.1 ENROLLMENT PROCEDURE

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

Complete details on patient enrollment procedures are provided in the Investigator Site File (ISF) at each site.

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

6.2 PATIENT NUMBERING

A unique patient number will be assigned at the time of enrollment (signing of consent) by Interactive Response Technology (IRT) system that will be used to identify the patient throughout the clinical study and must be used on all study documentation related to that patient.

6.3 RANDOMIZATION

The recruitment will be stratified based on age ($\geq$ 75 years versus < 75 years), number of previous lines (2 previous lines versus 3 to 4 previous lines) and International Staging System (ISS) score (1 versus $\geq$ 2).

Patient randomization will be managed by the IRT system. Details for interacting with this system can be found in the ISF. Treatment cannot begin prior to randomization and must begin $\leq$ 5 days after randomization. However, pretreatment tests/procedures must remain within the screening timelines specified in Table 8-1: Schedule of Events. Confirmation of patient eligibility by the medical monitor is required prior to randomization.

6.4 REPLACEMENT POLICY

Randomized patients will not be replaced.

7 TREATMENT

7.1 STUDY TREATMENT

Patients must begin treatment $\leq$ 5 days of randomization. However, pretreatment tests/procedures must remain within the screening timelines specified in Table 8-1 Schedule of Events. Treatment will be given in an outpatient treatment setting in cycles. Each cycle is 28 days. Patients will be randomized to one of 2 treatment arms:

Arm A:

- Melflufen 40 mg will be administered as a 30-minutes intravenous infusion on Day 1 of every 28 days via central catheter.
- Dexamethasone tablets for 40 mg administered orally on Days 1, 8, 15 and 22 of each 28-day cycle for patient < 75 years of age. OR
- Dexamethasone tablets for 20 mg administered orally on Days 1, 8, 15 and 22 of each 28-day cycle for patient ≥ 75 years of age.

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

Oral dexamethasone may be substituted with i.v. dexamethasone at the investigators discretion (USA only).

Dose modifications and delays may be implemented based on patient tolerance as detailed in Section 7.8. In the event of a cycle delay, unrelated to dexamethasone toxicity, it is recommended to continue dexamethasone weekly.

Arm B:

- Pomalidomide capsules 4 mg will be administered orally on Days 1 to 21 in each 28-day cycle.
- Dexamethasone tablets for 40 mg administered orally on Days 1, 8, 15 and 22 of each 28-day cycle for patient < 75 years of age. OR
- Dexamethasone tablets for 20 mg administered orally on Days 1, 8, 15 and 22 of each 28-day cycle for patient ≥ 75 years of age.

Oral dexamethasone may be substituted with i.v. dexamethasone at the investigators discretion (USA only).

All patients randomized to pomalidomide must agree to comply with all requirements of the pomalidomide REMS™ program or the pomalidomide PPP (See Appendix J), consistent with their geographic region of enrollment.

Dose modifications and delays may be implemented based on patient tolerance as detailed in Section 7.8. In the event of a cycle delay, unrelated to dexamethasone toxicity, it is recommended to continue dexamethasone weekly.

7.2 INITIATION OF THERAPY

Arm A and Arm B

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

- ANC ≥ 1,000 cells/ mm^3 (1.0 x 10^9/L) (Growth factors cannot be used within 10 days of initiation of therapy);
- Platelet count ≥ 75,000 cells/ mm^3 (75 x 10^9/L) (without transfusion during the previous 10 days to initiation of therapy).
- Hemoglobin ≥ 8.0 g/dl (RBC transfusions are permitted)

- Total Bilirubin ≤ 1.5 x upper limit of normal, except patients diagnosed with Gilberts syndrome that have been reviewed and approved by the medical monitor.
- AST (SGOT) and ALT (SGPT) ≤ 3.0 x ULN
- Renal function: Estimated creatinine clearance by Cockcroft-Gault formula ≥ 45 mL/min. (Appendix G).

7.3 MELFLUFEN

7.3.1 Melflufen Packaging and Labeling

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

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

7.3.2 Melflufen Storage

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

7.3.3 Preparation of Melflufen Solution for Infusion

Melflufen powder for solution for infusion is prepared by reconstitution with 5% glucose solution and then further diluted with 5% glucose solution in an infusion bag. Careful attention and documentation of the preparation procedures and time frames are required since melflufen rapidly degrades in solutions. The maximum allowed time from start of reconstitution until the start of iv infusion is 30 minutes, but this can be extended to a maximum of 45 minutes if the infusion bag with glucose solution is refrigerated prior to melflufen preparation according to guidelines defined in the pharmacy manual. A well-coordinated plan between the pharmacy and treatment room is recommended. (See Pharmacy Manual for details).

7.3.4 Melflufen Administration (Arm A)

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

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

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

- Document vital signs prior to start of infusion.
- The melflufen should be administered as a 30-minute intravenous infusion.
- Document vital signs at the end of the infusion.

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

7.4 DEXAMETHASONE

7.4.1 Dexamethasone Packaging and Labeling

Oral dexamethasone will be supplied by Oncopeptides AB to sites located outside the USA and Canada. Oral dexamethasone may be substituted with i.v. dexamethasone at the investigators discretion (USA only). Only oral dexamethasone will be supplied to sites outside of USA and Canada. USA and Canada sites will use commercially available dexamethasone supplies.

7.4.2 Dexamethasone Storage

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

7.4.3 Dexamethasone Administration (Arm A and Arm B)

Dexamethasone should be administered orally. Oral dexamethasone may be substituted with i.v. dexamethasone at the investigators discretion (USA only). Patients should be instructed to document oral dexamethasone administration on a patient diary and return unused tablets and packaging for review of compliance at the end of each cycle. Sites are responsible to maintain the diary as source documentation and record administration and patient compliance regarding dexamethasone dosing in the eCRF. Consult the package insert for additional instructions for dexamethasone administration. Dexamethasone is best taken prior to melflufen **(Arm A)** on days when both drugs are given on the same day (Day 1 of each cycle).

7.5 POMALIDOMIDE

7.5.1 Pomalidomide Supply USA and Canada Sites

Commercial supplies of pomalidomide should be used for patients enrolling at sites in the USA and Canada.

Pomalidomide should be provided in accordance with the Celgene Corporation's pomalidomide REMS™ programs. Per the standard REMS™ programs requirements, all physicians who prescribe pomalidomide for research subjects enrolled into this trial, and all research subjects enrolled into this trial, must be registered in and must comply with all requirements of the USA or Canada pomalidomide REMS™ programs.

Pomalidomide is available only from pharmacies that are certified in the pomalidomide REMS™ program. Only enough pomalidomide for one cycle of therapy will be supplied

to the patient each cycle. This is in accordance with the pomalidomide REMS™ programs.

7.5.2 Pomalidomide Supply for non-USA/Canada Sites

Pomalidomide will be supplied by Oncopeptides to sites other than USA and Canada. Please refer to the Pharmacy Manual for complete details on drug supply and ordering procedures. Only enough pomalidomide for one cycle of therapy will be supplied to the patient at the time. Patients will be required to follow the pomalidomide PPP (See Appendix J).

7.5.3 Special Handling Instructions

Female caregivers of childbearing potential should not handle or administer pomalidomide unless they are wearing gloves.

7.5.4 Pomalidomide Administration (Arm B only)

Pomalidomide is available in capsules of 1 mg, 2 mg, 3 mg and 4 mg for oral administration. Pomalidomide 4 mg is planned to be taken orally from Day 1 to Day 21 of each 28-day cycle. Pomalidomide may be taken with water and should be swallowed whole. Patients are not permitted to break, chew or open the capsules. Pomalidomide can be taken with or without food preferably at the same time every day.

If a dose of pomalidomide is missed, it should be taken as soon as possible on the same day. If it is missed for more than12 hours, it should not be taken, rather the patient should wait for the next scheduled time point.

Patients who take more than the prescribed dose of pomalidomide should be instructed to seek emergency medical care if needed and contact study staff immediately.

Patients should be instructed to document oral pomalidomide administration on a patient diary and return unused capsules and packaging for review of compliance at the end of each cycle. Sites are responsible to maintain the diary as source documentation and record administration and patient compliance regarding pomalidomide dosing in the eCRF.

7.6 STUDY DRUG COMPLIANCE AND ACCOUNTABILITY

7.6.1 Study Drug Compliance

Compliance will be assured by administration of the study treatment **(Arm A)** under the supervision of the investigator or his/her designee, and should be documented in the study drug administration and accountability records. In addition, a patient diary should be used to document administration of pomalidomide **(Arm B)** and oral dexamethasone **(Arm A** and **Arm B**). Patients should be instructed to return unused capsules and drug packaging for review of compliance at the end of each cycle.

7.6.2 Study Drug Accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Drug accountability will be 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 dexamethasone, melflufen, pomalidomide packaging and drug labels should be discarded

according to the site drug destruction policy following review and approval of the site CRO monitor. A copy of the drug destruction policy and the completed drug accountability log should be provided to the CRO monitor.

7.7 CONCOMITANT THERAPY

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

7.7.1 Required Concomitant Therapy

- **Anti-thrombotic therapy (Arm B)**

Pomalidomide increases the risk of thromboembolism. Anti-coagulation prophylaxis is required after an assessment of each patient's underlying risk factors. Unless there is an excess risk of bleeding, all patients should receive prophylactic anti-thrombotic treatment, unless contraindicated. The use of aspirin is an acceptable anti-thrombotic therapy. If aspirin is contraindicated, patients should receive another form of anti-thrombotic therapy according to hospital guidelines or physician preference.

- **Contraceptive measures**

Arm A

Males and females of child-bearing potential shall be required to use 2 effective contraceptive methods (or true abstinence) prior to randomization. If randomized to Arm A, at least one method of effective contraceptive (or true abstinence) must continue prior to initiation of melflufen, while on therapy and for 3 months for men or 28 days for women, after the last dose of melflufen. The best method should be determined in consultation with the Investigator.

True abstinence definition: When this is in line with the preferred and usual life-style of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Declaration of abstinence must be for the duration of the trial as defined above.

Females:

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

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

Males:

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

Arm B

Males and females of child bearing potential shall be required to use 2 effective contraceptive methods (or abstinence) according to the USA or Canada pomalidomide REMS™ programs if enrolled in USA or Canada or the pomalidomide PPP for all patients enrolled outside the USA or Canada. The best method should be in compliance with the REMS™ /PPP program and be determined in consultation with the Investigator.

See Appendix J for details on the PPP for all patients enrolled outside the USA or Canada.

7.7.2 Recommended Concomitant Therapy

- Pneumocystis prophylaxis (Arm A and B)
  - All patients are recommended to receive pneumocystis prophylaxis concomitant treatment according to the National Comprehensive Cancer Network (NCCN) or institutional guidelines:
  - http://www.nccn.org/professionals/physician_gls/pdf/infections.pdf
  - Trimethoprim/sulfamethoxazole – Prophylaxis: single or double strength daily or double strength 3 x per week. May require adjustment for renal insufficiency.
  - Patients who are found to be intolerant of pneumocystis prophylaxis while on study may continue on study at the discretion of the investigator
- Arm A: Prophylactic treatment with anti-emetic(s) prior to melflufen administration is recommended. Subsequent anti-emetic drugs against emesis should be administered at the discretion of the investigator.
- Patients should receive full supportive care, including transfusions of blood and blood products (including platelets), antibiotics, anti-diarrheals, analgesics, etc. and prophylactic treatment for tumor lysis syndrome when appropriate.
- Bisphosphonate therapy i.v. or p.o. should be administered if indicated in accordance with institutional guidelines.
- The prophylactic use of growth factors and platelet transfusions are not permitted to render the patient eligible for trial participation except as described within the entry criteria.
- Thrombocytopenia and neutropenia are known consequences of MM but also the most common expected adverse event (AE)s associated with melflufen and pomalidomide treatment. Careful attention is to be paid to the monitoring of blood counts. General supportive measures, together with appropriate blood and platelet transfusions and hematological growth factors should be instituted if necessary. It is recommended, at the investigator discretion, that platelet transfusion should be avoided within $\leq$ 5 days of the next dose in order to assess endogenous platelet recovery and avoid the possibility of excessive myelosuppression (refer to Section 7.8.2.2). (Excluding Cycle 1, Day 1 which adheres to the guidelines in Section 7.2 for use of growth factors and platelet transfusions prior to the first dose of therapy).

- Recommended Antimicrobial prophylaxis
  - For patients with history of cytomegalovirus (CMV) infection that required treatment, prophylactic treatment per NCCN or institutional guidelines is recommended. http://www.nccn.org/professionals/physician_gls/pdf/infections.pdf or NCCN.org
  - Patients with neutropenia are strongly recommended to receive antimicrobial prophylaxis throughout the treatment period per NCCN or institutional guidelines. http://www.nccn.org/professionals/physician_gls/pdf/infections.pdf or NCCN.org
  - Antiviral and antifungal prophylaxis should be considered.
- Antiviral and antifungal prophylaxis should be considered. Additional considerations Arm B: Reactivation of hepatitis B has been reported rarely in patients receiving pomalidomide in combination with dexamethasone who have previously been infected with the hepatitis B virus (HBV). Caution should be exercised when pomalidomide in combination with dexamethasone is used in patients previously infected with HBV, including patients who are anti-HBc positive but HBsAg negative. Investigators should consider closely monitoring for signs and symptoms of active HBV infection throughout therapy.
- Renal failure has been reported in patients receiving a single high dose of iv melphalan 140-250 mg/m^2 followed by common doses of cyclosporine for the prevention of graft-versus-host-disease after organ transplant. It is recommended to monitor renal function in patients receiving cyclosporine and melflufen concomitantly.

7.7.3 Contraindicated Concomitant Therapy

- Concurrent therapy with any approved or investigative anticancer therapeutic drug with activity against MM, including alpha interferon, 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 and approval of the medical monitor.
- The use of live vaccines is prohibited during the study and for 30 days after last dose of study drug.
- Avoid co-administration of strong inhibitors of CYP1A2 in combination with pomalidomide. (e.g. ciprofloxacin, enoxacin, fluvoxamine)
- Limitations on the use of growth factors and platelet transfusions prior to Cycle 1 Day 1 are detailed in Section 7.2 and 7.7.2.
- Because of the increased risk of venous thromboembolism in patients with MM taking pomalidomide and dexamethasone, combined oral contraceptive pills, although not contraindicated, are not recommended.

- Although erythropoietic agents or other agents that may increase the risk of thromboembolic events are not contraindicated, they should be used with caution.

7.8 DOSE MODIFICATIONS

Dose adjustments are permitted according to guidelines described in this section. Toxicity should be assessed using the common terminology criteria for adverse events (CTCAE) version 4.03 (Appendix B). All dose modifications should be based on the worst preceding toxicity. Dose modifications different from those stated in the protocol should only be made in consultation with the medical monitor or Sponsor; unless required for immediate patient safety.

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

7.8.1 Dose Modification Guidelines for Melflufen (Arm A)

Dose modifications of melflufen for drug related toxicity are permitted. Multiple dose reductions are permitted however, the lowest dose permitted is 20 mg. If a patient is unable to tolerate the lowest dose of melflufen due to drug related toxicity the patient must be withdrawn from treatment. Prior to each cycle of melflufen the criteria for initiation of therapy must be met. (See Section 7.8.1.4).

7.8.1.1 Dose Reduction Steps for Melflufen

Table 7-1 Dose Reduction Steps for Melflufen

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

7.8.1.2 Hematologic Toxicity (Arm A)

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

Please note: The guidelines in Table 7-2 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 7-2 Melflufen Hematologic Toxicity Dose Adjustment Guidelines:

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 • Optional to hold one week (to Day 43)	Hold dose. Evaluate in one week (to Day 43)
Day 43	Continue at same dose level* Investigator discretion: (consultation with medical monitor is encouraged) • Optional one level dose reduction • Optional to hold one week (to Day 50) NOTE: The cycle length may not exceed 43 days if criteria are met on Day 29 or 36	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 modification (prolongations/reductions, such as directly to 20 mg) may be considered in discussion with the medical monitor or the Sponsor. Continued dosing with or without dose reduction may be considered after contact with the medical monitor in case of non-study drug related cycle prolongations (for example: influenza).

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

7.8.1.3 Non-hematologic Toxicity (Arm A)

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

The following guidelines should be followed:

- If the criteria for initiation of a new cycle of therapy are not met on Day 29 (the next scheduled Day 1 of any given cycle), 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 investigators discretion based on the time lines in Table 7-2 above.
- If cycle prolongation of more than 28 days (beyond Day 57) is needed, study treatment is to be discontinued unless in the investigators opinion the patient is benefitting from therapy. Continuation must be discussed with the medical monitor or Sponsor on a case by case basis.
- Grade 3 or 4 treatment related non-hematologic toxicity that occurs or persists on Day 29 (scheduled Day 1) of any cycle requires a one-step dose reduction when the criteria for a new cycle are met with the following exceptions:
    - The toxicity can be managed with appropriate therapy or the risk of recurrence may be reduced by the use of appropriate prophylactic therapy (e.g. anti-emetics and anti-diarrheals for nausea, vomiting and diarrhea)

    AND/OR

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

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

7.8.1.4 Initiation of a New Cycle of Treatment (Arm A)

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

- ANC must be $\geq$ 1,000 cell/mm^3 (1.0 x10^9/L)
- Platelet count must be $\geq$ 50,000 cell/mm^3 (50.0 x 10^9/L) (platelet transfusions not recommended within $\leq$ 5 days of dosing (See Section 7.7.2)
- All non-hematologic toxicities must be $\leq$ Grade 1 or returned to baseline (except alopecia and fatigue $\leq$ Grade 2)

If these criteria are not met on the scheduled Day 1, the new cycle should be held, and patients should be re-evaluated weekly. A new cycle can only be initiated when the criteria are met.

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

7.8.2 Dose Modification Guidelines for Pomalidomide (Arm B)

7.8.2.1 Dose Reduction Steps for Pomalidomide

Table 7-3 outlines the dose reduction steps for pomalidomide based on the starting dose for Cycle 1 or subsequent cycles.

Table 7-3 Dose Reduction Steps for Pomalidomide

Starting Dose	Dose reduction Step – 1	Dose reduction Step - 2	Dose reduction Step - 3
4 mg	3 mg	2 mg	1 mg

Dose modifications of pomalidomide are permitted. Multiple dose reductions are permitted, however, the lowest dose permitted is 1 mg. If a patient is unable to tolerate the lowest dose of pomalidomide due to drug related toxicity the patient must be withdrawn from study treatment. Refer to Table 7-4 for dose modifications during a cycle of therapy and Section 7.8.2.2 for criteria for initiation of a new cycle of therapy **Arm B**.

Table 7-4 Pomalidomide Dose Modification during a Cycle of Therapy

Toxicity	Dose Modification During a cycle of therapy
Neutropenia • ANC < 0.5 x 10^9/l or Febrile neutropenia (fever ≥38.5°C and ANC <1 x 10^9/l)	Interrupt pomalidomide treatment, follow CBC weekly.
• ANC return to ≥1 x 10^9/l	Resume pomalidomide treatment at 3 mg daily.
• For each subsequent drop < 0.5 x 10^9/l	Interrupt pomalidomide treatment
• ANC return to ≥1 x 10^9/l	Resume pomalidomide treatment at 1 mg less than the previous dose.
Thrombocytopenia • Platelet count <25 x 10^9/l	Interrupt pomalidomide treatment, follow CBC weekly
• Platelet count return to ≥50 x 10^9/l	Resume pomalidomide treatment at 3 mg daily
• For each subsequent drop <25 x 10^9/l	Interrupt pomalidomide treatment
• Platelet count return to ≥50 x 10^9/l	Resume pomalidomide treatment at 1 mg less than the previous dose
Non Hematologic Toxicity	
Grade 2 or 3 rash	Consider interruption or discontinuation
Grade 4 rash, exfoliative, or bullous rash	Permanently discontinue pomalidomide
Any non-hematologic Grade 3 or 4 pomalidomide related toxicities	Hold treatment and restart treatment at one level dose reduction when toxicity has resolved to less

Toxicity	Dose Modification During a cycle of therapy
	than or equal to Grade 1 or baseline at the physician's discretion.

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

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

7.8.2.2 Initiation of a New Cycle of Treatment (Arm B)

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

- ANC must be $\geq$ 1000 cell/mm^3 (1.0 x10^9/L)
- Platelet count must be $\geq$ 50,000 cell/mm^3 (50.0 x 10^9/L) (platelet transfusions not recommended within $\leq$ 5 days of dosing (See Section 7.7.2)
- All non-hematologic toxicities must be $\leq$ Grade 1 or returned to baseline (except alopecia and fatigue $\leq$ Grade 2)

If these criteria are not met on the scheduled Day 1, the new cycle should be held, and patients should be re-evaluated weekly. A new cycle can only be initiated when the criteria are met. See Section 7.8.2.3 for guidelines on restating pomalidomide once criteria are met.

7.8.2.3 Restarting of Pomalidomide (Arm B)

If there are dose modifications or delays of pomalidomide in the previous cycle, these guidelines should be followed for the initiation of a new cycle.

- If there are no other toxicities that require a dose reduction of pomalidomide and thrombocytopenia and/or neutropenia can be managed by the use of platelet transfusions or G-CSF, no dose reductions of pomalidomide are required but may be made at the investigators discretion. Consultation with the medical monitor is recommended.
- If pomalidomide was held during the previous cycle and restarted at a reduced dose level within the cycle, without interruption for the remainder of the cycle, then this reduced dose level will be initiated on Day 1 of the new cycle. Note, if treatment is held during the cycle and then resumed, the treatment days remain unchanged (Day 1– 21 only)
- If pomalidomide dosing was omitted for the remainder of the previous cycle or if a new cycle is delayed due to pomalidomide-related toxicity newly encountered on the scheduled Day 1, then the new cycle will be started with one-level dose reduction.

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

No dose re-escalation is permitted once a dose reduction has been implemented.

7.8.3 Dose Modification Guidelines for Dexamethasone

Multiple dose reductions are permitted. If a patient is unable to tolerate dexamethasone due to dexamethasone related toxicity, dexamethasone may be further reduced or discontinued following consultation with the medical monitor. However, the patient may continue on treatment with single agent melflufen (**Arm A**) or pomalidomide (**Arm B**), at the investigators discretion. In the event of a cycle delay, unrelated to dexamethasone toxicity, it is recommended to continue dexamethasone weekly.

7.8.3.1 Dose Reduction Steps for Dexamethasone

Table 7-5 outlines the dose reduction steps for dexamethasone. Dose reductions of dexamethasone other than those listed in Table 7-5 or discontinuation may be considered in consultation with the medical monitor. Table 7-6 outlines the dose modification guidelines for toxicity related to dexamethasone.

Table 7-5 Dose Reduction Steps for Dexamethasone

Starting Dose	Dose reduction Step - 1	Dose reduction Step - 2
40 mg	20 mg	12 mg
20 mg	12 mg	8 mg

Table 7-6 Dose Modifications for Toxicity Related to Dexamethasone

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

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

7.9 TREATMENT DURATION

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

8 VISIT SCHEDULE AND ASSESSMENTS

8.1 STUDY FLOW AND VISIT SCHEDULE

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

Table 8–1 Schedule of Events

Evaluation	Screening Days -21 to -1	Arm A and Arm B All Cycles[t] Day 1	Day 8	Day 15	Day 22	End of Treatment[q]	PFS - FU[r]	OS-FU[s]
Informed consent [a]	X							
Inclusion/exclusion criteria / Randomization	X	X						
Medical and disease history [b]	X							
Physical examination/symptom assessment[c]	X	X	(X)	(X)	(X)	X		
Vital signs[d]	X	X				X		
ECOG performance status	X	X				X		
Pregnancy test [e]	X	X	(X)	(X)	(X)	X		
Pomalidomide REMS™/PPP counseling Arm B [e]	X	X						
Electrocardiogram[f]	X					X		
Chest X-ray	X							
Hematology[g]	X (X)	X	X	X	X	X		
Coagulation [h]	X	X						
Blood chemistries [i]	X	X				X	(X) [r]	
Hepatitis B screening (HBsAg, Anti-HBs, Anti-HBc)	X							
Urinalysis	X							
Bone marrow aspiration [j]	X	(X)				(X)	(X)[r]	
M protein assessments (SPEP/UPEP, IFE, SFLC) [k]	X[k]	X				X	(X)[r]	
Serum β2-microglobulin	X							
Assessment of extramedullary plasmacytoma[l]	X	(X)				(X)	(X)[r]	
Skeletal survey or CTscan [m]	X	(X)				(X)	(X)[r]	
Pharmacokinetic samples[n]		(X)[n]						
Dexamethasone administration[o] and review patient compliance		X	X	X	X			
Melflufen administration [o] **Arm A**		Arm A only						
Pomalidomide administration[o] **Arm B** and review patient compliance		Arm B only -Daily days 1 – 21						
Concomitant medications [p]	X	→				X		
AE monitoring		→				X		

Follow-up (PFS, OS)				X[r,]	X

(X) Only if indicated

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

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

c) A complete physical exam, including height (screening only) and weight, neurologic assessment and assessment for extramedullary myeloma (if present on PE) will be conducted at screening, Day 1 of each cycle and End of Treatment visit. A symptom directed physical examination will be conducted as needed during a cycle. A site visit is required for Cycle 1 and 2 for weekly symptom assessment. Plasmacytomas that can be followed by physical exam are to be evaluated on Day 1 of each cycle. Baseline symptoms and residual toxicity from previous therapy is to be assessed within 21 days prior to initiation of therapy.

d) Vital signs including blood pressure, pulse, respiration rate, temperature. To be assessed at screening and pre and post melflufen infusion (Arm A) and on Day 1 of each cycle for Arm B

e) All FCBP must have a medically supervised negative serum or urine pregnancy test with a sensitivity according to local REMS and PPP requirements within 10 to 14 days prior to planned start and again within 24 hours of starting therapy (24 hours required if prior to knowledge of randomization or randomized to Arm B) and thereafter according to the randomized treatment arm. **Arm A**: repeat pregnancy test prior to each dose of each cycle and at End of Treatment visit. **Arm B**: within 24 hours of starting pomalidomide Cycle 1, Day 1. While on pomalidomide, repeat pregnancy test every week for the first 4 weeks and then every 28 days while on therapy and during interruptions in therapy and 4 weeks following discontinuation of pomalidomide. Women with irregular menstruation must have pregnancy testing every 14 days while on therapy and during interruptions and 14 and 28 days after discontinuation of pomalidomide. A FCBP is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months). All patients in Arm B must be counseled at the start of each cycle according to the commercial REMS™ program in the USA and Canada or according to the PPP in Appendix J for sites outside the USA and Canada.

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

g) Hematology: CBC with differential, and platelet count. Patients are required to have all laboratory evaluations completed at the study center during Cycles 1 and 2. Following Cycle 2, CBC evaluations may be done at the study center laboratory or other local laboratory as long as the results are reviewed by the study center within 24 hours and toxicity assessment is completed. Exceptions may be made only in consultation with the medical monitor. All CBC values collected in addition to protocol specified time points must be recorded in the eCRF. See Section 9.1.5.1 for reporting requirements of scheduled and unscheduled results of thrombocytopenia and neutropenia. A screening CBC may need to be repeated just prior to randomization if the initial value was

trending downward, not reached nadir from last dose of prior therapy or based on clinical presentation (this may be done at the Investigators discretion or upon request of the medical monitor.

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

i) Blood chemistry: sodium, chloride, potassium, magnesium, phosphate, uric acid, BUN (urea), glucose (fasting at baseline), ALT/AST (SGPT/SGOT), alkaline phosphatase, total protein, total bilirubin, albumin, serum creatinine, and estimated creatinine clearance by Cockroft-Gault Equations (Appendix G) calcium and lactate dehydrogenase (LDH). Patients are required to have all evaluations completed at the treatment center during Cycles 1 and 2. Following Cycle 2, Chemistry evaluations may be done at the study center laboratory or other local laboratory as long as the results are reviewed by the study center within 24 hours and toxicity assessment is completed. Exceptions may be made only in consultation with the medical monitor.

j) Bone marrow aspirate (BMA) to be collected at screening for % plasma cells, morphology, and cytogenetics by Fluorescence In Situ Hybridization (FISH). Minimum FISH probes include 17p, 4;14 and 14;16. In addition, a BMA sample is to be collected at screening and stored for possible MRD. If a bone marrow aspirate and/or biopsy has been collected within 6 weeks, with the appropriate evaluations, prior to initiation of therapy, it does not need to be repeated. A repeat BMA is required to confirm a suspected CR and to assess MRD status. Stored BMA samples may be used for optional future testing if requested by Oncopeptides in consenting patients and where regionally acceptable. Refer to Laboratory manual.

k) SPEP, UPEP, serum and urine IFE (if SPEP or UPEP are not detectable and to confirm CR) quantitative immunoglobulins per routine lab practice and serum free light chain (SFLC) assay (only required if SPEP and UPEP are not measurable [UPEP is < 200 mg/24 hrs and SPEP is < 0.5 g/dL] and to confirm a sCR), are to be conducted at screening, Cycle 1 Day 1 and on the planned day 1 of each cycle (i.e., Day 29 of the previous cycle) (quantitative immunoglobulins only need to be repeated for patients with IgA or IgD myeloma) even if treatment is delayed. All assessment of SPEP, UPEP, IFE and FLC must be completed in the same laboratory for a given patient*(See footnote r). In the event treatment for a new cycle is delayed beyond Day 43 of the previous cycle, M protein disease status is required to be repeated on the day the new cycle starts, i.e. Day 1 of the new cycle (e.g. Day 50 or 57 of the previous cycle). If treatment is discontinued beyond Day 43, the assessment should be repeated on the day of that determination (or as soon as possible 30 days after the last dose of study drug) as part of end of treatment (EoT) visit. Refer to Laboratory manual.

l) Known or suspected extramedullary plasmacytomas are to be assessed at screening, as clinically indicated and to confirm response or progression. The same method of evaluation should be used throughout the study (eg. Computerized tomography [CT]/ magnetic resonance imaging [MRI]/ positron emission tomography [PET]). All imaging assessments should be completed within 28 days prior to randomization and documented in the eCRF.

m) Skeletal survey includes lateral radiograph of the skull, and anterioposterior views of femur and humeri. Anterioposterior and lateral views of the spine, and anterioposterior views of the pelvis and ribs. (low dose CT scan may be used in addition or in place of conventional X-ray with the same technique to be used with each evaluation). Required if previous survey > 6 weeks from randomization and at any time when clinically indicated. Limited X-rays may be performed as clinically indicated to confirm PD.

n) PK samples will be collected only in patients randomized to Arm A. Three plasma samples for determination of melphalan concentrations will be drawn in connection to the first two melflufen treatment cycles, 10 – 15 minutes after the end of infusion, 1 hour after the end of infusion and after 2-4 hours after the end of infusion (as late as possible within the time frame). Refer to the Laboratory Manual for details on specimen collection and processing

o) See Section 7 in the protocol for complete details on study drug administration, dose modifications and start of a new cycle of therapy and study drug compliance.
p) Concomitant medications and procedures: - all blood products and medications within 21 days prior to first dose until the End of Treatment Visit.
q) End of Treatment visit should be scheduled 30 days (accepted time window ±3 days) after last dose of melflufen or pomalidomide or as soon as possible if the decision to remove patient from therapy occurs later than 30 days after last dose (such as in the case of a prolonged cycle) with evaluation of safety variables including recording of new and ongoing AEs, review of concomitant medications and any other new disease related therapy. If a new treatment for MM is to be introduced sooner than 30 days after last dose of study drug the EoT visit should occur as close as possible before the first dose of the new drug. **Ongoing neutropenia and thrombocytopenia grade 3-4 at the EoT visit are to be followed until resolution (≤ Grade 2) or initiation of subsequent therapy.** SAEs should be followed until resolution or stabilization with no expected resolution.
r) Progression Free Survival Follow-Up (PFS-FU): Patients who discontinue therapy for reasons other than disease progression should continue to have monthly disease assessments done until documented progression (confirmed on 2 consecutive assessments) or initiation of subsequent therapy. (Confirmed PD should be verified by medical monitor prior to discontinuation of therapy). If PD has not been confirmed prior to the initiation of subsequent therapy the reason for the subsequent therapy should be documented. Documentation of the date and regimen of the first subsequent therapy is required. Serum calcium and albumin (corrected calcium) required only if hypercalcemia is the only evidence of PD. If the patient enters PFS-FU, the first PFS M protein assessment should be scheduled 4 weeks after the EoT visit. *Patients unwilling or unable to return to the site for PFS evaluations may have the lab done locally following approval by the medical monitor. If the patient is discontinued mid-cycle, prior to Day 28, the EoT visit should be scheduled 30 days (+/- 3days) after the last dose of study drug.
s) Overall Survival Follow-up (OS-FU): Following confirmed disease progression or initiation of subsequent therapy, follow-up for overall survival status and second primary malignancies will take place every three months +/- 7 days for 24 months. In the event that Oncopeptides AB would like to determine the OS status of patients following 24 months, future inquiries about their health status may be conducted at any time beyond this time point. This information may be recorded outside of the eCRF established for this study. Documentation of the date and regimen of the first subsequent therapy should be done if it occurs during OS -FU. Follow-up may be completed by phone contact. SAEs should be followed until resolution or stabilization with no expected resolution. Death information from public sources, e.g. death registry, obituary listing, etc. can also be used when it is available and verifiable.
t) +/- 3 day window permitted (except Cycle 1 Day 1) for holidays/administrative reasons.

8.2 STUDY ASSESSMENTS

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

8.2.1 Screening Disease Assessments

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

8.2.2 Efficacy Assessments

Efficacy Assessments

- M-protein determination using the following procedures:
  - SPEP and serum protein IFE with quantitative immunoglobulins (For patients with IgA and IgD myeloma);

    - Immunofixation of serum is required at any time when M protein by SPEP becomes non-detectable and confirm a CR.
- UPEP and urine protein IFE (all using the same 24-hour urine collection);
    - Immunofixation of urine is required at any time when M protein by UPEP becomes not detectable and to confirm a CR.
- SFLC and SFLC ratio
    - FLC assessment is not required in the presence of measurable SPEP and/or UPEP (SPEP $\geq$ 0.5 g/dL and/or UPEP $\geq$ 200 mg/24 hours),
    - FLC is required to confirm sCR, regardless of type of measurable disease.

It is up to the site to work with the laboratory that performs the response analyses to ensure that the laboratory completes the immunofixation and FLC evaluations when required, to enable response assessments according to IMWG criteria.

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

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

Starting with Cycle 2, M-protein response to treatment should be assessed every cycle. Disease status, including skeletal x-rays and/or CT scan of bones, and imaging procedures of known or suspected extramedullary plasmacytomas, should be performed at screening and if indicated according to the IMWG-URC. Bone marrow aspirate should be performed at screening and to confirm suspected CR and MRD status in patients who have negative immunofixation. Additional skeletal x-rays and/or imaging assessments may be performed if the patient has symptoms suggestive of progression of lesion(s) documented at screening or new lesions. If extramedullary plasmacytomas are present at screening and measurable on physical examination, they should be assessed at every cycle. Extramedullary plasmacytomas documented and measurable only by imaging assessments should be assessed by the same relevant modality to confirm response or progression according to the IMWG-URC (Rajkumar et al. 2011, Appendix C).

8.2.3 Safety and Tolerability Assessments

Safety Assessments:

- Assessment and grading of AE
- Physical examination with vital signs, neurologic assessment and assessment of performance status;
- Routine safety laboratory tests (CBC with differential and platelets; clinical chemistry, coagulation tests and urinalysis) with calculation of creatinine clearance according to the Cockcroft-Gault equation)
- Chest X-ray (postero-anterior/lateral)
- Hepatitis B screen (HBsAg, Anti-HBs, Anti-HBc)
- Pregnancy testing
- Electrocardiogram

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

8.2.4 Electrocardiogram Assessments

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

8.2.5 Pharmacokinetic Assessments

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

8.2.6 End of Treatment

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

eCRF. At the end of the trial, any patient having signed the ICF will be allowed to proceed with treatment according to protocol. Patients ongoing on treatment that continue to have benefit from treatment will be able to continue therapy until there is disease progression or unacceptable toxicity. All patients on treatment will continue to be followed for safety.

8.2.7 Follow Up Assessments

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

8.2.7.1 Progression Free Survival Follow-up

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

8.2.7.2 Overall Survival Follow-up

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

8.2.8 Lost to Follow-Up

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

8.2.9 Criteria for Premature Patient Withdrawal

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

- Documented confirmed disease progression verified by the medical monitor (2 consecutive evaluations).
- Patients may choose to withdraw from the study treatment at any time and continue in follow-up.
- AEs that, in the judgment of the investigator, may cause severe or permanent harm or which require study drug discontinuation (See Section 7.8).
- Clinical judgment of the investigator: A patient may be withdrawn from the study treatment, if in the opinion of the investigator, it is not in the patient's best interest to continue.

- Requiring other anti-neoplastic therapies.
- Major deviation of the study protocol (i.e., unable to adhere to study schedule).
- Confirmed pregnancy.
- Lost to follow-up.

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

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

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

9 SAFETY MONITORING AND REPORTING

9.1 ADVERSE EVENTS

9.1.1 Definitions

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

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

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

9.1.2 Grading of severity

Whenever possible, the CTCAE version 4.03 should be used to describe the event and for assessing the severity of AEs (See Appendix B). Any events representing a change in the CTCAE Grade need to be reported on the AE eCRF. This includes any abnormal laboratory values that the investigator considers clinically significant (Section 9.1.5).

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

Table 9-1 Adverse Event Severity

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

9.1.3 Causality

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

Causality should be assessed using the following categories:

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

The investigator must appraise all abnormal laboratory results for their clinical significance. Only if an abnormal laboratory result is considered clinically significant, should it be reported as a treatment emergent adverse event. (See Section 9.1.5.1).

9.1.4 Adverse Event Reporting

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

1. The severity grade (CTCAE Grade 1-5).
2. Its duration (Start and end dates).
3. Its relationship to the study treatment (causality).
4. Action taken with study drug (eg. none, dose reduced, dose held, permanently discontinued).

5. Whether medication or therapy was given (concomitant medication or procedure,).
6. Outcome (eg; not resolved, resolved, resolved with sequalae, fatal, unknown).
7. Whether it is a SAE as defined in Section 9.2.1.

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

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

9.1.5 Laboratory Test Abnormalities

9.1.5.1 Definitions and Reporting

Laboratory abnormalities are usually not recorded as AEs; however, signs and/or symptoms that are associated with laboratory findings requiring treatment discontinuation, dose modification, or medical intervention (eg, anemia requiring transfusions or hyperglycemia requiring treatment) or other abnormal assessments (eg, ECG, radiographs, vital signs) must be recorded as AEs (or serious adverse events) if they meet the definition of an AE (or serious adverse event) as described in Section 9.1 or 9.2. In addition, laboratory abnormalities assessed as clinically significant should also be recorded as AEs. The Investigator will record the grade of the clinically significant laboratory abnormality and will evaluate its relationship to the study drug and clinical condition. Laboratory AEs should be recorded using only one event term per event such as thrombocytopenia for low platelet count but not as both (thrombocytopenia and low platelet count).

Clinically significant laboratory abnormalities are those that:

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

Additional laboratory reporting guidelines.

Extra attention should be given to reporting all Grade 3 and 4 thrombocytopenia and neutropenia events. They must be:

- Collected and reported during the study period and the EoT visit.
- Ongoing grade 3 and 4 thrombocytopenia and neutropenia at the time of the EoT visit are to be followed until resolution ($\leq$ Grade 2), or stabilization, or initiation of a subsequent therapy.
- All ANC and platelet counts collected during the protocol participation, i.e. both those collected at protocol specified time points and any additional time points (unscheduled assessments), must be reported in the eCRF and if applicable also in the SAE report.

- All ANC and platelet counts associated with a SAE regardless of the nature of the event, must be reported in the details of the SAE report.
- Supportive care such as platelet transfusions and G-CSF given for adverse events or prophylactic reasons must be reported in the eCRF and if applicable also in the SAE report.

9.2 SERIOUS ADVERSE EVENTS

9.2.1 Definitions

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

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

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

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

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
- Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
- Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event
- Disease progression: In instances of SAE's due to "disease progression" the event or condition that met the criteria for the SAE should be indicated as the event term or condition rather than disease progression to the extent possible (e.g. "respiratory failure" or "renal failure" due to progressive MM).

9.2.2 Serious Adverse Event Reporting

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

An SAE reporting form must be filled out and sent via fax or email. Local fax numbers are provided it the ISF.

- Email: safetydesk@psi-cro.com

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

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

Any SAE that occurs after the above defined regular SAE reporting period, should also be reported if the investigator suspects a causal relationship to the study treatment. All deaths occurring during the regular SAE reporting period must be reported, regardless of cause (See Section 9.2.2.1).

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

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

9.2.2.1 Reporting of Death

- Death is an outcome of a serious adverse event and not a serious adverse event in itself. When death is an outcome, the event(s) resulting in death should be reported (eg, "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 (eg, "respiratory failure" due to progressive MM).

- Deaths that occur later than 30 days after the last study drug administration should be reported as SAEs only if assessed as related to the study treatment.

9.3 PREGNANCY

All instances of pregnancy or suspected pregnancy occurring in a patient or partner of a patient taking pomalidomide must be reported according to the regional REMS™/PPP program and the guidelines detailed below.

Arm A and B

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

A pregnancy reporting form must be filled out and sent via fax or email. Local fax numbers will be provided in the ISF.

- Email: safetydesk@psi-cro.com

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

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

10 DATA COLLECTION AND MANAGEMENT

10.1 DATA CONFIDENTIALITY

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

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

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

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

10.2 SITE MONITORING

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

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

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

10.3 DATA COLLECTION

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

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

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

10.4 DATABASE MANAGEMENT AND QUALITY CONTROL

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

11 STATISTICAL METHODS AND DATA ANALYSIS

11.1 STUDY ENDPOINTS

11.1.1 Primary Endpoint

PFS is defined as time (months) from date of randomization to the earlier of confirmed disease progression or death due to any cause. Progression dates will be assessed by the IRC using the IMWG-URC, (Rajkumar et al. 2011). The conventions for censoring of PFS are described in Table 11-1.

11.1.2 Secondary Endpoints

11.1.2.1 Key Secondary Endpoints

Unless stated otherwise, response and progression status will be assessed by the IRC using the IMWG-URC, (Rajkumar et al. 2011, Appendix C).

ORR: defined as a best confirmed response of sCR, CR, VGPR, or PR using local laboratory evaluation.

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

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

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

11.1.2.2 Other Secondary Endpoints

Unless stated otherwise, response and progression status will be assessed by the IRC using the IMWG-URC, (Rajkumar et al. 2011 Appendix C).

- CBR, i.e. ≥ MR: is the rate of response evaluable patients that achieve a confirmed MR or better.
- TTR: is defined as the time from the date of randomization to the date of the first documented confirmed response in a patient that has responded with ≥ PR.
- TTP: is defined as the time from the date of randomization to the date of the first documented confirmed PD.
- Duration of clinical benefit (DOCB): defined as the time 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. DOCB is defined only for patients with a confirmed MR or better.
- Best response during the study (sCR, CR, VGPR, PR, MR, stable disease [SD] or PD) using the IMWG-URC, (Rajkumar et al. 2011 Appendix C)
- Primary and secondary endpoint as assessed by Investigators

11.1.3 Exploratory Endpoints

- PK parameters of melphalan (Arm A)
- MRD for patients that achieve a CR

11.2 SAMPLE SIZE CALCULATION

The sample size calculation is based on comparing the melflufen + dexamethasone arm and the pomalidomide + dexamethasone arm in terms of PFS. The sample size estimation is based on the following assumptions:

Power	90 %
Significance level	0.05 % two-sided
HR (melflufen+dex/pomalidomide+dex)	0.70
Distribution of survival times	exponential
Accrual time	24 months
Follow up time	6 months after last patient randomized
Total study time	30 months
Early censor rate	approximately 15 %
Time to full recruitment speed	6 months
Median PFS for control arm	3.6 months (FDA Pomalyst Precribing Information 2015)

The final analysis will take place when 339 patients have experienced a PFS event. Based on the assumptions, it is anticipated that a total of 450 patients will be randomized over 24 months in order to reach 339 events 6 months after the randomization of the last patient.

11.3 STATISTICAL METHODS

11.3.1 General Considerations for the Statistical Analyses

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

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

11.3.2 Analysis Populations

11.3.2.1 Enrolled Analysis Set

The Enrolled analysis set is defined as all subjects who are assigned a subject ID. This analysis set includes randomized subjects and non-randomized subjects, identified as screen failures. The Enrolled analysis set will be the primary population for the summaries of

disposition. Randomized subjects will be summarized according to the treatment assigned at randomization.

11.3.2.2 Full Analysis Set

The Full analysis set is defined as all subjects who are randomized. Subjects will be analyzed according to the treatment assigned at randomization. The primary analysis (PFS) will be performed using the Full analysis set.

11.3.2.3 Safety Analysis Set:

The Safety analysis set is defined as all subjects who received at least one or partial dose of melflufen, pomalidomide, or dexamethsone. The Safety analysis set will be the primary population for the summaries of all exposure and safety data. Subjects will be summarized according to the treatment actually received.

11.3.2.4 Per Protocol Analysis Set

The Per Protocol analysis set is defined as all subjects who received at least one dose of melflufen, pomalidomide, or dexamethasone and have a baseline assessment of disease status and at least one post-baseline assessment for disease response. Subjects who have major protocol deviations, related to critical eligibility criteria, the assessment of efficacy or the safety of the subject that could significantly impact the interpretation of study results, will be excluded from the Per Protocol analysis set. The supporting analysis of the primary and secondary efficacy endpoints will be evaluated using the Per Protocol analysis set. Subjects will be analyzed according to the treatment actually received.

11.3.3 Analysis of Efficacy Endpoints

11.3.3.1 Primary Endpoint, PFS

PFS is measured from the date of randomization to the date of documented disease progression or death. PFS will be right-censored for patients who meet one of the following conditions:

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

These conventions are based on the May 2007 FDA Guidance for Industry, 'Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics'.
(http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071590.pdf)
For such patients, the primary analysis of PFS will be right-censored according to the conventions described in Table 11-1.

Table 11-1 Conventions for Censoring for PFS

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

Sensitivity analyses regarding different PFS definitions and censoring approaches will be further specified in the SAP. These analyses will include, but are not limited to:

- Investigator claim of clinical progression, i.e. using investigator assessment instead of IRC assessments for defining PFS
- Considering start of new anticancer treatment as a progression instead of censoring

The primary statistical analysis of PFS will be performed using a two-sided, 0.05 level stratified Cox proportional hazards regression model based on the Full analysis set stratified by the stratification factors.

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

Non-inferiority of melflufen and dexamethasone versus pomalidomide and dexamethasone for the Full analysis set will be demonstrated if the upper limit of the 95 % confidence interval is below 1.2. This assessment is relevant for non-FDA submissions.

Superiority of melflufen and dexamethasone versus pomalidomide and dexamethasone for the Full analysis set will be demonstrated if the upper limit of the 95 % confidence interval is below 1.0.

11.3.3.2 Subgroup Analyses for PFS

The PFS data will be analyzed and presented by a number of prospectively identified subgroups based on the Full analysis set such as the following:

- Age (< 65, ≥ 65 and < 75, and ≥ 75)
- Number of prior lines of therapy
- ISS Score
- Subgroups of refractoriness to previous therapies

- Race (American Indian or Alaskan native, Black or African American, Asian, Caucasian/White, Native Hawaiian or other Pacific Islander, other)

The full list of prospectively identified subgroups are identified in the SAP. In addition, subgroups may be identified on a data driven basis, and such analyses will be considered as exploratory.

11.3.3.3 Analysis of Secondary Endpoints

All inferential analyses of the key secondary endpoints will be performed using two-sided tests at a significance level of 0.05. The key secondary endpoints will be tested in a closed testing procedure in a hierarchal fashion, starting with ORR, followed by DOR and OS, where the test of ORR is conditional on the test of the primary analysis of PFS being significant, the test of DOR is conditional on the test of ORR being significant, and the test of OS conditional on the test of DOR being significant. This closed testing procedure will control the family-wise type 1 error rate. The analyses will primarily be based on the Full analysis set followed by the Per-protocol analysis set.

The ORR will be estimated as the proportion of patients in each treatment group who achieve a confirmed response of sCR, CR, VGPR, or PR as their best response. The treatment groups will be compared using the Cochran Mantel Haenszel chi square test. The exact binomial 95% CI for ORR will be calculated for each treatment arm.

The DOR will be calculated for subjects who achieve a confirmed response of PR or better. The DOR is defined as the time from first documentation of response to disease progression or death due to any cause. Dates of progression and censoring will be determined as described for the analysis of PFS. The treatment arms will be compared with respect to DOR using a log-rank test at a significance level of 0.05 with no adjustment for covariates. OS is defined as time (months) from the date of randomization to date of death due to any cause. Subjects who are alive will be censored at the last follow up visit. The treatment arms will be compared with respect to OS using a stratified Cox proportional hazards regression model based on the Full analysis set stratified by the stratification factors.

K-M methods will be used to estimate the distribution of OS and the median and other quartiles with their 95% confidence intervals; a figure showing the estimated OS distribution will be provided.

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

CBR will be summarized without analysis. The approximate 95% CI for CBR will be calculated for each treatment arm.

TTR will be summarized without analysis.

TTP will be summarized without analysis.

Duration of MR and SD will be summarized without analysis.

The methods for the analysis of the PK data will be described in a separate population PK-PD plan.

11.3.4 Analysis of Safety Endpoints

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

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

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

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

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

Grade 3 and 4 thrombocytopenia and neutropenia will be evaluated to determine their frequency, duration, relationship to treatment, associated clinical consequences/medical management and associated significant AEs.

Actual value and change from baseline for all hematology, serum chemistry, and coagulation parameters will be summarized at each scheduled visit. Selected laboratory test results will be assigned toxicity grades using CTCAE 4.03. Shift tables assessing the toxicity grade at baseline versus worst toxicity recorded on study will be presented. A listing of all grade 3 or higher laboratory values will be provided.

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

11.4 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.

11.5 INTERIM ANALYSIS

No interim analysis is planned.

11.6 NON-INFERIORITY ANALYSIS AND CHOICE OF NON-INFERIORITY MARGIN

According to EU guidelines, the choice of non-inferiority margin is based on a combination of statistical reasoning and clinical judgment (Guideline of the choice of the non-inferiority margin EMEA/CPMP/EWP/2158/99). The proposed comparator has, in a previous Phase 3 trial, shown superiority over an active control (high-dose dexamethasone) with a PFS HR of 0.45 (2-sided 95% confidence interval 0.35-0.59) (Pomalidomide Celgene EPAR 2013). The upper limit of the confidence interval (0.59) would then correspond to a HR of 1.69 (1/0.59). A non-inferiority trial comparing melflufen and dexamethasone versus pomalidomide and dexamethasone where the upper limit of the 95% confidence interval is less than 1.69 can then be interpreted as superiority over high-dose dexamethasone since the 95% confidence interval of the melflufen study will not overlap with the 95% confidence interval of the historical study data. Since high-dose dexamethasone is an active compound, the difference against a hypothetical placebo would be even larger.

Even though a non-inferiority margin of 1.69 might satisfy the statistical regulatory requirements, it would allow melflufen and dexamethasone to be substantially worse than the pomalidomide and dexamethasone comparator arm and this is clearly not clinically acceptable. In the current trial a non-inferiority margin of 1.2 will be used. With the planned sample size, this margin will ensure that the point estimate of the HR will be 1 or better (≤ 1). A non-inferiority margin of 1.2 will thus ensure a roughly similar or better efficacy of melflufen versus pomalidomide with the respect to the primary endpoint of PFS.

11.7 PHARMACOKINETIC ANALYSIS

The pharmacokinetic (PK) evaluation will be performed only in patients randomized to melflufen + dexamethasone treatment (Arm A).

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

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

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

Covariates in the analysis will include, age, gender, ethnicity, renal function (as calculated by the Cockcroft-Gault formula), body weight, melflufen dose, and concomitant medications. Additional variables may be added. All covariates with the exception of ethnicity and concomitant medications will be analyzed as continuous variables. Concomitant medication will be entered as present/absent, dose data will not be used.

The optimal structural population PK model will be determined with estimation of fixed and random effects. Data from previous pharmacokinetic studies in other populations will be included as appropriate for a more accurate determination of the structural PK model. Covariate relationships on the PK parameters of the structural model will be explored using graphical and statistical methods.

Details on the modeling approach will be described in a separate population PK-PD plan which will be developed in parallel with the phase 3 program for melflufen.

11.8 EXPOSURE-RESPONSE ANALYSES

The relationship between melphalan exposure as determined by the population PK analysis and by the administered melflufen doses, and safety and efficacy variables will be explored. The incidence of typical melphalan adverse drug reactions including neutropenia, thrombocytopenia, mucositis, nausea, vomiting, and diarrhea will be evaluated. Similarly, the relationship between melphalan exposure and disease response as described by the key efficacy variables will be explored. The methods will be detailed in a separate population PK-PD plan which will be developed in parallel with the phase 3 study. Data from other melflufen studies may be included in this analysis as appropriate.

12 ETHICAL CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES

12.1 REGULATORY AND ETHICAL COMPLIANCE

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

12.2 DATA MONITORING COMMITTEE

An independent data monitoring committee (DMC) will perform surveillance of efficacy/safety balance at regular intervals during the study, using unblinded treatment-aggregated data. All activities and processes surrounding the DMC will be outlined in the DMC Charter.

- The Clinical Research Organizations (CROs) and the Sponsor will be unblinded to individual patient data during the study but will not have access to the unblinded, aggregate data listings used by the DMC for their review.
- The CROs' medical monitors and the Sponsor's safety officer may have access to aggregate safety data and treatment assignment as needed to fulfill the obligation of safety oversight of the study.

12.3 INDEPENDENT REVIEW COMMITTEE

An IRC will assess all tumor responses and PD assessments during the study. The IRC members will be blinded to all treatment data and perform their reviews in closed-meeting sessions. All activities and processes surrounding the IRC will be outlined in the IRC Charter.

12.4 RESPONSIBILITIES OF THE INVESTIGATOR AND IRB/IEC/REB

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

12.5 INFORMED CONSENT PROCEDURES

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

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

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

12.6 DISCONTINUATION OF THE STUDY

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

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

12.7 PUBLICATION OF STUDY PROTOCOL AND RESULTS

Oncopeptides AB assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results. Any publication will

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

12.8 STUDY DOCUMENTATION, RECORD KEEPING AND RETENTION OF DOCUMENTS

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

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

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

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

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

12.9 CONFIDENTIALITY OF STUDY DOCUMENTS AND PATIENT RECORDS

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Oncopeptides AB, their agents or Health Authorities. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site. Refer to Section 10.1 for additional details regarding patient confidentiality.

12.10 AUDITS AND INSPECTIONS

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

12.11 FINANCIAL DISCLOSURES

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

13 PROTOCOL ADHERENCE

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

13.1 AMENDMENTS TO THE PROTOCOL

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

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15 APPENDICES

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

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

Source: Oken MM, et al. 1982.

Appendix B. National Cancer Institute CTCAE Version 4.03

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

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

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

Appendix C. IMWG Uniform Response Criteria

Response	*IMWG criteria (Rajkumar, et al. 2011)*
Stringent Complete Response (sCR)	CR as defined below plus: • normal FLC ratio and • absence of clonal cells in bone marrow by immunohistochemistry or 2 – 4 color flow cytometry
Complete Response (CR)	• Negative immunofixation on the serum and urine and • disappearance of any soft tissue plasmacytomas and • < 5% plasma cells in bone marrow. • In patients with only FLC disease, a normal FLC ratio of 0.26–1.65 is required.
Very Good Partial Response (VGPR)	• Serum and urine M-protein detectable by immunofixation but not on electrophoresis or • ≥ 90% reduction in serum M-protein plus urine M-protein level < 100 mg/24 h. • In patients with only FLC disease, > 90% decrease in the difference between involved and uninvolved FLC levels is required.
Partial Response (PR)	• 50% reduction of serum M-protein and reduction in 24 hours urinary M-protein by ≥ 90% or to < 200 mg/24 h • If the serum and urine M-protein are unmeasurable, a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria • If serum and urine M-protein are not measurable, and serum free light assay is also not measureable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥ 30% • In addition to the above listed criteria, if present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required
Minimal response (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/24hrs. • In addition to above; if present at baseline, 25-49% reduction in the size of soft tissue plasmacytomas is also required • No increase in size or number of lytic bone lesions (development of compression fractures does not exclude response)
Stable Disease (SD)	• Not meeting criteria for CR, VGPR, PR or progressive disease
Progressive	Increase of ≥ 25% from lowest response value in any one of the following:

disease (PD)	• Serum M-component (the absolute increase must be ≥ 0.5 g/dL) and/or • Urine M-component (the absolute increase must be ≥ 200 mg/24 h) and/or • Only in patients without measurable serum and urine M-protein, the difference between involved and uninvolved FLC levels. The absolute increase must be > 10 mg/dL • Only in patients without measurable serum and urine M-protein and without measurable disease by FLC levels, bone marrow plasma cell percentage (absolute % must be ≥ 10%) • Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas • Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL) that can be attributed solely to the plasma cell proliferative disorder

All response categories (CR, sCR, VGPR, PR, MR and PD) require two consecutive assessments made at any time before the institution of any new therapy; all response categories and SD also require no known evidence of progressive or new bone lesions if radiographic studies were performed. VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable in serum, urine both or either. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. For progressive disease, serum M-component increases of ≥ 1 g/dl are sufficient to define relapse if starting M-component is ≥ 5 g/dl

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

Appendix D. Line of Therapy Definition

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

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

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

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

New line of therapy

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

Appendix E. Definition of Relapsed Disease

This study will use the IMWG definitions:

Refractory Myeloma:

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

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

Relapsed myeloma:

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

Appendix F. Declaration of Helsinki

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

Appendix G. Estimated Creatinine Clearance rate using Cockcroft-Gault Formula

For males:

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

For females:

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

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

Appendix H. Assessment of QTC Interval

QTc Fridericia Formula

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

Appendix I. ISS and R-ISS Score

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

(Palumbo et al. 2015)

Appendix J. Pomalidomide Pregnancy Prevention Plan.

Sites and patients randomized to Arm B in Canada or USA should be enrolled in and comply with the Celgene REMS™ program specific to the country of enrolment.

Sites and patients randomized to Arm B outside Canada or USA are required to comply with the following pomalidomide Pregnancy Prevention Plan (PPP). Components of this plan are detailed below:

1. Pomalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods.

   This document provides the following information for reference by the health care professional:

   - Potential risks to the fetus associated with pomalidomide exposure
   - Definition of Female of Childbearing Potential (FCBP)
   - Pregnancy testing requirements for patients receiving Pomalidomide who are females of childbearing potential
   - Acceptable birth control methods for both females of childbearing potential and male patients receiving pomalidomide in the study
   - Requirements for counselling of all study patients receiving pomalidomide about pregnancy precautions and the potential risks of fetal exposure to pomalidomide

2. Pomalidomide Education and Counseling Guidance Document

   - The Pomalidomide Education and Counselling Guidance Document must be completed and signed by either a trained counselor or the Investigator at the participating clinical center prior to each dispensing of pomalidomide study treatment. A copy of this document must be maintained in the patient records.

3. Pomalidomide Information Sheet

   - The Pomalidomide Information Sheet must be given to each patient receiving pomalidomide study therapy. The patient must read this document prior to starting pomalidomide study treatment and each time they receive a new supply of study drug.

Pomalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods

Risks Associated with Pregnancy

Pomalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. An embryofetal development study in animals indicates that pomalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy. The teratogenic effect of pomalidomide in humans cannot be ruled out. Therefore, a risk minimisation plan to prevent pregnancy must be observed.

Definition of females of childbearing potential (FCBP)

This protocol defines a female of childbearing potential as a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Pregnancy testing requirements for FCBP

Before starting pomalidomide

FCBP must have two negative medically supervised pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting pomalidomide including female patients who commit to complete abstinence, as outlined below. The first pregnancy test must be performed within 10 to 14 days prior to receiving the prescription for pomalidomide and the second pregnancy test must be performed within 24 hours prior to receiving the prescription for pomalidomide. The patient may not receive study drug until the Investigator has verified that the results of these pregnancy tests are negative.

Pregnancy testing during the entire duration of pomalidomide treatment and for 28 days following discontinuation of pomalidomide

- FCBP with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 4 weeks of study participation and then every 4 weeks while on pomalidomide treatment, and 4 weeks following pomalidomide discontinuation. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 4 weeks and then every 2 weeks while on pomalidomide treatment, and 2 weeks and 4 weeks following discontinuation of pomalidomide.
- Pregnancy testing and counselling must be performed if a patient misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Pomalidomide treatment must be discontinued during this evaluation.
- At each visit, the Investigator must confirm with the FCBP that she is continuing to use two reliable methods of birth control.

Acceptable birth control methods

Birth control for FCBP

FCBP taking pomalidomide must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual contact during the following time periods related to this study: for at least 28 days before starting pomalidomide treatment; throughout the entire duration of pomalidomide treatment; during dose interruptions; and for at least 28 days after discontinuation of pomalidomide.

The two methods of reliable contraception must include one highly effective method and one additional effective (barrier) method. FCBP must be referred to a qualified provider of contraceptive methods if needed.

The following are examples of highly effective and additional effective methods of contraception:

- Highly effective methods:
  - Intrauterine device (IUD)
  - Hormonal (birth control pills, injections, implants)
  - Tubal ligation
  - Partner's vasectomy
- Additional effective methods:
  - Male condom
  - Diaphragm
  - Cervical Cap

Because of the increased risk of venous thromboembolism in patients with multiple myeloma taking pomalidomide and dexamethasone, combined oral contraceptive pills are not recommended. If a patient is currently using combined oral contraception the patient should switch to one of the effective methods listed above. The risk of venous thromboembolism continues for 4 to 6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone.

Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in patients with neutropenia.

Birth control for males

Males taking pomalidomide must practice complete abstinence or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential throughout the entire duration of pomalidomide treatment, during dose interruptions and for at least 4 weeks following discontinuation of pomalidomide, even if he has undergone a successful vasectomy.

Counselling

Counselling for FCBP

For a female of childbearing potential, must be counselled about pregnancy precautions and the potential risks of fetal exposure prior to the start of pomalidomide and at a minimum of every 4 weeks. The counsellor should verify that:

- She understands the potential teratogenic risk to the unborn child

- She understands the need for effective contraception, without interruption 4 weeks before starting pomalidomide treatment, throughout the entire duration of pomalidomide treatment, dose interruption in therapy and 4 weeks after the end of pomalidomide treatment
- She agrees and is capable of complying with effective contraceptive measures
- She is informed and understands the potential consequences of pregnancy and the need to notify her study doctor immediately if there is a risk of pregnancy
- She understands the need to commence the pomalidomide treatment as soon as pomalidomide is dispensed following a negative pregnancy test
- She understands the need and accepts to undergo pregnancy testing based on the frequency outlined above.
- She acknowledges that she understands the hazards and necessary precautions associated with the use of pomalidomide
- She understands never to give pomalidomide to another person and to return any unused capsules to the Investigator each cycle and at the end of treatment.
- She understands not to donate blood during therapy and for at least 4 weeks following discontinuation of pomalidomide.
- She understands and agrees to abstain from breastfeeding while on pomalidomide, and for at least 4 weeks after discontinuation of pomalidomide.

The investigator must verify that females of childbearing potential:

- Comply with the conditions of the PPP, including confirmation that she has an adequate level of understanding
- If pregnancy or a positive pregnancy test does occur in a study patient, pomalidomide must be immediately discontinued.

Counselling for females NOT of childbearing potential

All females NOT of childbearing potential must be counselled concerning the following risks and requirements prior to the start of pomalidomide study therapy:

- She acknowledges that she understands the hazards and necessary precautions associated with the use of pomalidomide
- She understands never to give pomalidomide to another person and to return any unused capsules to the Investigator each cycle and at the end of treatment.
- She understands not to donate blood during therapy and for at least 4 weeks following discontinuation of pomalidomide.

Counselling for male patients

- Traces of pomalidomide have been found in semen. Male patients must be counselled concerning the risks and requirements prior to the start of pomalidomide therapy and at a minimum of every 4 weeks.

The counsellor must verify that the following:

- He understands the potential teratogenic risk if engaged in sexual activity with a pregnant female or female of childbearing potential
- He understands the need for the use of a condom even if he has had a vasectomy, if engaged in sexual activity with a pregnant female or female of childbearing potential.
- He understands the requirement for complete abstinence or condom use during sexual contact with a pregnant female or female of childbearing potential and the potential risks of fetal exposure to pomalidomide
- He understands that if pregnancy or a positive pregnancy test does occur in the partner of a male study patient during study participation, the investigator must be notified immediately.
- He understands never to give pomalidomide to another person and to return any unused capsules to the Investigator each cycle and at the end of treatment.
- He understands he should not donate blood, semen or sperm during therapy or for at least 4 weeks following discontinuation of pomalidomide.

For ALL patients:

Only enough pomalidomide for one cycle of therapy may be dispensed at any given time.

Pomalidomide Education and Counselling Guidance Document

To be completed prior to each dispensing of study drug.

Protocol Number: OP-103 Patient ID:_____

(Check the appropriate box to indicate risk category)
Female: □
If female, check one:

□ FCBP sexually mature female who: 1) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time during the preceding 24 consecutive months)
□ NOT FCBP

Male: □

Do not dispense study drug if:

- **The patient is pregnant.**
- **No pregnancy tests were conducted for a FCBP.**
- **The patient states she did not use TWO reliable methods of birth control (unless practicing complete abstinence of heterosexual contact) [at least 28 days prior to therapy, during therapy and during dose interruption].**

FCBP:
1. I verified that the required pregnancy tests performed are negative.

2. I counseled FCBP regarding the following:

- Potential risk of fetal exposure to pomalidomide: If pomalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby. Females are advised to avoid pregnancy while taking pomalidomide. The teratogenic potential of pomalidomide in humans cannot be ruled out. FCBP must agree not to become pregnant while taking pomalidomide.
- Using TWO reliable methods of birth control at the same time or complete abstinence from heterosexual contact [at least 28 days prior to therapy, during therapy, during dose interruption and 28 days after discontinuation of study drug].
- That even if she has amenorrhea she must comply with advice on contraception.

Use of one highly effective method and one additional method of birth control AT THE SAME TIME. The following are examples of highly effective and additional effective methods of contraception:

- Highly effective methods:
  - Intrauterine device (IUD)
  - Hormonal (birth control pills, injections, implants)
  - Tubal ligation
  - Partner's vasectomy
- Additional effective methods:
  - Male condom
  - Diaphragm
  - Cervical Cap

- Pregnancy tests are required before and during treatment, even if the patient agrees not to have reproductive heterosexual contact. Two pregnancy tests will be performed prior to receiving study drug, one within 10 to 14 days and the second within 24 hours of the start of study drug.

Frequency of pregnancy tests to be done:

- Every week during the first 28 days of this study and a pregnancy test every 28 days during the patient's participation in this study if menstrual cycles are regular or every 14 days if cycles are irregular.
- If the patient missed a period or has unusual menstrual bleeding.
- When the patient is discontinued from the study and at Day 28 after study drug discontinuation if menstrual cycles are regular. If menstrual cycles are irregular, pregnancy tests will be done at discontinuation from the study and at Days 14 and 28 after study drug discontinuation.
- Stop taking study drug immediately in the event of becoming pregnant and to call their study doctor as soon as possible.
- NEVER share study drug with anyone else.
- Do not donate blood while taking study drug and for 28 days after stopping study drug.
- Do not breastfeed a baby while participating in this study and for at least 28 days after study drug discontinuation.
- Do not break, chew, or open study drug capsules.
- Return unused study drug to the study doctor.

3. Provide Pomalidomide Information Sheet to the patient.

Female Not of Childbearing Potential
(Natural menopause for at least 24consecutive months, a hysterectomy, or bilateral oophorectomy):

1. I counseled the female NOT of child bearing potential regarding the following:

- Potential risks of fetal exposure to pomalidomide (Refer to item #2 in FCBP)
- NEVER share pomalidomide with anyone else.
- Do not donate blood while taking pomalidomide and for 28 days after stopping pomalidomide
- Do not break, chew, or open pomalidomide capsules
- Return unused pomalidomide capsules to the study doctor.

2. Provide Pomalidomide Information Sheet to the patient.

Male:

1. I counseled the Male patient regarding the following:
   - Potential risks of fetal exposure to pomalidomide (Refer to item #2 in FCBP).
   - To engage in complete abstinence or use a condom when engaging in sexual contact (including those who have had a vasectomy) with a pregnant female or a female of childbearing potential, while taking pomalidomide, during dose interruptions and for 28 days after stopping pomalidomide.
   - Males should notify their study doctor when their female partner becomes pregnant and female partners of males taking pomalidomide should be advised to call their healthcare provider immediately if they get pregnant.
   - NEVER share pomalidomide with anyone else.
   - Do not donate blood, semen or sperm while taking study drug and for 28 days after stopping pomalidomide.
   - Do not break, chew, or open pomalidomide capsules.
   - Return unused pomalidomide capsules to the study doctor.
2. Provide Pomalidomide Information Sheet to the patient.

Investigator/Counselor Name (Print): _____
(circle applicable)

Investigator/Counselor Signature _____
(circle applicable)

Date __ __/ __ __ / ____

Maintain a copy of the Education and Counseling Guidance Document in the patient records.

Pomalidomide Information Sheet

Please read this Pomalidomide Information Sheet before you start taking pomalidomide and each time you get a new supply. This Pomalidomide Information Sheet does not take the place of an informed consent to participate in clinical research or talking to your study doctor or healthcare provider about your medical condition or your treatment.

What is the most important information I should know about pomalidomide?

For all patients; male and female:

Pomalidomide may cause birth defects (deformed babies) or death of an unborn baby. Pomalidomide is similar to the medicine thalidomide. It is known that thalidomide causes life-threatening birth defects. Pomalidomide has not been tested in pregnant women but may also cause birth defects. Findings from a monkey study indicate that pomalidomide caused birth defects in the offspring of female monkeys who received the drug during pregnancy.

Restrictions in sharing pomalidomide and donating blood:

- Do not share pomalidomide drug with other people. It must be kept out of the reach of children and should never be given to any other person.
- Do not break, chew, or open pomalidomide capsules.
- You will get no more than a 28-day supply of pomalidomide at one time.
- Return unused pomalidomide capsules to your study doctor.
- Do not donate blood while you take pomalidomide and for 28 days after stopping pomalidomide

For females who are able to become pregnant:

You may be able to get pregnant if you have not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or have not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time during the preceding 24 consecutive months)

- Do not take pomalidomide if you are pregnant or plan to become pregnant
- You must practice complete abstinence or use two reliable, separate forms of effective birth control at the same time:
    - for 28 days before starting pomalidomide
    - while taking pomalidomide
    - during dose interruptions of pomalidomide
    - for 28 days after stopping pomalidomide
- You must have pregnancy testing done at the following times:
    - within 10 to 14 days and again 24 hours prior to the first dose of pomalidomide

- weekly for the first 28 days
- every 28 days after the first month or every 14 days if you have irregular menstrual periods
- if you miss your period or have unusual menstrual bleeding
- 28 days after the last dose of pomalidomide (14 and 28 days after the last dose if menstrual periods are irregular)

- Stop taking pomalidomide if you become pregnant during treatment
  - If you suspect you are pregnant at any time during the study, you must stop study drug immediately and immediately inform your study doctor. Your study doctor will report all cases of pregnancy to Oncopeptides, the sponsor of this study and to Celgene, the manufactures of pomalidomide
- Do not breastfeed while taking pomalidomide
- The study doctor will be able to advise you where you can obtain additional advice on contraception

For all males

Pomalidomide is detected in trace quantities in human semen. The risk to the fetus in females of child bearing potential whose male partner is receiving pomalidomide is unknown at this time.

- Male patients (including those who have had a vasectomy) must practice complete abstinence or must use a condom during sexual contact with a pregnant female or a female that can become pregnant:
  - While you are taking pomalidomide
  - During dose interruptions of pomalidomide
  - For 28 days after you stop taking pomalidomide
- Male patients should not donate sperm or semen while taking pomalidomide and for 28 days after stopping pomalidomide.
- If you suspect that your partner is pregnant any time during the study, you must immediately inform your study doctor. The study doctor will report all cases of pregnancy to Oncopeptides and Celgene. Your partner should call their healthcare provider immediately if they get pregnant.

Additional information is provided in the informed consent form and you can ask your study doctor for more information