A PROTOCOL FOR ASSESSING THE EFFICACY OF POMALIDOMIDE IN PATIENTS WITH RELAPSED AND/OR REFRACTORY MULTIPLE MYELOMA

By

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A dissertation submitted in partial fulfillment of the requirements of the University of Thessaly for the degree of Master of Science in Research Methodology in Biomedicine, Biostatistics and Clinical Bioinformatics

The Laboratory of Biomathematics,
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CLINICAL STUDY PROTOCOL

A PHASE 3, MULTICENTER, RANDOMIZED, OPEN-LABEL STUDY TO COMPARE THE EFFICACY OF POMALIDOMIDE AND LOW-DOSE DEXAMETHASONE (Pom/dex) VERSUS HIGH-DOSE DEXAMETHASONE (DEX) IN SUBJECTS WITH RELAPSED AND/OR REFRACTORY MULTIPLE MYELOMA

INVESTIGATIONAL PRODUCT (IP): POMALIDOMIDE (CC-4047), DEXAMETHASONE

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SPONSOR NAME: GENCOM CORPORATION

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SIGNATURE PAGE

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Z. ANAGNOSTOPOULOS, 2015

PROTOCOL ACCEPTANCE PAGE (SITE PRINCIPAL INVESTIGATOR)

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PRICIPAL INVESTIGATOR (NAME, SIGNATURE AND DATE)

TITLE OF INSTITUTION (STUDY SITE):

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1. PROTOCOL SUMMARY

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1.1 Objectives

Primary: to compare progression-free survival in subjects with RRMM who are receiving Pom/dex vs subjects receiving DEX alone in a randomized multicenter setting.
Secondary: to compare the Overall Survival (OS) in subjects with RRMM who are receiving Pom/dex vs subjects receiving DEX alone in a randomized multicenter setting.

1.2 Study design

This is a Phase 3, randomized, open-label, multicenter study comparing two treatment regimens for subjects with RRMM. Eligible subjects will be randomized in a 1:1 ratio to receive either the control DEX or Pom/dex. Randomization will be stratified by β2 microglobulin levels (< vs ≥ 3 mg/L), prior lines of anti-MM treatment (3 vs >3) and subjects' age (≤ vs >75 years). The primary endpoint of this Phase 3 study is progression-free survival. Subjects will receive the treatment determined by randomization in 28-day cycles until disease progression or unacceptable toxicity (whichever occurs first).

Long-term follow-up for disease status and survival will continue until the subject has withdrawn consent for further participation, is lost to follow-up, has died, or the Sponsor makes a decision to close the study.

1.3 Trial population and sample

The trial population will comprise patients with multiple myeloma (MM) who are relapsed or refractory to the following prior therapies:
- IMiDs (Immunomodulatory drugs), e.g. lenalidomide (Revlimid®) ± dexamethasone,
- proteasome inhibitors, e.g. bortezomib (Velcade®) ± dexamethasone,
±autologous stem cell transplantation (ASCT)
Relapse is defined as progression of disease after an initial response to previous treatment, more than six months after cessation of treatment.
Refractory is defined as resistance to treatment due to lack of response or progression of disease during treatment or within six months after cessation of treatment.
The patients must be ≥ 18 years of age.

The patients must have given informed consent before any study related procedures are performed.
The patients must meet all eligibility criteria in chapter 5.
Approximately 250 subjects will be enrolled, in 20 different sites.

1.4 Study treatment
- Control Arm: **High-dose Dexamethasone** 40 mg PO or IV on Days 1-4, 9-12, 17-20.
- Interventional Arm: **Pomalidomide** 4 mg PO on Days 1–21 of a 28 days cycle **and Low-dose Dexamethasone** 40 mg (20 mg for >75 years) PO or IV on Days 1, 8, 15, 22.

1.5 Primary endpoint
Progression-free survival (PFS)

1.6 Secondary endpoint
Overall Survival (OS)

1.7 Statistical methods
The primary efficacy endpoint is PFS, defined as the number of months from randomization to the earlier of disease progression or death due to any cause. The primary analysis of PFS will include all randomized subjects (intention-to-treat population). PFS distribution times will be summarized descriptively using the Kaplan-Meier method. Median PFS will be estimated for each treatment group from the 50th percentile of the corresponding Kaplan-Meier estimates. The primary inferential comparison between treatment groups will use the log-rank test stratified by the randomization stratification factors. The hazard ratio for treatment group will be estimated using a stratified Cox proportional hazards model. A total of 125 progression events will provide 90% power to detect, with a 1-sided significance level of 0.025, a 50% increase in median PFS for the Pom/dex arm vs the DEX arm (3 vs 2 months, respectively).
The distribution of overall survival times will be summarized descriptively using the Kaplan-Meier method. Median overall survival will be estimated for each treatment group from the 50th percentile of the corresponding Kaplan-Meier estimates. The primary inferential comparison between treatment groups will use the stratified log-rank test. The hazard ratio for treatment group will be estimated using a stratified Cox proportional hazards model.

2. BACKGROUND (Disease & Treatment)

2.1 Multiple Myeloma
MM is a plasma cell disorder, characterized by uncontrolled and progressive proliferation of a plasma cell clone. In the majority of patients, the malignant plasma cells produce a monoclonal protein (M protein or paraprotein), which is an immunoglobulin (Ig) or a fragment of one that has lost its normal function. The majority of M proteins are IgG (~50%) and IgA (~20%). The proliferation of myeloma

cells causes displacement of the normal bone marrow. In MM, the major clinical findings include anemia, monoclonal immunoglobulin (M protein) in serum, abnormal bone radiographs (bone resorption seen as diffuse osteoporosis and/or characteristic lytic lesions), hypercalcemia, renal insufficiency or failure, and neurological complications. MM accounts for approximately 1% of all malignancies and 10% of all hematologic malignancies with a higher frequency in African Americans where MM accounts for 20% of all hematologic malignancies (2). In the US, approximately 11,000 deaths each year are related to MM, and the estimated number of new cases of MM is rising from 15,270 in 2004 to 16,500 in 2006, a rise of approximately 8% (3). At present, no cure is available, and the mean survival is approximately 3-5 years, with a 10% 10-year survival.

2.2 Current Treatment of Multiple Myeloma

Current treatments include combination chemotherapy, proteasome inhibitors, immunomodulatory drugs (IMiDs) high dose chemotherapy and stem cell support. Allogeneic transplantation is performed only in a minority of younger patients and its role as treatment modality is not determined.

Combination Chemotherapy:

Chemotherapy includes the use of alkylating agents, such as melphalan and cyclophosphamide, vincristine, antracyclines (e.g. doxorubicin) or lucocorticosteroids or combinations of these. Overall response rates (ORR) are in the range of 20-60%.

Melphalan is an alkylating agent and a derivative of meclorethamine. The main target is doublestranded DNA, and melphalan causes both strand breaks and induces cross-links between the two DNA strands, thus interfering with gene transcription. Melphalan is described to be cell cycle nonspecific, however it is believed that proliferating cells are more susceptible due to less time for DNA repair to occur. Long term side effects include increased risk of developing myelodysplasia, treatment-related acute myeloid leukemia, infections, thrombocytopenia, neutropenia, nausea and alopecia. Furthermore, due to alkylating activity, melphalan should not be administered to patients eligible for transplantation before stem cells are harvested.

The **melphalan/prednisone** (MP) regimen was introduced more than 40 years ago, and a response rate of 65% in treatment naïve patients has been reported (4). However, in the vast majority of cases patients responding to the MP treatment only obtain a partial response (PR). In general melphalan combination regimens have only had limited impact on overall survival (OS). The MP regimen is widely used as 1st line treatment for elderly patients. Additions to the MP regimen seem to have a positive effect on complete response (CR) rates and OS (see below under bortezomib, thalidomide and lenalidomide). Such triplet combination might become standard treatment for elderly patients with myeloma within a few years. In summary, MP is approved and until recently applied as 1st line for elderly patients with some response but no effect on OS, but novel combinations, e.g. MP + thalidomide (MPT) seem to offer improved response rates and survival benefit.

Proteasome inhibitors

Bortezomib (Velcade®) is an anti-neoplastic agent which was approved by the FDA in 2003 (3rd line) and 2005 (2nd line) for relapsed/refractory patients with MM. Response rates of around 30% in relapsed patients have been reported with <3% CR (5). However, AEs occurring in 30-70% of patients include anorexia, constipation,

thrombocytopenia, neutropenia, pyrexia, vomiting, and anemia. Of particular importance, treatment-associated peripheral neuropathy is frequently reported. Recently, bortezomib has been tested in 1st line setting as induction therapy with an ORR of 49%, with no CR (n=43, phase II) (6) and in 2nd and 3rd line settings with an ORR of 70% and CR of 3-12% (Phase III studies of n=624, n=104, and n=333) (7;8), (9). Furthermore, clinical trials with bortezomib in combination with other therapies, including dexamethasone, dexamethasone/doxorubicin, revlimid, and melphalan/prednisone have been conducted. Especially, bortezomib in combination with melphalan/prednisone as 1st line has yielded high response rates of 89% including CR of 32% and a 2-year survival of 86% (n=60, phase I/II) (10). However, high frequencies of side-effects were observed, including thrombocytopenia (51% of the patients), neutropenia (43%) and neuropathy (17%). Recently, combination of bortezomib with thalidomide as 1st line therapy has also yielded high response rates (82%) (n=30), however all patients developed neurological AEs (11). Also, bortezomib in combination with dexamethasone, 1st line, is shown to yield high response rates of 90% with CR/near CR of 19% (n=48, phase II) (12). Additionally, a quadruple combination with bortezomib, MP and thalidomide in 2nd/3rd line has shown high response rates (70-80%) with CR in around 30% of the patients (n=30, phase I/II) (13). However, the high frequency of associated SAEs of grade 3 and 4 such as thrombocytopenia (~30%), neutropenia (~40%) and peripheral neuropathy (~5%) should be noted. In summary, bortezomib is currently used as 2nd and 3rd line therapy for relapsed/refractory patients with MM. Future bortezomib combination regimens are likely to include MP or dexamethasone for 1st line therapy.

Carfilzomib (formerly known as PR-171) is a tetrapeptide epoxyketone-based inhibitor of the chymotrypsin-like activity of the 20S proteasome. Carfilzomib, which is structurally and mechanistically different from the dipeptide boronic acid proteasome inhibitor bortezomib, showed less off-target activity when measured against a broad panel of proteases including metallo, aspartyl, and serine proteases compared to bortezomib; the latter showed off-targetinhibitory activity in the nanomolar range against several serine proteases (29). In addition, carfilzomib is more selective for the chymotrypsin-like protease activity of the proteasome than bortezomib. This selectivity may be responsible for the reductions in myelosuppression and neuropathy observed in preclinical studies comparing carfilzomib with bortezomib. Carfilzomib is approved (in the US) for the treatment of patients with relapsed MM who have received one to three previous lines of therapy, in combination with lenalidomide and dexamethasone.

Thalidomide and analogues (Immunomodulatory Drugs - IMiDs)

Thalidomide has been used as a single agent in the treatment of relapsed patients with MM. Response rate in monotherapy is approximately 30% with a progression-free survival (PFS) in the range of 5 to 9 months (14), (15). In 2006, thalidomide was approved for 1st line treatment in combination with dexamethasone. This combination results in response rates of around 60%, however only very few CRs (4%) were observed and a high frequency of side effects including deep venous thromboembolism (DVT) and neuropathy was reported (n=103, phase III) (16), (17). In particular, the occurrence of neuropathy increases with duration of therapy, an issue which is important for maintenance therapy (18). Thalidomide has now also

been tested in elderly patients in combination with standard MP-regimen, in particular with improved CRs (MPT, 15% vs. MP, 4%) and a 3-year survival of 80% (n=129 and 126 respectively, phase III) (19).

Lenalidomide (Revlimid®) is approved 1st line treatment in combination with dexamethasone. As monotherapy in refractory patients, a response rate of 37% with 10% CR has been reported (20). Severe side effects include thrombocytopenia and neutropenia. Lenalidomide plus dexamethasone versus dexamethasone alone in relapsed patients show increased overall response (59% vs. 23%) with CR of 8-17% vs. less than 3%, and increased overall survival (n=346 in each arm, two phase III studies) (21), (22). In addition this combination has also been tested as 1st line treatment showing an ORR of 91% including 18% CR and a 2-year overall survival of 91% (n=34, Phase II) (23), (24). Lenalidomide is also tested in a 1st line setting as an add-on to MP (MPR) vs. MP alone with a reported RR of 85% including a CR of 23% (n=34, Phase I/II) (25). Interestingly, peripheral neuropathy does not seem to be an issue with lenalidomide – in contrast to thalidomide.

Pomalidomide (Investigational Product) is approved for the treatment of MM in patients who have received at least two prior therapies (including lenalidomide and velcade) and have demonstrated disease progression after the last treatment. Pomalidomide is a novel immunomodulatory drug, which shares some of the beneficial pharmacologic properties of lenalidomide and thalidomide. It has shown a 10-fold higher potency for T-cell stimulation than lenalidomide (30) and is more potent than both lenalidomide and thalidomide in inducing G1 growth arrest and apoptosis in MM cell lines and in patients MM cells that are resistant to melphalan, doxorubicin and dexamethasone, as well as enhancing the antimyelomatic activity of dexamethasone (31). Moreover, pomalidomide does not inhibit the proliferation of normal B cells but rather protects them from apoptosis, assisting the repopulation of normal blood cells (32).

Transplantation

In younger patients, autologous stem cell transplantation (ASCT) has been performed following induction therapy. This resulted in CR rates in the range of 20-40%, (26) and in prolonged OS, i.e. 21% 7-year survival rate, which could be improved if an additional transplantation was performed, especially in patients obtaining less than a very good partial response to the first transplantation (27). ASCT is now used as front line treatment in younger patients and in patients with high performance score. Each year more than 4,000 patients with MM in the US receive a stem cell transplant, thus only offered to approximately 25% of newly diagnosed patients. Allogeneic stem cell transplantation can lead to prolonged disease-free survival in only a small percentage of treated patients, and is associated with high treatment-related morbidity and mortality (28).

3. STUDY OBJECTIVES

3.1 Primary Objective

The primary objective of this study is to compare progression-free survival in subjects with RRMM who are receiving Pom/dex vs subjects receiving DEX alone in a randomized multicenter setting.

3.2 Secondary Objective

The secondary objective of this study is to compare the Overall Survival (OS) in subjects with RRMM who are receiving Pom/dex vs subjects receiving DEX alone in a randomized multicenter setting.

3.3 Primary Endpoint

Progression-free survival (PFS)

The primary endpoint of progression-free survival (PFS) defined as the time from randomization to the date of the first documented disease progression using the EBMT criteria or to death due to any cause.

3.4 Secondary Endpoint

Overall Survival (OS)

Survival is defined as the time from randomization to the date of death. Subjects, who do not die, will be censored at the date of last contact ('last known date alive").

4. STUDY DESIGN

4.1 Overall design

This is a Phase 3, randomized, open label, multicenter study comparing the efficacy of Pom/dex vs DEX in subjects with RRMM.

Eligible subjects will be randomized in a 1:1 ratio to receive a regimen consisting of either lenalidomide and dexamethasone (Rd arm) or carfilzomib, lenalidomide, and dexamethasone (CRd arm). Approximately 780 subjects will be enrolled. The primary endpoint is PFS.

The study population includes subjects with RRMM with at least 2 prior lines of MM therapy, which must include lenalidomide and bortezomib.

The general treatment plan is as follows (and is illustrated in the STUDY SCHEMA - 4.2).

-Interventional (investigational) arm:

(28-day cycle)

Pomalidomide: 4 mg/day PO for days 1-21

Low-Dose Dexamethasone:

40 mg/day (*20 mg for >75 years*) PO or IV on days 1, 8, 15, 22

- Control arm:

(28-day cycle)

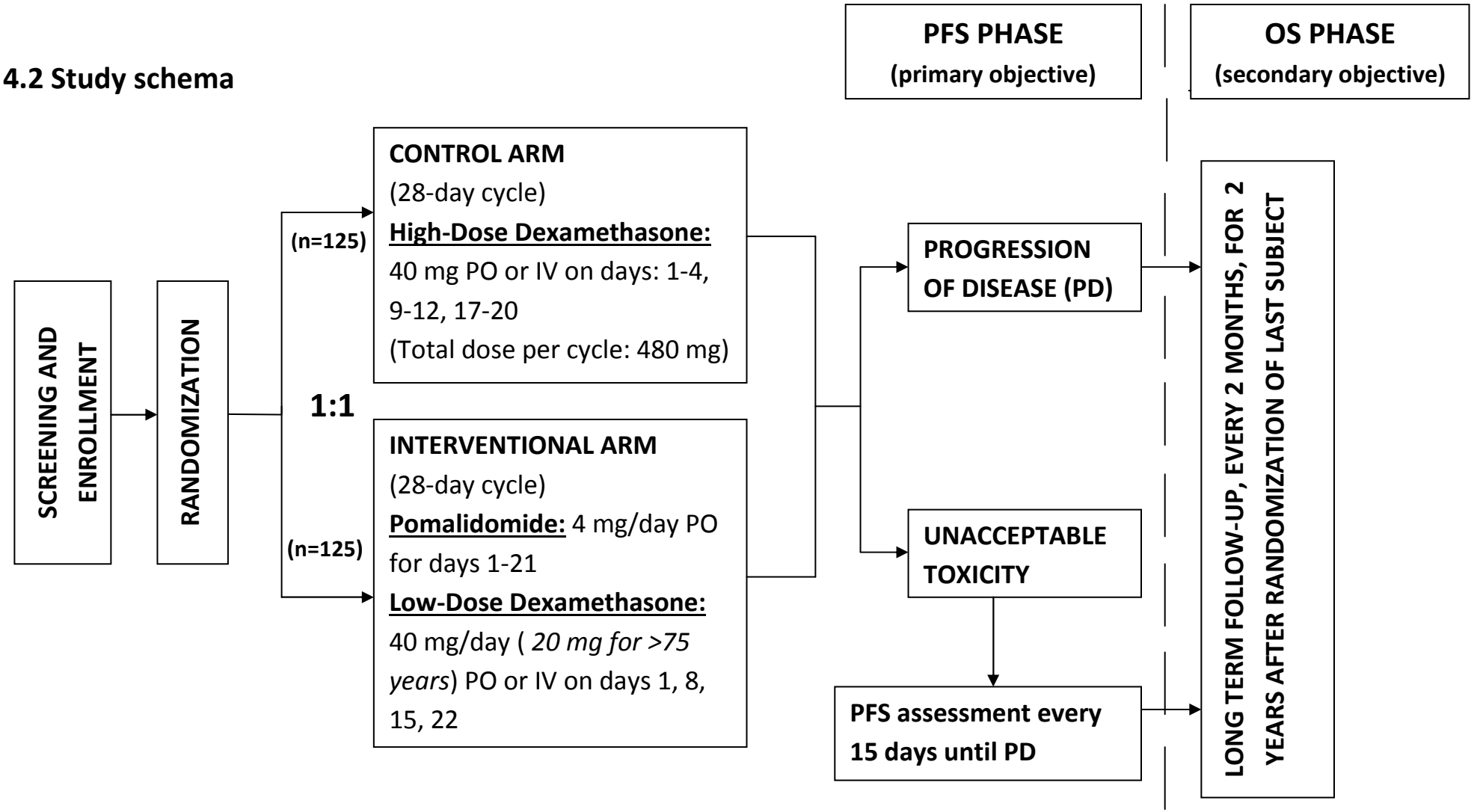
High-Dose Dexamethasone:

40 mg PO or IV on days: 1-4, 9-12, 17-20

Approximately 250 subjects will be enrolled, in 20 different sites in North America and Europe and approximately 125 disease progression events are required.
Subjects will be randomized in a 1:1 ratio to the Pom/dex and DEX arms.
The recruitment, screening and enrollment period is expected to be 12 months.
Subjects will remain on their assigned protocol treatment until disease progression or unacceptable toxicity (whichever occurs first). The patients who discontinued treatment because of toxicity will be assessed twice monthly until disease progression. All patients will go through long-term follow-up to calculate overall survival until a subject has withdrawn consent, is lost to follow-up, has died, or until the Sponsor makes a decision to close the study. Assuming that the last randomized subject has a survival time close to the median expected survival of 9 months for this population, the total study duration including LTFU will be approximately 3.5 years.

INSERT STUDY SCHEMA

4.2 Study schema



4.3 Subject screening

The screening period for a particular subject commences when the subject undergoes the first study-specific screening assessment. Written informed consent must be obtained before any protocol-specific tests or procedures may be conducted. After informed consent is obtained, the following screening assessments will be performed within 21 days before the planned day of randomization unless otherwise stated.

Subjects must have a wash-out period (from any MM treatment) of minimum 21 days prior to randomization.

Subjects who have failed screening because of cytopenias are not allowed to use growth factors to become eligible.

Subject who failed screening will be allowed to be reevaluated for eligibility.

Confirmation of diagnosis, medical history and concomitant medications should also be verified during the screening period.

The start of study treatment dosing is considered as Cycle 1 Day 1. All efficacy assessments should take place on Day 1 of every Cycle (±2 days) for the PFS phase of the study. LTFU will be performed every 2 months (±7 days) for the OS part of the study.

4.4 Subject enrollment and randomization

Each subject enrollment must be approved by the study sponsor or designee before randomization can take place (see separate study manual). Key eligibility criteria must be made available.

Randomization is recognized as an appropriate means to minimize bias in subject selection for efficacy assessment in clinical trials with 2 (or more) treatment arms. The randomization schedule will be prepared using a blocked randomization scheme. A unique subject number will be assigned at the time of randomization that will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

To minimize potential imbalances between groups in subject characteristics that may influence the study results randomization will be stratified by β2 microglobulin levels (< vs ≥ 3 mg/L), prior lines of anti-MM treatment (3 vs >3) and subjects' age (≤ vs >75 years).

4.5 Blinding

As this is an open-label study, there is no blinding for treatment assignment, but any review of the collective data will be performed in a blinded manner.

4.6 Treatment

See chapter 6.

4.7 Long-Term Follow Up

After completion of the PFS phase of the study, subjects will be followed for survival status by telephone contact or other method every 2 months for 2 years from disease progression. Long-term follow-up will continue until the subject has withdrawn consent for further participation, is lost to follow-up, has died, or the Sponsor makes a decision to close the study. For any subject who is lost to follow-up,

the study site will attempt to ascertain survival information via public database search. Informed consent to obtain these data will be obtained from subjects at the time of enrollment.

4.8 Premature Termination of the Trial

If the sponsor, the Lead Principal Investigators, or the Data Monitoring Committee discovers conditions arising during the trial, which indicate that the clinical investigation should be halted, the trial can be terminated after appropriate consultation the aforementioned parts. The Regulatory Authorities and Independent Ethics Committees/Institutional Review Board will be notified in writing. The reason will be stated.

Conditions that may warrant termination of the trial include, but are not limited to the following:

- The discovery of an unexpected and significant or unacceptable risk to the patients enrolled in the trial
- The discovery of lack of efficacy
- Failure of the investigators to enter patients at an acceptable rate in the trial as a whole
- A decision on the part of the Sponsor to suspend or discontinue development of the drug.

5. SUBJECT SELECTION AND WITHDRAWAL

5.1 Number of subjects and study sites.

Approximately 250 subjects will be enrolled (125 in each arm), in 20 different sites in North America and Europe.

5.2 Inclusion criteria

- Age ≥ 18 years when signing the informed consent form (ICF).
- The subject must understand and voluntarily sign the ICF prior to any study related activities.
- Must be able to adhere to the study visit schedule and other protocol requirements
- Subjects must have documented and measurable Symptomatic multiple myeloma.
- Subjects must have had at least 2 prior regimens of anti-MM therapy, including lenalidomide and bortezomib.
- Subjects must have documented relapsed disease during or after their last treatment. Subjects refractory to the most recent line of therapy are also eligible. Relapse is defined as progression of disease after an initial response to previous treatment, more than six months after cessation of treatment. Refractory is defined as resistance to treatment due to lack of response or progression of disease during treatment or within six months after cessation of treatment.
- Platelet count ≥ 50 × 109/L.
- Hemoglobin ≥ 8 g/dL (80 g/L) within 21 days prior to randomization

(subjects may be receiving red blood cell transfusions in accordance

with institutional guidelines).
- Absolute neutrophil count ≥ 1.0 × 109/L within 21 days prior to randomization.
- Life expectancy > 3 months.
- Eastern Cooperative Oncology Group (ECOG) performance status: 0-2.
- Females of childbearing potential must agree to ongoing pregnancy testing and to practice contraception.
- Male subjects must agree to practice contraception.
- All subjects must agree not to share medication.

5.3 Exclusion criteria
- Subjects with severe renal impairment (Creatinine Clearance <30 ml/min).
- Subjects with prior history of malignancies.
- Prior pomalidomide treatment.
- Use of other investigational anti-MM agents 21 days prior to randomization.
- Any condition that would place the subject at unacceptable risk if participated in the study.
- Pregnant or breastfeeding females.
- Discontinuation of previous lenalidomide or dexamethasone treatment due to intolerance.
- Chemotherapy or investigational agent within 3 weeks prior to randomization or antibody therapy within 3 weeks prior to randomization.
- Pregnant or lactating females.
- Acute active infection requiring treatment (systemic antibiotics, antivirals, or antifungals) within 14 days prior to randomization.
- Known human immunodeficiency virus infection.
- Active hepatitis B or C infection.
- Ongoing graft-vs-host disease.
- Any other clinically significant medical disease or condition that, in the Investigator's opinion, may interfere with protocol adherence or a subject's ability to give informed consent.

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and to ensure that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.

5.4 Subject withdrawal (from medicine and/or trial)

A patient should be withdrawn from treatment with investigational drug if at any time:
- It is the wish of the patient (or their legally acceptable representative) for any reason.
- The investigator judges it necessary due to medical reasons.
- Patient becomes pregnant.
- Patient experience a Critical Adverse Event.

A patient should be withdrawn from the study at any time if:
-It is the wish of the patient (or their legally acceptable representative) for any reason.

- The investigator judges it necessary due to medical reasons.
- In case of disease progression.
- The patient receives prohibited therapy or procedures during the study.

6. TREATMENTS

6.1 Treatment Characterization

Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined as follows: A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.
The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.
In this protocol, investigational product is pomalidomide.

Non-investigational Product

Other medications used in the study as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, are considered non-investigational products.
In this protocol, the non-investigational product is dexamethasone.

6.2 Treatment description

Pomalidomide is a potent immunomodulatory drug in the same class as thalidomide and lenalidomide. It has proven antimyelomatic properties in RRMM patients either as monotherapy or in combination with Low-dose dexamethasone (33) regardless of prior lenalidomide and bortezomib treatment (relapsed and refractory) (34).
Pomalidomide will be supplied by the Sponsor as 1, 2, 3, 4, mg capsules for oral administration. It will be packaged in bottles containing 21-day supply (1 cycle) and should be stored as labeled, accessible exclusively to study personnel.

Dexamethasone is commercially available and for this study it will be prescribed to the subjects.

6.3 Treatment administration and Schedule

Subjects randomized to Pom/dex:
Oral pomalidomide, 4 mg/day on days 1-21 out of a 28-day cycle.
Subjects should take their dose as close to every 24h as possible. If the dose is delayed more than 6 hours, it should be skipped and considered missed.

PO or IV Low-Dose Dexamethasone, 40 mg/day (*20 mg for >75 years*) PO or IV on days 1, 8, 15, 22 out of a 28-day cycle.

Subjects randomized to DEX:
PO or IV High-Dose Dexamethasone, 40 mg on days: 1-4, 9-12, 17-20
out of a 28-day cycle.

6.4 Treatment overdose, dose delay and interruption/discontinuation
Overdose, as defined in this protocol, refers to pomalidomide dosing only.
It is defined as any amount over the specified dose or anything more frequently than the required schedule of frequency.

6.5 Dose Delay, Interruption, or Discontinuation
If the dose of one drug in the regimen (ie, pomalidomide or dexamethasone) is delayed, interrupted, or discontinued, the treatment with the other drugs may continue as scheduled.
Subjects experiencing a 28 day delay in all study drugs (pomalidomide and low-dose dexamethasone) due to an adverse event(s) related to study
treatment must be discontinued from study drug. Subjects experiencing delays unrelated to study therapy, for example due to radiation therapy may delay study treatment up to 42 days. Delays greater than 28 days must be discussed with the medical monitor.
Patients are considered still on study therapy even if they continue solely on pomalidomide.

6.6 Dose modifications
Dosing interruption and titration is permitted during the study, Subjects will be evaluated for AEs at each visit. The severity of AEs will be measured. Thus, the dose can be modified if a subject experiences a dose-limiting toxicity (DLT).
Pomalidomide dosing cab be reduced to 1 mg starting from 4 mg, in 1 mg increments.
If an AE is resolved in 28 days, then pomalidomide can be re-initiated at full dose. If not, then the dose should be decreased by one increment.

6.7 Treatment Accountability and Disposal
The study site personnel is responsible for the accountability of pomalidomide and dexamethasone. The investigator will dispense the proper number of each strength tablet to the subject to satisfy dosing requirements until the subject's next visit. The subject must be instructed to return all unused study medications in the provided packaging at each subsequent visit. The investigator is responsible for the inventory of each batch of IP received and for accounting for all IP that is issued to and returned by the subjects during the study. Any remaining IP after the completion of the study, will be counted, documented and destroyed according to standard operating procedure.

7. EFFICACY ASSESSMENTS

7.1 Efficacy assessment

It must be conducted at the same time points for all subjects during their participation in the study in order to accurately compare PFS between the two treatment arms. These assessments include: myeloma paraprotein protein electrophoresis and immunofixation, serum immunoglobulins, serum free light chain assay, serum hematology (hemoglobin), serum chemistry (corrected serum calcium and creatinine) and bone marrow aspirate. They must be performed at the start of each cycle (28 days). Treatment response must be assessed using results from the central study laboratory.

7.2 Response assessment

Starting from the second Cycle, response will be evaluated by the investigators according to the EBMT criteria, using results from central site laboratories, at every Day 1 of every cycle until PD (PFS phase). All treatment discontinuation decisions will be made by treating physicians based on the central laboratory results. In the Long-term follow-up phase (OS phase) subjects will be contacted every 2 months for 2 years after the randomization of the last subject. Survival time, cause of death and any subsequent anti-MM treatments should be recorded on CRFs.

7.3 Definitions of Response Based on EBMT Criteria

Complete Response (CR)/stringent CR (sCR)

A CR requires that all of the following criteria be achieved:

1. Negative immunofixation ("IF") on both serum and urine, maintained for a minimum of 6 weeks and
2. A bone marrow aspirate or biopsy containing < 5% plasma cells. It is not essential to perform a trephine biopsy, but if a biopsy is performed this must also contain <5% plasma cells (although not required for documentation of CR using the EBMT criteria, light chain restriction (flow or IHC for kappa and lambda light chain in the bone marrow should also be assessed to assist in classification of stringent CR using the IMWG criteria)17 and
3. If skeletal survey showed osteolytic bone lesions, there should be no increase in the size or number (development of a compression fracture does not exclude response) and 4. If screening scans showed extramedullary plasmacytomas, complete disappearance of any must be noted.

For assessment of stringent CR, per IMWG criteria, all criteria for CR must be upheld. In addition, bone marrow sample must be assessed for light chain restriction (as mentioned in bullet 2 above) and serum free light chains must be normalized at two time points at least 6 weeks apart, at the time of CR assessment.

Partial Response (PR)

Subjects in whom some, but not all, the criteria for CR are fulfilled are classified as PR, providing the remaining criteria satisfy the requirements for PR. This includes subjects in whom routine electrophoresis is negative but in whom IF has not been performed.

1. Greater than or equal to 50% reduction in serum M-protein, maintained for a minimum of 6 weeks.
2. Reduction of 90% in urinary light chain excretion or a decrease to < 200 mg/ 24 hours, maintained for a minimum of 6 weeks.
3. Greater than or equal to 50% reduction in the size of extramedullary plasmacytomas present at baseline (by radiography or clinical examination using bidimensional measurements).
4. If a skeletal survey is performed, no increase in the size or number of lytic lesions (development of a compression fracture does not exclude response).

Very Good Partial Response (VGPR)

VGPR, a subset of PR, is not formally included in the EBMT criteria but is derived from the IMWG criteria.
Because VGPR is commonly used to measure depth of response in MM, this response must be reported by investigator and IRC and is defined by:
1. Serum and Urine M-protein detectable by immunofixation but not on electrophoresis and that is confirmed in a subsequent assessment OR
2. 90% or greater reduction in serum M-protein plus urine M-protein level < 100 mg per 24 h and that is confirmed in a subsequent assessment.

Minor (Minimal or Marginal) Response (MR)

Subjects who have reduction in M-protein or plasmacytoma but do not meet the criteria for PR are classified as MR if they meet all the following definition:
1. Between 25 - 49% reduction in serum M-protein, maintained for a minimum of 6 weeks.
2. Between 50 - 89% reduction in urinary light chain excretion which still exceeds 200 mg/24 hours, maintained for a minimum of 6 weeks.
3. Between 25 - 49% reduction in the size of extramedullary plasmacytomas.
4. If a skeletal survey is performed, no increase in the size or number of lytic lesions (development of a compression fracture does not exclude response).

Progression of Disease (PD)

Progression: Progression describes a definite increase in disease activity relative to the nadir in 2 consecutive assessments in subjects not in CR, whereas the term “relapse from CR” applies to a recurrence of evident disease in subjects previously in CR. The date of EBMT based disease progression is the first date of two consecutive values fulfilling the criteria for disease progression. Any of the following list is sufficient for PD:
1. Increase of > 25% in serum M-protein (also an absolute increase of at least 5 g/L) and confirmed by at least 1 investigation.
2. Increase of > 25% urinary light chain excretion (which must also be an absolute increase of at least 200 mg/24-hours and confirmed by at least 1 investigation.
3. Increase of > 25% plasma cell percentage in the marrow (which must also be an absolute increase of at least 10%).
4. Definite increase in the size or number of lytic bone lesions or extramedullary plasmacytomas (development of a compression fracture does not exclude continued response and may not indicate progression).

5. Development of hypercalcemia (corrected serum calcium greater than 11.5 mg/dL; 2.8 mmol/L) not attributable to any other cause.

Relapse from CR (for subjects in CR): Subjects who have documented CR and then achieve at least one of the following criteria are classified as relapse from CR. According to the EBMT criteria, relapse from CR is considered to be progression of disease. The date of EBMT based relapse from CR is the first date of two consecutive values fulfilling the criteria for relapse.
1. Reappearance of serum or urinary M-protein on immunofixation or routine electrophoresis, confirmed by at least one further investigation and excluding oligoclonal reconstitution. 2. Greater than or equal to 5% plasma cells in a bone marrow aspirate or on trephine bone biopsy.
3. Any of the definitions met for Progression

Stable Disease/No Change
Does not meet criteria for any of the categories above.

8. MANAGEMENT OF ADVERSE EVENTS

8.1 Adverse events definitions
A treatment-emergent AE is any untoward medical occurrence in a study subject administered an investigational product and that does not necessarily have a causal relationship with this treatment. An unexpected AE is any adverse drug event, the specificity or severity of which is not consistent with the current Investigator's Brochure 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 Investigator's Brochure would be considered "unexpected". An AE, therefore, can be any unfavorable and unintended sign (including clinically significant laboratory finding, as determined by the investigator), symptom, or disease temporally associated with participation in an investigational study, whether or not considered treatment-related. In addition to new events, any increase in the severity or frequency of a preexisting condition that occurs after the subject signs a consent form for participation is considered an AE. This includes any side effect, injury, toxicity, or sensitivity reaction.

8.2 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

8.3 Causality

Using the following criteria, the relationship of the AE to the study drug should be assessed as follows:

Yes: The event is suspected to be related if:

- there is a clinically plausible time sequence between onset of the AE and administration of study treatment; and/or
- there is a biologically plausible mechanism for the study treatment to cause or contribute to the AE; and/or
- the event responds to withdrawal of the study medication (dechallenge) and/or recurs with rechallenge (when clinically feasible); and/or
- the AE cannot be reasonably attributed to concurrent/underlying illness, other drugs, or procedures

No:

- the AE is more likely to be explained by the subject's clinical state, underlying disease, concomitant medication, study or non-study procedure; and/or
- the time of occurrence of the AE is not reasonably related to administration of study treatment; and/or
- the event is unlikely to be related to the investigational product(s)

In the event of a possible drug-related AE, the investigator should reasonably attempt to assess its relationship to Pomalidomide and dexamethasone.

8.4 Adverse events reporting procedures

All AEs (eg, any new event or worsening in severity or frequency of a preexisting condition or laboratory finding) for randomized subjects with an onset date after the subject signs consent for study participation must be promptly documented on the AE CRF. Details of the event must include severity, relationship to study drug, duration, action taken, and outcome. Non-serious AEs will not be recorded for subjects who screen fail. All SAEs will be recorded from the time of informed consent in the CRF for all subjects.

All AEs for randomized subjects will be collected from the time the subject signs informed consent through PD. In addition, the Investigator should report any AE that may occur after this time period that is believed to have a reasonable possibility of being associated with study drug. All AEs that are considered related to study drug must be followed to resolution or stabilization if improvement is not expected. Adverse events which completely resolve and then recur should be recorded as a new AE. For the OS phase, a follow up of ongoing AEs should be attempted by telephone, and documented in the subject's source file. The Principal Investigator is responsible for evaluating all AEs, obtaining supporting documents, and determining that documentation of the event is adequate. Laboratory abnormalities should be recorded as AEs on the CRF only if they require treatment or are otherwise considered clinically significant by the Investigator.

All deaths during PFS phase are to be reported as SAEs.
The corresponding entry for progression-related deaths on the AE CRF should use the verbatim term “Disease Progression” rather than the specific sign or symptom that may have been the immediate cause of death. Additional details of the event (such as the primary and contributory causes of death) should be reported on the Death CRF.

8.5 Serious adverse events definitions
An SAE is one that meets one or more of the following criteria:
- Death
- Life-threatening experience defined as any adverse experience that places the subject, in the view of the Investigator, at immediate risk of death at the time of occurrence; ie, it does not include a reaction that, had it occurred in a more severe form, might have caused death.
- Requires inpatient hospitalization or prolongation of an existing hospitalization (except scheduled hospitalizations for a non-acute, unrelated cause such as an elective surgery)
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect in the offspring of an exposed subject
- Important medical events that may not result in death, be life threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, it jeopardizes the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
Any death occurring within 30 days of the subject receiving study drug—regardless of the subject having discontinued from the study—must be reported to the sponsor as an SAE.

8.6 Serious adverse event reporting and documentation requirements
The Sponsor must be notified of the occurrence of any SAE within 24 hours of the Investigator, designee, or site personnel’s knowledge of the event. To report an SAE, the site representative must complete an SAE form in English and submit to the sponsor as instructed in the separate study manual.
Follow-up reports must be submitted in a timely fashion as additional information becomes available.
The Investigator is responsible for notifying the IRB or IEC in accordance with local regulations, of all SAEs. The sponsor may request additional source documentation pertaining to the SAE to be sent to the Sponsor. If a subject is permanently withdrawn from the study because of a SAE, this information must be included in the initial or follow-up SAE report form as well as the CRF.
The sponsor is responsible for notifying the appropriate global Health Authorities, when required, and in accordance with applicable laws and regulations.
All SAEs occurring from the time that the subject signs consent for study participation through 30 days after the last administered dose of study drug or initiation of new anticancer therapy (whichever occurs first) must be reported. All SAEs regardless of relationship to study drug must be followed to resolution or to stabilization if improvement or resolution is not expected.

9. STATISTICAL METHODS

This section outlines the statistical analysis strategy and procedures for the study

9.1 Sample size determination
Approximately 250 subjects will be enrolled (1:1 randomization) in order to show a 40% increase in median PFS (from 50% median PFS after 2 months in the control arm to 70% in the interventional arm) with a statistical power of 90% and the two-sided statistical significance level at 0.05.

9.2 Populations for Analyses
The intention-to-treat (ITT) population will be the basis for the primary analysis of efficacy in this study, and constitutes all randomized subjects. Subjects in the ITT population will be included in the treatment group to which they were randomized.

9.3 Demographics and Baseline Characteristics
Subject characteristics including demographics, baseline performance status, disease characteristics, and baseline laboratory parameters will be summarized by randomized treatment arm as well as pooled across randomized arms using descriptive statistics.

9.4 Primary Efficacy Analysis
The primary analysis of PFS, will be to compare the two randomized arms via a two-sided, log-rank test stratified by β2 microglobulin levels (< vs ≥ 3 mg/L), prior lines of anti-MM treatment (3 vs >3) and subjects' age (≤ vs >75 years).
Further analysis of PFS will include the computation of hazard ratios and estimation of PFS functions.
The PFS hazard ratio of Pom/dex to DEX will be computed using a stratified Cox proportional hazards model with treatment arm as the sole covariate. The PFS functions for each randomized arm will be estimated using the Kaplan-Meier product-limit method.
Two-sided, 95% confidence intervals for median PFS will be computed by randomized arm. PFS rates at 1, 2, 3, 6 and 12 months will be estimated from the Kaplan-Meier curve. Each analysis will be performed after all subjects had been followed for the given time point estimate (ie, the 2-month PFS rate estimate will be estimated when all subjects have been followed for a minimum of 2 months).
A total of 125 progression events will provide 90% power to detect, with a 1-sided significance level of 0.025, a 50% increase in median PFS for the Pom/dex arm vs the DEX arm (3 vs 2 months, respectively).

9.5 Secondary Efficacy Analysis
Survival will be compared between arms using a stratified group sequential log-rank test procedure. The stratification factors will be the same as those used for the analyses of PFS. The OS function for each randomized arm will be estimated using the Kaplan-Meier method. Two-sided, 95% confidence intervals for median OS will be computed by randomized arm. OS rates at 4, 6, 9 and 12 months will be

estimated from the Kaplan-Meier curve. Each analysis will be performed after all subjects had been followed for the given time point estimate (ie the 8-month OS rate estimate will be estimated when all subjects have been followed for a minimum of 8 months). The hazard ratio for treatment group will be estimated using a stratified Cox proportional hazards model.

9.6 Sub-group analysis

The effect of treatment on the key efficacy variables PFS and OS will be evaluated within subgroups such as:

- Region.
- Age (≤ vs >75 years).
- Gender
- ECOG performance status (0 vs 1 vs 2).
- baseline cytogenetic categories.
- Number of previous anti-MM therapies (3 vs >3).
- Prior ASCT

Additional multivariate analysis on PFS and OS will be carried out to evaluate the treatment effect while adjusting for the aforementioned factors (subgroups).

10. STUDY MANAGEMENT

10.1 Monitoring

Monitoring visits to the trial site will be made periodically during the trial, to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of agreement with data on CRFs. The investigator/institution guarantees direct access to source documents by the Sponsor and appropriate regulatory agencies.

The trial site may also be audited (quality assurance) by the Sponsor as well as inspected by appropriate regulatory agencies.

It is important that the investigator and their relevant personnel area are available during the monitoring visits and possible audits and that sufficient time are devoted to the process.

10.2 Investigational Site Training

The Sponsor will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details and procedure, electronic CRFs, study documentation, informed consent.

10.3 Source documents

Source records are original documents, data, and records (eg, medical records, raw data collection forms, pharmacy dispensing records, recorded data from automated instruments, laboratory data) that are relevant to the clinical study. The Investigator will prepare and maintain adequate and accurate source documents. These

documents are designed to record all observations and other pertinent data for each subject enrolled in this clinical study. Source records must be adequate to reconstruct all data entered into the CRFs. Case report forms will be completed in English.

10.4 Case Report Forms

As part of the responsibilities assumed by participating in the study, the Investigator agrees to maintain adequate case histories for the subjects treated as part of the research under this protocol. The Investigator agrees to maintain accurate electronic CRFs (eCRFs) and source documentation as part of the case histories. These source documents may include subject diaries, laboratory reports, etc. The Sponsor will supply the eCRF, which will be completed in English.

10.5 Data Retention

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by the Sponsor, whichever is longer. The investigator must contact the Sponsor prior to destroying any records associated with the study. The Sponsor will notify the investigator when the study records are no longer needed. If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another investigator, IRB). Notice of such transfer will be given in writing to the Sponsor.

10.6 Data quality assurance

The clinical research associates will visit each study site, at a frequency documented in the monitoring plan, to review (e)CRFs for completeness and accuracy. Any discrepancies found between source documents and completed CRFs will be entered as a discrepancy in the EDC system by the clinical research associate, which will then be addressed by the study site personnel. Uniform procedures for CRF correction (queries) will be discussed at the Investigator meeting, during the study site initiation visits, and will be documented in the study operations manual.

Data from CRFs and other external data sources will be entered into a clinical database as specified in the data management plan. Quality control and data validation procedures will be applied to ensure the validity and accuracy of the clinical database.

10.7 Data Monitoring Committee

A data monitoring committee (DMC) will be charged with monitoring safety and trial conduct throughout the course of this study. The DMC will also review the final efficacy analysis of PFS.

11. REGULATORY OBLIGATIONS

11.1 Compliance with Good Clinical Practice, Laws and Regulations

This Trial Protocol is designed to comply with the Guideline produced by the International Conference on Harmonization (ICH) on the topic Good Clinical Practice (GCP-E6) and published by the European Agency for the Evaluation of Medicinal Products as “Note for Guidance on Good Clinical Practice” (CPMP/ICH/135/95) and in accordance with the general ethical principles outlines in the Declaration of Helsinki. The Investigator will conduct all aspects of this study in accordance with applicable national and local laws of the pertinent regulatory authorities. The study will receive approval from an IRB/IEC prior to commencement.

11.2 Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by the Sponsor. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects. Any significant deviation must be documented in the CRF. If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion
- the Sponsor
- Regulatory Authority(ies), if required by local regulations.

Documentation of approval signed by the chairperson or designee of the RB(s)/IEC(s) must be sent to the Sponsor.

If an amendment substantially alters the study design or increases the potential risk to the subject:

(1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion;

(2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and

(3) the new form must be used to obtain consent from new subjects prior to enrollment.

If the revision is an administrative letter, investigators must inform their IRB(s)/IEC(s).

11.3 Institutional Review Board/Independent Ethics Committee review and approval

Before the initiation of the study, the protocol, the informed consent document and any other appropriate documents will be submitted to the IRB/IEC for approval. If applicable the same documents will also be submitted to the authorities in accordance to legal requirements.

Only after the sponsor receives the approval, can the investigational drug be supplied to a study site. The formal approval by the IRB/IEC should mention the

protocol title, number, amendment number, study site and any other documents reviewed. It must mention the date of the approval decision and signed by a Committee member.

12. COMMUNICATION OF RESULTS AND PUBLICATION POLICY

12.1 Use of Information

All unpublished information relating to this trial and/or to the trial drug is considered confidential by the sponsor and shall remain the sole property of the sponsor.
The investigator must accept that the Sponsor may use the information from this clinical trial in connection with the development of the product, and therefore, may disclose it as required to other investigators, to government licensing authorities, to regulatory agencies of other government, stock exchange market, and commercial partners.

12.2 Publication

The Sponsor acknowledges the investigators right to publish the entire results of the trial, regardless of the outcome.
The International Coordinating Investigator will together with the Sponsor decide on the publication strategy and has the right to publish and present the results and methods as first author of multicenter publications. Co-authorship will be decided by the Sponsor and International Coordinating Investigator and will be limited to a number of persons, who have contributed substantially in the conduct of the trial.
The Sponsor will have representation in the list of authors.
Publications are subject to the following conditions:
- No publication prior to the completion of the trial at all participating sites without written approval from the Sponsor.
- All proposed publications and presentations, including any modifications or amendments shall be submitted to the Sponsor for its review at least 30 days before such presentation or publication is submitted to any third party.
- Publications shall not disclose any Sponsor Confidential Information and Property (not including the trial results, which can be published as described elsewhere in this section).

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14. LIST OF ABBREVIATIONS

AE: Adverse Event
ASCT: Autologous Stem Cell Transplantation
CBC: complete blood count
CR: Complete Response
(e)CRF: (electronic) Case Report Form
dex: Low-dose dexamethasone
DEX: High-dose dexamethasone
DLT: Dose-Limiting Toxicity
DMC: Data Monitoring Committee
EBMT: European Group for Blood and Marrow Transplantation
ECOG: Eastern Cooperative Oncology Group
EDC: Electronic Data Capture
ICF: Informed consent Form
IMiDS: Immunomodulatory Drugs
IMWG: International Myeloma Working Group
IND: Investigational New Drug
I(M)P: Investigational (Medicinal) Product
IEC: Independent Ethics Committee
IRB: Institutional Review Board
IRC: Independent Review Committee
ITT: Intention To Treat
IV: Intravenous
LTFU: Long-Term Follow-Up
(s)MM: (symptomatic)Multiple Myeloma
MP: Melphalan/Prednisolon
MR: Marginal Response
OS: Overall Survival

PD: Progressive Disease
PFS: Progression Free Survival
PO: Per Os
Pom: Pomalidomide
Pom/dex: Pomalidomide in combination with low-dose dexamethasone
PR: Partial Response
RRMM: Relapsed and/or Refractory Multiple Myeloma
SAE: Serious Adverse Event
SPEP: Serum Protein ElectroPhoresis
UPEP: Urine Protein ElectroPhoresis
VGPR: Very Good Partial Response