A Multi-Center Phase 1b/2 Study of Daratumumab with Pomalidomide and Dexamethasone in Combination with All-Transretinoic Acid in Patients with Multiple Myeloma Previously Exposed to Daratumumab-Based Regimens

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SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Signature of Site Principal Investigator	dd mmm yyyy
Printed Name of Site Principal Investigator Institution Name:_____ By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, Institutional Review Board (IRB)/Ethics Committee (EC) procedures, instructions from Janssen representatives, the Declaration of Helsinki, International Council for Harmonisation (ICH) Good Clinical Practices Guidelines, and local regulations governing the conduct of clinical studies.	

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ABBREVIATIONS

ADCC	Antibody-Dependent Cell-Mediated Cytotoxicity
ATRA	All-Trans Retinoic Acid
CDC	Complement Dependent Cytotoxicity
CR	Complete Response
Dara	Daratumumab
Dex	Dexamethasone
DOR	Duration Of Response
FDA	Food and Drug Administration
HDAC	Histone Deacetylase Inhibitors
IMiDs	Immunomodulatory drugs
MRD	Minimal Residual Disease
MM	Multiple Myeloma
nCR	Near Complete Response
Len	Lenalidomide
ORR	Overall Response Rate
PD	Progression of Disease
PR	Partial Response
Pom	Pomalidomide
PFS	Progression Free Survival
PIs	Proteasome Inhibitors
PQC	Product Quality Complaint
sCR	Stringent Complete Response
TOS	Time On Study
TTP	Time To Progression
VGPR	Very Good Partial Response

PROTOCOL SUMMARY

Study Title

A Multi-Center Phase 1b/2 Study of Daratumumab with Pomalidomide and Dexamethasone in Combination with All-Transretinoic Acid in Patients with Multiple Myeloma Previously Exposed to Daratumumab-Based Regimens.

Indication

Relapsed or refractory multiple myeloma (MM) after treatment with Lenalidomide and Daratumumab (LENDara)-based therapy.

Brief Background

Multiple Myeloma (MM) is an incurable plasma cell malignancy affecting 32,000 new patients/year and accounting for over 10,000 deaths in the US annually. Despite new advances in treatment, the disease is still characterized by a relapsing course and is invariably fatal. Nearly all patients with MM relapse eventually and become refractory to treatment. This population is particularly challenging to treat and with low survival rates due to a number of patient- and disease-related factors, including patient comorbidities, biological heterogeneity, and toxicities from prior treatments. For example, patients with MM whose disease develops resistance to bortezomib and Lenalidomide have a median OS of 9 months (Kumar et al, 2012).

Daratumumab (Dara) is a human IgG1-k monoclonal antibody to CD-38 that effectively mediates destruction of CD-38 expressing malignant plasma cells. It was approved by the Food and Drug Administration (FDA) in the United States in November 2015 as a single agent for the treatment of patients with MM who have received at least three prior therapies. CD38 serves not only as an antigen but also as an enzyme that catalyzes the metabolism of cyclic adenosine diphosphate ribose and nicotinic acid adenine dinucleotide phosphate(Lee 2006). Thus representing an important immunotherapy target due to its high expression on malignant plasma cells and low expression on other normal lymphoid and myeloid cells as well as being an important modulator of intracellular signaling (Chillemi et al, 2013).

Dara has been shown to have efficacy in combination with immunomodulatory (IMiD) agents such as lenalidomide (Len) and pomalidomide (Pom). The POLLUX trial was a randomized trial which examined the combination of Dara with Len and dexamethasone (Dex) compared to Len-Dex alone in patients relapsed or refractory multiple myeloma who had ≥ 1 prior therapy. With a median follow-up of 13.5 months, median progression free survival (PFS) had not yet been reached in the triplet combination compared to 18.4 months with Len-Dex alone (HR 0.37; 95% CI: 0.27, 0.52; p<0.0001)(Dimopoulos et al, 2017). Overall response rate (ORR) with Dara-Len-Dex was 91.3%. A phase 2 single arm trial evaluated Dara with Pom and Dex in patients who had received ≥2 prior therapies. Overall response rate was 60% with 13.6% achieving a complete response (CR) or better (Chari et al, 2017).

Factors that determine susceptibility of MM cells to Daratumumab include levels of target antigen CD38 and expression levels of the complement inhibitory proteins CD55 and CD59. Experiments with isogenic MM cell lines expressing different levels of CD38 revealed that the level of CD38 expression is an important determinant of Dara-mediated Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC), and Complement Dependent Cytotoxicity (CDC) (Nijhof et al, 2015). At time of progression, there is a reduced level of CD38 on MM cells, whereas CD55 and CD59 are increased. In a cohort of 102 patients treated with Daratumumab monotherapy, pretreatment levels of CD38 expression on MM cells were significantly higher in patients who achieved at least a partial response (PR) compared with patients who achieved less than PR. CD38 expression was reduced in both bone marrow-localized and circulating MM cells, following the first Daratumumab infusion. CD38 expression levels on MM cells were again increased following Daratumumab discontinuation. In contrast CD55 and CD59 levels were significantly increased on MM cells at the time of progression (Nijhof et al, 2016). These preclinical and clinical data indicate that the downregulation of CD38 and the upregulation of CD55 and CD59 are involved in the development of Dara-resistant multiple myeloma.

All-trans retinoic acid (ATRA) has been shown in both cell lines and primary MM samples to increase CD38 expression levels and also to reduce expression of the complement-inhibitory proteins CD55 and CD59(Nijhof et al, 2015). This resulted in significant enhancement of activity of Daratumumab in vitro and in humanized MM mouse models. Daratumumab and ATRA exhibit a strong synergy in MM cells derived from Dara-naïve patients and from patients with Dara-refractory disease, providing preclinical rationale for further evaluation of Daratumumab combined with ATRA in MM patients. Preliminary data from phase 1 trials combining Daratumumab and ATRA have shown that the combination is safe using ATRA 45 mg/m^2/day dose.[20]

It is our hypothesis that therapy with the addition of ATRA to the combination of Dara and Lenalidomide (Len) or Pomalidomide (Pom) with Dexamethasone (Dex) in patients progressing on Dara plus an IMiD + Dex will result in a significant clinical response. The aim of this study is to determine the ORR of Dara + Pom + Dex + ATRA in patients progressing on Daratumumab + Lenalidomide + Dex and to determine whether this combination is suitable for clinical use and evaluation in subsequent randomized trials. To this end, the ORR of Dara + Pom + Dex in combination with ATRA will be determined for patients relapsing on Dara + Len + Dex or Dara + Pom + Dex.

Objectives

Primary Objectives:

Phase 1b: The primary objective is to determine the safety and tolerability of the combination of Dara + Pom + Dex + ATRA.

Phase 2: To determine the ORR of the combination of Dara + Pom + Dex + ATRA in patients progressing on Dara + Len + Dex

Secondary Objectives:

1) To determine the ORR of the combination of Dara + Pom + Dex + ATRA in patients progressing on Dara + Pom + Dex
2) To determine the best stringent complete response (sCR)/CR/near CR (nCR) and >/= very good partial response (VGPR) rates.
3) To estimate time on study (TOS), duration of response (DOR), time to progression (TTP), progression-free survival (PFS) and overall survival (OS) distributions.
4) To define the toxicity using CTCAE V5 criteria.
5) To evaluate the status of minimal residual disease (MRD) in patients who achieve sCR, CR, or nCR.
6) To determine prognostic factors for PFS and OS.

Exploratory Objectives

1) To identify predictive factors for clinical response to Dara in combination with ATRA, Pom, and Dex.
2) To identify risk factors for Dara in combination with ATRA, Pom, and Dex- induced immune-related adverse events.
3) To correlate immune profiles (baseline, on-treatment, end of treatment, remission or PD) with ORR/PD.
4) To determine if any peripheral blood laboratory values during patient's routine clinical care are associated with ORR/PD or risk for treatment-related adverse events.
5) To correlate molecular profiles (baseline, on-treatment, end of treatment, remission or relapse) with ORR/PD.
6) To identify intestinal microbiota associated biomarkers that predict response and risk for development of treatment-related toxicities at baseline, on-treatment, post-treatment and relapse.

Study Endpoints

Primary Endpoints:

Phase 1b: The number of patients with treatment emergent adverse events (TEAEs) overall and per dose level.

- Patients with DLTs at each dose level.
- Patients with Grade ≥3 TEAEs
- Patient with serious adverse events (SAEs)
- Patients who discontinue because of TEAEs
- Patients with dose modifications (delays, interruptions, dose reductions)
- Clinically significant laboratory values

Phase 2: ORR as defined by IMWG criteria (subjects progressing on Dara + Len + Dex)

Secondary Endpoints:

1) ORR as defined by IMWG criteria (subjects progressing on Dara + Pom + Dex)

2) Rate of CR, sCR, or nCR
3) Rate of VGPR
4) TTP
5) DOR
6) PFS using Kaplan Meier method
7) OS using Kaplan Meier method

Exploratory Endpoints:

Explorative endpoints of samples collected before, during and after treatment with Dara + ATRA, + Pom + Dex and include but are not limited to the following:

1) Gut Microbiome analysis
2) Immune cell subset analyses
3) Analyses of cytokine, chemokine, inflammatory/anti-inflammatory and bacterial translocation markers
4) Basic peripheral blood laboratory variables
5) Genetic and epigenetic profiles

Study Design

This is a multi-institution phase 1b/2 study of ATRA in combination with fixed dose Daratumumab, Pomalidomide and Dex for patients with relapsed multiple myeloma who have progressed on the combination of Dara + Len + Dex. During the dose escalation phase (phase 1b) and after the first cycle, patients who have not experienced a drug-limiting toxicity (DLT), have not shown signs of progressive disease (PD), and in the opinion of the investigator would continue to benefit from additional Dara + Pom + Dex + ATRA may receive additional cycles of treatment (see section 7.4 for details). The phase 2 portion will allow further enrollment at the maximum tolerated dose (MTD) to further evaluate safety and efficacy.

Study Population

Patients with relapsed or refractory multiple myeloma who have progressed on the combination of Dara + Len + Dex or Dara + Pom + Dex. We will include a maximum of 42 patients (among 20-32 subjects previously exposed to Dara + Len + Dex or 10-22 subjects previously exposed to Dara + Pom + Dex).

Length of Study

The overall study duration is expected to be three (3) years, two years for enrollment, one year to complete follow-up.

Treatment Plan

During 28-day treatment cycles, patients will receive Dara 1800 mg subcutaneous (SC) administration at their current dose upon enrollment onto the study depending on their cycle. (If they are on cycles 1-2

then they will receive Dara 1800 mg SC days 1,8,15,22; if they are on cycles 3-6 they will receive Dara 1800 mg SC days 1 and 15; if they are on cycle 7 or beyond they will receive Dara 1800 mg SC on day 1).

Pomalidomide will be administered at the patient's currently tolerated dose (4,3, or 2 mg po daily) on days 1-21. Patients who are progressing on daratumumab + lenalidomide + dexamethasone will start with the 4 mg dose (standard of care starting dose) of pomalidomide.

Dexamethasone will be administered at 40 mg once weekly on days 1,8,15 for patients 75 years old and younger and at 20 mg once weekly on days 1,8,15 for patients older than 75. Patients may stay on their currently administered steroid regimen if it does not match the above.

For the Phase 1b portion, ATRA will be escalated as follows: 35.5 mg/m2/day, then 45mg/m2/day (see section 7.4 for details). The first administration of ATRA will be given in the morning, two days before the scheduled Dara infusion. The last administration of ATRA will be given in the evening of the day that Dara was administered (days -2, -1, and 0; day 0 is the day of Dara infusion).

Treatment repeats every 28 days for at least 8 cycles in the absence of disease progression or unacceptable toxicity. Patients achieving stable disease may continue to receive treatment in the absence of disease progression or unacceptable toxicity.

After completion of the study treatment, patients are followed up at 28 days and then every 3 months for up to 12 months. Subjects will be evaluated for disease response during each cycle and at the end of study.

Key Inclusion Criteria

1. Documented multiple myeloma with prior exposure to an immunomodulatory agent (IMiD), proteasome inhibitor (PI), and monoclonal antibody to CD-38 (CD-38 mo-Ab).
2. Patients must have 2 or more prior lines of therapy.
3. Patients must have been previously exposed to:
    a. Dara+Len+Dex and must have achieved at least stable disease to this combination.
    or;
    b. Dara + Pom + Dex and must have achieved at least stable disease to this combination.
4. Histologically confirmed and relapsed multiple myeloma with measurable disease, defined by at least one of the following:
    a. Serum monoclonal protein ≥0.5 g/dL;
    b. Monoclonal protein in the urine on 24-hour electrophoresis ≥200 mg;
    c. Serum immunoglobulin free light chain (FLC) ≥10 mg/dL (100 mg/L) provided serum FLC ratio is abnormal;
    d. New or progressing biopsy proven plasmacytoma on exam or imaging; or
    e. Bone marrow plasma cells ≥20%;
5. Cycle 1 day 1 of study treatment must be within 3 months of last exposure to Daratumumab.
6. Life expectancy >3 months
7. ECOG PS 0-2
8. Age ≥18

9. Adequate organ function, including bone marrow, renal, hepatic, pulmonary, and cardiac function based on the last assessment performed within the Screening Period, defined as:
    a. Absolute neutrophil count (ANC) ≥1,000/μL;
    b. Platelet count ≥50,000/μL, (≥30,000/μL if bone marrow plasma cells are ≥50% of cellularity);
    c. Hemoglobin ≥7.5g/dL;
    d. Creatinine clearance ≥60 mL/min (assessed as glomerular filtration rate using the Cockcroft-Gault formula);
    e. Alanine aminotransferase or aspartate aminotransferase ≤2.5 x upper limit of normal (ULN);
    f. Total bilirubin ≤1.5 x ULN (except for patients with Gilbert's syndrome confirmed by UGT1A1 mutation);
    g. Left ventricular ejection fraction ≥50% as assessed by echocardiography or multi-gated acquisition (MUGA) scan; and
    h. Must have a minimum level of pulmonary reserve defined as Grade <2 dyspnea and pulse oxygenation ≥92% on room air;
10. Prior to first dose of study drug, a woman must be either:

- Not of childbearing potential: premenarchal; postmenopausal (>45 years of age with amenorrhea for at least 12 months or any age with amenorrhea for at least 6 months and a serum follicle stimulating hormone level >40 IU/L or mIU/mL]); permanently sterilized (eg, bilateral tubal occlusion [which includes tubal ligation procedures as consistent with local regulations], hysterectomy, bilateral salpingectomy, bilateral oophorectomy); or otherwise be incapable of pregnancy
- Of childbearing potential and practicing 2 highly effective methods of birth control at time of informed consent and will continue through study and for at least one month after final dose of study drug. Must be consistent with local regulations regarding the use of birth control methods for subjects participating in clinical studies: e.g., established use of oral, injected or implanted hormonal methods of contraception; placement of an intrauterine device or intrauterine system; barrier methods: condom with spermicidal foam/gel/film/cream/suppository or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository; male partner sterilization (the vasectomized partner should be the sole partner for that subject); true abstinence (when this is in line with the preferred and usual lifestyle of the subject)

    Note: If the childbearing potential changes after start of the study (e.g., woman who is not heterosexually active becomes active, premenarchal woman experiences menarche)
- A woman must begin 2 highly effective methods of birth control, as described above, and must not donate eggs during the study and for at least three months after final dose of study drug.

11. A woman of childbearing potential must have 2 negative serum (β human chorionic gonadotropin) or urine pregnancy tests during screening, the first one within 28 days prior to the first dose of study drug and the second within 24 hours prior to the first dose of study drug.
12. A man who is sexually active with a woman of childbearing potential and has not had a vasectomy must agree to use a barrier method of birth control e.g., either condom with spermicidal foam/gel/film/cream/suppository or partner with occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository, and all men must also not donate sperm during the study and for 3 months after receiving the last dose of study drug.
13. Subjects must be willing and able to adhere to the prohibitions and restrictions specified in this protocol and referenced in the informed consent form (ICF).

Key Exclusion Criteria

1. Major concurrent illness or organ dysfunction
2. Active GVHD requiring systemic corticosteroids in a subject who previously received allogeneic-SCT.
3. Cord compression or CNS involvement
4. Recent/Prior active malignancy requiring active therapy 2 years prior to enrollment excluding non-melanoma skin cancer.
5. Prior life-threatening hypersensitivity to daratumumab or an IMiD
6. Plasma cell leukemia
7. Pregnant or lactating females
8. Men donating sperm during study
9. Seropositive for human immunodeficiency virus (HIV)
10. Seropositive for hepatitis B (defined by a positive test for hepatitis B surface antigen [HBsAg]). Subjects with resolved infection (ie, subjects who are HBsAg negative but positive for antibodies to hepatitis B core antigen [anti-HBc] and/or antibodies to hepatitis B surface antigen [anti-HBs]) must be screened using real-time polymerase chain reaction (PCR) measurement of hepatitis B virus (HBV) DNA levels. Those who are PCR positive will be excluded. EXCEPTION: Subjects with serologic findings suggestive of HBV vaccination (anti-HBs positivity as the only serologic marker) AND a known history of prior HBV vaccination, do not need to be tested for HBV DNA by PCR
11. Seropositive for hepatitis C (except in the setting of a sustained virologic response [SVR], defined as aviremia at least 12 weeks after completion of antiviral therapy)
12. Chronic obstructive pulmonary disease (COPD) with a Forced Expiratory Volume in 1 second (FEV1) less than 50% of predicted normal
13. Moderate or severe persistent asthma within the past 2 years, or uncontrolled asthma of any classification. Note that participants who currently have controlled intermittent asthma or controlled mild persistent asthma are allowed to participate
14. History of prolonged QTc > 480ms or ventricular arrythmia on screening EKG or history of ventricular arrythmiaQTc or ventricular arrhythmia
15. Myocardial infarction within 6 months before randomization, or unstable or uncontrolled disease/condition related to or affection cardiac function (e.g., unstable angina, congestive heart failure, New York Heart Association Class III-IV)
16. Received any prior anti-myeloma therapy within 14 days of planned study treatment

Statistical Considerations:

Brief Statistical Rationale

The phase 1b will estimate the maximum tolerated dose (MTD) by a standard 3+3 design using data collected in the dose escalation phase. MTD will be defined for each dosing level. A maximum of 2 dose levels are planned (35.5 mg/m2/day to 45 mg/m2/day). For phase 1b the number of evaluable patients is planned to be 12.

The phase 2 portion will evaluate the clinical activity of Dara + Pom + Dex + ATRA. A Simon's two-stage minimax design will be used. The null hypothesis that the true response rate is ≤ 30% will be tested against a one-sided alternative of 50% or higher at the one-sided type I error of 0.10 at 80% power. In the first stage, 12 patients will be accrued. If there are 4 or fewer responses in these 12 patients, the study will be stopped due to futility. Otherwise, 16 additional patients will be accrued for a total of 28. The null hypothesis will be rejected if 12 or more responses are observed in 28 patients.

Adverse events (AEs) will be summarized by treatment group and overall. Categorical variables such as ORR will be tabulated by treatment group and overall. Time to event variables will be analyzed using Kaplan-Meier survival curves and Kaplan-Meier medians will be provided.

Statistical Power Calculations

This Simon's two-stage design yields a type I error rate of 0.095 and power of 0.802 when the true response rate is 48%. The probability of early stopping due to futility is approximately 49.2%.

Primary Analysis

After a maximally 42 patients are enrolled in the phase 1b and phase 2 portions combined, a primary interim efficacy analysis and the second safety analysis will be conducted. The subset safety analysis will be also descriptively performed based on the previous exposure groups (Dara + Len + Dex or Dara + Pom + Dex).

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Overall response rate (ORR) and stringent complete response (sCR)/CR/near CR (nCR) according to IMWG criteria will be determined and corresponding 2-sided 80% exact binomial confidence interval will be calculated. The subset ORR analysis will be also performed based on the previous exposure groups (Dara + Len + Dex or Dara + Pom + Dex).

The Kaplan-Meier (KM) method will be used to estimate the time-to-event endpoints such as time on study (TOS), duration of response (DOR), time to progression (TTP), progression-free survival (PFS) and overall survival (OS) distributions. The subset time-to-endpoint outcome analysis will be also performed using the KM method based on the previous exposure groups (Dara + Len + Dex or Dara + Pom + Dex).

Adverse events and tolerability from all subjects who receive at least one dose of study drug will be evaluated for safety and tolerability. Data will be tabulated to examine the frequency.

Study Sites

1. Hackensack University Medical Center - John Theurer Cancer Center - Hackensack, NJ
2. Georgetown-Lombardi Cancer Center - Washington, DC

1. INTRODUCTION

Multiple myeloma (MM) is a rare and incurable progressive neoplastic disease that accounts for 10% of all hematological malignancies. It was estimated that in 2017 30,280 new cases and 12,590 deaths from the disease occurred in the United States (Siegel, 2017; The Cancer Society, 2017). It was estimated in 2016 that 8,700 new cases and 4,200 deaths from the disease occurred in Japan (Cancer Statistics in Japan, 2016).

Multiple myeloma (MM) is typically sensitive to a variety of cytotoxic drugs. Although responses are typically durable, relapse is an expected part of the disease course and MM is not considered curable with current approaches. Treatment of MM has been rapidly evolving with the introduction of new classes and new generation of drugs: immunomodulating drugs (IMiDs), proteasome inhibitors (PIs), monoclonal antibodies, and histone deacetylase (HDAC) inhibitors.

In addition, there is increasing understanding of the tumor biology, creating the rationale of new combination therapies (Anderson, 2011; Hideshima, 2002; NCCN, 2018). In recent years, innovative therapies such as proteasome inhibitors and immunomodulators have improved the prognosis for previously treated MM subjects (Kumar, 2008). However, the disease follows a relapsing course in the majority of patients, regardless of treatment regimen or initial response to treatment. Multiple myeloma remains incurable using conventional treatments, with a median survival duration of approximately 5 years (Richardson, 2007a). Therefore, there is a need for more effective therapeutic options for the treatment of relapsed or refractory multiple myeloma.

Despite new advances in treatment, the disease is still characterized by a relapsing course and is invariably fatal. Nearly all patients with MM relapse eventually become refractory to treatment. This population is particularly challenging to treat and with low survival rates due to a number of patient- and disease-related factors, including patient comorbidities, biological heterogeneity, and toxicities from prior treatments. For example, patients with MM whose disease develops resistance to bortezomib and Lenalidomide have a median OS of 9 months (Kumar et al, 2012).

Daratumumab (Dara) is a human IgG1-k monoclonal antibody to CD-38 that effectively mediates destruction of CD-38 expressing malignant plasma cells. It was approved by the Food and Drug Administration (FDA) in the United States in November 2015 as a single agent for the treatment of patients with MM who have received at least three prior therapies. CD38 serves not only as an antigen but also as an enzyme that catalyzes the metabolism of cyclic adenosine diphosphate ribose and nicotinic acid adenine dinucleotide phosphate(Lee, 2006). Thus, representing an important immunotherapy target due to its high expression on malignant plasma cells and low expression on other normal lymphoid and myeloid cells as well as being an important modulator of intracellular signaling (Chillemi et al, 2013).

Daratumumab has been shown to have efficacy in combination with immunomodulatory (IMiD) agents such as Lenalidomide (Len) and Pomalidomide (Pom). The POLLUX trial was a randomized trial which examined the combination of Dara with Len and Dexamethasone (Dex) compared to Len-Dex alone in patients relapsed or refractory multiple myeloma who had ≥ 1 prior therapy. With a median follow-up of 13.5 months, median progression free survival (PFS) had not yet been reached in the triplet combination

compared to 18.4 months with Len-Dex alone (HR 0.37; 95% CI: 0.27, 0.52; p<0.0001)(Dimopoulos et al, 2016). Overall response rate (ORR) with Dara-Len-Dex was 91.3%. A phase 2 single arm trial evaluated Dara with Pom and Dex in patients who had received ≥2 prior therapies. Overall response rate was 60% with 13.6% achieving a complete response (CR) or better (Chari et al, 2017).

Daratumumab has been evaluated with Pomalidomide and Dexamethasone (Pom-Dex) in patients with relapsed/refractory multiple myeloma with ≥2 prior lines of therapy and who were refractory to their last line of treatment (Chari A, Suvannasankha A, Fay JW, Arnulf B, et al. Blood, 2017). The safety profile of Daratumumab plus Pom-Dex was similar to that of Pom-Dex alone, with the exception of Daratumumab-specific infusion-related reactions (50%) and a higher incidence of neutropenia although without an increase in infection rate. ORR was 60% and was generally consistent across all subgroups, with an ORR of 58% in double refractory patients. At a median follow-up of 13.1 months, the median PFS was 8.8 months and median OS was 17.5 months. The estimated 12-month survival rate was 66% (Ajai et al, 2017).

Factors that determine susceptibility of MM cells to Daratumumab include levels of target antigen CD38 and expression levels of the complement inhibitory proteins CD55 and CD59. Experiments with isogenic MM cell lines expressing different levels of CD38 revealed that the level of CD38 expression is an important determinant of Dara-mediated ADCC and CDC (Nijhof et al, 2015). At time of progression, there is a reduced level of CD38 on MM cells, whereas CD55 and CD59 are increased. In a cohort of 102 patients treated with Daratumumab monotherapy, pretreatment levels of CD38 expression on MM cells were significantly higher in patients who achieved at least a partial response (PR) compared with patients who achieved less than PR. CD38 expression was reduced in both bone marrow-localized and circulating MM cells, following the first Daratumumab infusion. CD38 expression levels on MM cells were again increased following Daratumumab discontinuation. In contrast CD55 and CD59 levels were significantly increased on MM cells at the time of progression (Nijhof et al, 2016). These preclinical and clinical data indicate that the downregulation of CD38 and the upregulation of CD55 and CD59 are involved in the development of Dara-resistant multiple myeloma.

All-trans retinoic acid (ATRA) has been shown in both cell lines and primary MM samples to increase CD38 expression levels and to reduce expression of the complement-inhibitory proteins CD55 and CD59(Nijhof et al, 2015). This resulted in significant enhancement of activity of Daratumumab in vitro and in humanized MM mouse models. Daratumumab and ATRA exhibit a strong synergy in MM cells derived from Dara-naïve patients and from patients with Dara-refractory disease, providing preclinical rationale for further evaluation of Daratumumab combined with ATRA in MM patients. Preliminary data from phase 1 trials combining Daratumumab and ATRA have shown that the combination is safe using ATRA 45 mg/m2/day dose.

It is our hypothesis that therapy with the addition of ATRA to the combination of Dara and Pomalidomide (Pom) with Dexamethasone (Dex) in patients progressing on Dara plus an IMiD + Dex will result in a significant clinical response. The aim of this study is to determine the ORR of Dara + Pom + Dex + ATRA in patients progressing on Daratumumab + Lenalidomide + Dex and to determine whether this combination is suitable for clinical use and evaluation in subsequent randomized trials. To this end, the ORR of Dara +

Pom + Dex in combination with ATRA will be determined for patients relapsing on Dara + Len + Dex or Dara + Pom + Dex.

1.1. Treatment Options for Relapsed or Refractory Multiple Myeloma

The treatments approved for use in relapsed and/or refractory MM are used in combination of or doublets (see NCCN guidelines for multiple myeloma) and currently include the following therapies:

Lenalidomide plus Dexamethasone: Lenalidomide in combination with Dex is approved in the US, Canada, European Union (EU), Japan and many other countries around the world for the treatment of patients with MM (Benboubker, 2014; Dimopoulos, 2007; Weber, 2007).

Bortezomib: Bortezomib monotherapy is approved in the US, Canada, European Union, Japan and many other countries around the world for the treatment of patients with MM (Richardson, 2005).

Pegylated liposomal doxorubicin plus bortezomib: Pegylated liposomal doxorubicin in combination with BTZ is approved in the US for the treatment of patients with MM who have not previously received BTZ and have received at least one prior therapy (Orlowski, 2007).

Carfilzomib: Carfilzomib is a proteasome inhibitor that is indicated in the US, Canada, Japan and many other countries around the world in combination with Dexamethasone or with Lenalidomide plus Dexamethasone for the treatment of patients with relapsed or refractory multiple myeloma who have received one to three lines of therapy. Carfilzomib is also indicated as a single agent in the US for the treatment of patients with relapsed or refractory MM who have received one or more lines of therapy (Berenson, 2012a; Siegel, 2012).

Pomalidomide: Pomalidomide is approved in the US, Canada, Japan and many other countries around the world for the treatment of patients with MM who have received at least two prior therapies including Lenalidomide and a proteasome inhibitor and have demonstrated disease progression on or within 60 days of completion of the last therapy (Pomalidomide, 2018).

Ixazomib: Ixazomib is a proteasome inhibitor approved in the US and other countries including Japan in combination with Lenalidomide and Dexamethasone for the treatment of patients with multiple myeloma who have received at least 1 prior therapy (Ixazomib, 2015).

Elotuzumab: Elotuzumab is a SLAMF7-directed immunostimulatory antibody approved in the US, EU and other countries including Japan in combination with Lenalidomide and Dexamethasone for the treatment of patients with multiple myeloma who have received one to three prior therapies (Elotuzumab, 2015).

Daratumumab: Daratumumab is a CD38-directed cytolytic antibody approved in the US, EU, Japan and many other countries in combination with Lenalidomide and Dexamethasone, or bortezomib and Dexamethasone for the treatment of patients with MM who have received at least one prior therapy. Daratumumab is approved in the US and EU with bortezomib, melphalan and prednisone for the treatment of patients with newly diagnosed MM who are ineligible for autologous stem transplant. Daratumumab is also approved in the US in combination with Pomalidomide and Dexamethasone for the treatment of patients with MM who have received at least two prior therapies including Lenalidomide

and a proteasome inhibitor and as monotherapy and as a monotherapy for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent (Daratumumab, 2018). In this setting Daratumumab is considered investigational.

Panobinostat: Panobinostat is a histone deacetylase inhibitor, approved in the US and many other countries in combination with bortezomib and Dexamethasone is indicated for the treatment of patients with MM who have received at least two prior regimens, including bortezomib and in immunomodulatory agent (Panobinostat, 2015).

The main considerations for choosing an appropriate treatment for relapsed MM are: patient comorbidities, risk status, prior therapy, duration of response to prior therapy, residual toxicity, age, physical condition, and whether or not the patient is a candidate for allogeneic stem cell transplantation (Kastritis, 2009; NCCN, 2016).

1.2. Daratumumab

Daratumumab, is a human IgG1k anti-CD38 monoclonal antibody. CD38 is a transmembrane receptor with enzymatic activity that is highly and consistently expressed on the surface of myeloma cells (Deaglio, 2007). CD38 is involved in signal transduction for lymphoid and myeloid cells and presents a therapeutic target in MM because of low levels of expression on other hematologic and nonhematologic tissues. Daratumumab induces directed cell killing through complement dependent cytotoxicity, antibody-dependent cell cytotoxicity, and other potential mechanisms (Lokhorst, 2015).

Results from multiple studies conducted thus far including two phase III studies (Janssen - POLLUX MMY3003 and CASTOR MMY3004) indicate that Daratumumab has activity in patients with relapsed and/or refractory MM, including patients who are refractory to LEN and BTZ.

Confirmed response rates range between 29% and 36% for DARA monotherapy and for the Japanese participants response rates are 44%. Confirmed response rates range between 83% and 92% in combination therapy with LEN or BTZ and for Japanese patient population, the combination response rates range from 45% to 100%. The response rate for Daratumumab in combination with Pom-Dex is 60% (Chari A, et al, Blood 2017). The most common hematological toxicity experience by subjects across all studies were thrombocytopenia and neutropenia, which can be managed by dose reductions or interruptions. The most common non-hematological toxicities are pneumonia and infusion related reactions.

1.3. Pomalidomide

Pomalidomide (POM) (CC-4047, 4-amino-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione) is a novel immunomodulatory drug under development for the treatment of MM. Pomalidomide shares a number of the beneficial pharmacologic properties of thalidomide and LEN. An in vitro model of anti-tumor necrosis factor (TNF) activity has shown that Pomalidomide has a half maximal inhibitory concentration (IC50) of approximately 0.013 µM (13 nM) against TNF produced by lipopolysaccharide (LPS)-stimulated human peripheral blood mononuclear cells.

Thalidomide and LEN, by comparison, have an IC50 of ~194 µM and 0.10 µM (100 nM), respectively (Corral, 1999; Muller, 1999). In LPS-stimulated human whole blood, IC50 for Pomalidomide is 0.025 µM (25 nM) (Muller, 1999). In addition, Pomalidomide has demonstrated a 10-fold higher potency for T-cell co-stimulation than LEN (Corral, 1999; Teo, 2005). Pomalidomide also augmented the activity of natural killer cells and enhanced antibody-dependent cell-mediated cytotoxicity of targeted tumor cells in combination with therapeutic antibodies to tumor-specific surface antigens (Hayashi, 2005; Hernandez-Ilizaturri, 2005). Moreover, Pomalidomide is also a potent inhibitor of the proliferation of MM cell lines in vitro. Concentrations of 2.73 to 27.3 ng/mL (0.01 to 0.1 µM) achieved a 50% inhibition of MM.1S and Hs Sultan cell proliferation. In contrast, at concentrations of 25.8 µg/mL (100 µM), thalidomide inhibited the proliferation of MM.1S and Hs Sultan cells by only 15% and 20%, respectively. Pomalidomide is also more potent than thalidomide or LEN in inducing G1 growth arrest and apoptosis in MM cell lines and in patient MM cells that are resistant to melphalan, doxorubicin, and Dex as well as in enhancing the anti-MM activity of Dex (Hideshima, 2000). However, Pomalidomide does not inhibit the proliferation of normal B cells but rather protects them from apoptosis, suggesting an additive property of this compound in helping the repopulation of the normal blood cells (Verhelle, 2007).

Of potential relevance to the refractory MM setting, Pomalidomide appears to retain antiproliferative activity against H929 and KMS-12-BM MM cells that have increased resistance to acute LEN treatment following chronic exposure to LEN (Adams, 2009; Rychak, 2011a). Pomalidomide and Dex were also synergistic at inhibition of cell proliferation in LEN-resistant cell lines. Preliminary results from an in vitro experiment performed by the Janssen Research group (Adams, 2009; Rychak, 2011a) demonstrate that MM cells treated long-term with LEN plus Dex and with POM + Dex became resistant to LEN/Dex but retained their sensitivity to POM/Dex. This suggests that the combination of POM + Dex may be useful in the treatment of MM that is refractory to LEN + Dex.

The results of studies conducted thus far, including 3 phase II clinical trials and one phase III (Janssen – CC-4047-MM-003) indicate that Pomalidomide has activity in patients with relapsed and/or refractory MM, including patients who are refractory to LEN and BTZ.

Confirmed response rates range between 30% and 60% at POM doses of between 2 and 4 mg/day in combination with Dex. Notably, Pomalidomide produces responses in subjects who are refractory to LEN, another IMiDs® compound, aligning with the nonclinical results observed in LEN-resistant cells (Adams, 2009; Rychak, 2011a). The most common hematological toxicity experienced by these subjects is neutropenia (non-febrile), which can be managed by dose reductions or interruptions. The most common non-hematological toxicities are fatigue and pneumonia.

1.4. All-Trans Retinoic Acid (ATRA)

All-Trans Retinoic Acid (ATRA) is a derivative of Vitamin A that functions as a ligand for the retinoic acid receptor (RAR, IC_{50} = 14 nM). RARs heterodimerize with retinoid X receptors (RXRs) and bind to retinoic acid response elements (RAREs) in DNA and act as transcription factors, altering gene expression. (Apfel et al., Chambon). ATRA has a number of effects on pluripotent stem cells and embryonic cells. It promotes differentiation of motor neurons from mouse and human pluripotent stem cells and promotes terminal differentiation fo granulocytes (Dimos et al., Wichterle et al, Collins et al).

All-trans retinoic acid induces complete remission in acute promyelocytic leukemia (APL), a subtype of leukemia in which a balanced reciprocal translocation between chromosomes 15 and 17 results in the union of the promyelocytic leukemia gene with the gene for retinoic acid receptor alpha. This chimeric gene encodes the promyelocytic leukemia-retinoic acid receptor alpha fusion protein (de The H, Chomienne et al, 1990). Although 65-80% of patients with APL have a complete remission with standard chemotherapy (Kantarjian et al, 1986), 10-20% die either before or during chemotherapy of bleeding attributable to disseminated intravascular coagulation, fibrinolysis, and proteolysis (Cordonnier et al, 1985) . All-*trans*-retinoic acid differentiates leukemic promyelocytes into mature cells (Chomienne et al, 1990) . All *trans* retinoic acid plus chemotherapy is shown to be superior to chemotherapy alone in patients with APL (Martin et al, 1997). Of the 174 patients treated with chemotherapy, 120 (69 percent) had a complete remission, as did 124 of the 172 (72 percent) given all-*trans*-retinoic acid (P = 0.56). By intention-to-treat analysis, the rates of overall survival at one, two, and three years after entry into the study were 75, 57, and 50 percent, respectively, among patients assigned to chemotherapy, and 82, 72, and 67 percent among those assigned to all-*trans*-retinoic acid (P = 0.003).

A series of in vitro studies suggests that ATRA may have an inhibitory effect on the proliferation of myeloma cells both by the downregulation of interleuki-6 receptor and/or its signal transducer glycoprotein 130 (gp130) surface expression on neoplastic cells and by inhibition of IL-6 production by myelomatous stromal cells. (Pgata et al, 1994) . Other in vitro studies, also suggesting an inhibitory effect on myeloma cell proliferation, showed that ATRA affects myeloma cell growth via a mechanism distinct from IL-6 modulation (Siegel et al, 1992) . A pilot study was conducted using single agent ATRA in 24 patients with relapsed refractory or resistant multiple myeloma after 3 prior lines including melphalan, prednisone, intermediate-dose cyclophosphamide, anthracyclines or their analogues (Musto et al, 1005) . There were no serious adverse events observed. In 3 patients administration of the drug was stopped after 12-21 days because of nausea, vomiting, or volumetric increase of skin verrucae). The remaining patients received ATRA for at least 2 months without significant toxicity. Although the clinical data do not encourage the use of ATRA as a single agent, its therapeutic role in combination with other agents, more specifically Daratumumab, remains to be elucidated.

1.5. ATRA in combination with Daratumumab

Although Daratumumab is an effective treatment for patients with relapsed or refractory multiple myeloma, some patients do not respond to the treatment, and many patients who do respond will eventually develop resistance to the drug.

Nijhof et al analyzed CD38 expression of multiple myeloma cells taken from 102 patients prior to undergoing treatment with 16 mg/kg Daratumumab as part of a phase II clinical trial. All myeloma cells expressed CD38, but expression levels varied greatly among patients. Thirty of the 102 patients achieved a partial response or better. Among those patients, baseline CD38 expression was significantly greater compared with patients who achieved less than partial response. Those patients with the highest levels of CD38 expression on their tumor cells had better response to Daratumumab compared with those patients with the lowest levels of expression (partial response or better, 48.5% vs 18.2%).

Furthermore, the CD38 levels on multiple myeloma cells were similar in patients with or without double-refractory (Lenalidomide and bortezomib refractory), triple-refractory (Lenalidomide,

bortezomib, and either Pomalidomide or carfilzomib refractory), or quadruple refractory disease (Lenalidomide, Pomalidomide, bortezomib, and carfilzomib refractory). Cell surface expression of the complement-inhibitory proteins CD46, CD55 and CD59 on pre-treatment myeloma cells was not associated with response to Daratumumab.

Peripheral blood and bone marrow aspirate myeloma cells were evaluated in a subset of 21 patients and it was determined that CD38 expression was reduced 14 weeks after the first infusion of Daratumumab. At time of progression from Daratumumab, CD38 expression was significantly reduced in myeloma cells. However, expression in myeloma cells increased again approximately 6 months after the drug was discontinued. In contrast, CD55 and CD59 levels were significantly increased on myeloma cells only at the time of disease progression. Thus, reduced CD38 expression and increased CD55/CD59 expression, as well as other tumor-related and tumor microenvironment factors, is associated with acquired resistance to Daratumumab. ATRA, which has been shown to increase CD38 expression and decrease CD55 and CD59 expression may have the potential to reverse resistance, or resensitize, to Daratumumab.

1.6. ATRA in combination with Daratumumab, pomalidomide, and dexamethasone

In the phase 2 single arm study, the response rate of the combination of daratumumab in combination with pomalidomide and dexamethasone was 60%. However, all patients eventually progressed with a median PFS of 8.8 months with a median follow-up of 13.1 months with a median overall survival of 17.5 months (Chari A et al, Blood, 2017). There is a marked heterogeneity of response with 40% of patients achieving less than stable disease to this regimgen. Mechanisms of resistance to the combination of daratumumab + pomalidomide + dex are poorly understood. It is hypothesized that it is a combination of loss of CD38 expression as well as host- and tumor-related factors.

An improved understanding of mechanisms that may contribute to innate or acquired resistance may result in the rational design of new daratumumab plus pomalidomide-based combinations with higher antimyeloma activity. All-trans retinoic acid (ATRA) has been shown in mice models even in IMID and daratumumab-refractory myeloma to improve daratumumab-mediated antibody-dependent cell mediated cytotoxicity (ADCC) and complement mediated cytotoxicity (CDC). Furthermore, in the subgroup of cell lines refractory to IMiDS and daratumumab, ATRA reduced the expression of the complement inhibtiors CD55 and CD59 on myeloma cells, thereby further enhancing daratumumab-mediated CDC (Nijhof IS e tal, Leukemia, 2015).

Thus, we intend to evaluate the combination of ATRA with daratumumab, pomalidomide, and dexamethasone in patients progressing on daratumumab + IMiD. The hypothesis is that sensitivity to the CD38-mo-Ab, IMiD, dex combination will be restored.

2. STUDY OBJECTIVES

Primary Objectives:

Phase 1b: To determine the safety and toxicity profile of the combination of Dara + Pom + Dex + ATRA.

Phase 2: To determine the ORR of the combination of Dara + Pom + Dex + ATRA in patients progressing on Dara + Len + Dex

Secondary Objectives:

1) To determine the ORR of the combination of Dara + Pom + Dex + ATRA in patients progressing on Dara + Pom + Dex
2) To determine the best stringent complete response (sCR)/CR/near CR (nCR) and >/= very good partial response (VGPR) rates.
3) To estimate time on study (TOS), duration of response (DOR), time to progression (TTP), progression-free survival (PFS) and overall survival (OS) distributions.
4) To define the toxicity using CTCAE V5 criteria.
5) To evaluate the status of minimal residual disease (MRD) in patients who achieve sCR, CR, or nCR.
6) To evaluate prognostic markers and markers of response to the combinations in patients by analyzing pre and post-treatment clinical covariates and immune cell subsets as well as gene expression profiling.
7) To determine prognostic factors for PFS and OS.

Exploratory Objectives

1) To identify predictive factors for clinical response to Dara in combination with ATRA, Pom, and Dex.
2) To identify risk factors for Dara in combination with ATRA, Pom, and Dex- induced immune-related adverse events.
3) To correlate immune profiles (baseline, on-treatment, end of treatment, remission or PD) with ORR/PD.
4) To determine if any peripheral blood laboratory values during patient's routine clinical care are associated with ORR/PD or risk for treatment-related adverse events.
5) To correlate molecular profiles (baseline, on-treatment, end of treatment, remission or relapse) with ORR/PD.
6) To identify intestinal microbiota associated biomarkers that predict response and risk for development of treatment-related toxicities at baseline, on-treatment, post-treatment and relapse.

3. STUDY ENDPOINTS

Primary Endpoints:

Phase 1b: The percentage of patients with treatment emergent adverse events (TEAEs) overall and per dose level.

- Patients with DLTs at each dose level.
- Patients with Grade ≥3 TEAEs
- Patient with serious adverse events (SAEs)
- Patients who discontinue because of TEAEs
- Patients with dose modifications (delays, interruptions, dose reductions)
- Clinically significant laboratory values

Phase 2: ORR as defined by IMWG criteria (subjects progressing on Dara + Len + Dex)

Secondary Endpoints:

1) ORR as defined by IMWG criteria (subjects progressing on Dara + Pom + Dex)
2) Rate of CR, sCR, or nCR
3) Rate of VGPR
4) TTP
5) DOR
6) PFS using Kaplan Meier
7) OS using Kaplan Meier

Exploratory Endpoints:

Explorative endpoints of samples collected before, during and after treatment with Dara + ATRA, + Pom + Dex and include but are not limited to the following:

1) Gut Microbiome analysis
2) Immune cell subset analyses
3) Analyses of cytokine, chemokine, inflammatory/anti-inflammatory and bacterial translocation markers
4) Basic peripheral blood laboratory variables
5) Genetic and epigenetic profiles

4. OVERALL STUDY DESIGN

4.1. Study Design

This is a multicenter, open label study of Dara+Pom+Dex combined with ATRA in patients progressing on a Dara+Len+Dex regiment. The study is expected to enroll up-to a maximum of 42 patients (20-32 subjects previously exposed to Dara + Len + Dex; 10-22 subjects previously exposed to Dara + Pom + Dex)..

The phase 1b portion will follow a standard 3+3 dose escalation design with two dose levels and up to 12 patients. Under this design, the investigators will evaluate dose levels as follows:

- Dose level 1 - ATRA 35.5 mg/m2/day on days -2,-1 and 1 on a 28-day cycle in combination with daratumab, pomalidomide, and dexamethasone
- Dose level 2 – ATRA 45 mg/m2/day on days -2,-1 and 1 on a 28-day cycle in combination with daratumab, pomalidomide, and dexamethasone

During the dose-escalation phase and after the first cycle, and after the first cycle, patients who have not experienced a DLT, have not shown signs of PD, and in the opinion of the investigator would continue to benefit from treatment may receive additional cycles of treatment.

The phase 2 portion will be conducted in two stages. In the first stage, 10 patients will be accrued. A safety and efficacy analysis will be conducted 3 months after accrual of the first 10 patients. If there are 2 or fewer responses in these 10 patients, the study will be stopped due to futility. If the stopping rules for safety are met, then the study will be stopped due to toxicities. Otherwise, accrual will continue for a maximum of 42 in phase 1b and phase II combined.

During 28-day treatment cycles, patients will receive Dara 1800 mg subcutaneous (SC) at their current dose upon enrollment onto the study depending on their cycle. (If they are on cycles 1-2 then they will receive Dara 1800 mg SC days 1,8,15,22; if they are on cycles 3-6 they will receive Dara 1800 mg SC days 1 and 15; if they are on cycle 7 or beyond they will receive Dara 1800 mg SC on day 1).

Pomalidomide will be administered at the patient's currently tolerated dose (4,3, or 2 mg po daily) on days 1-21. For patients progressing on daratumumab, lenalidomide, and dexamethasone, the starting dose of pomalidomide will be 4 mg per standard of care.

Dexamethasone will be administered at 40 mg once weekly on days 1,8,15 for patients 75 years old and younger and at 20 mg once weekly on days 1,8,15 for patients older than 75. Patients may stay on their currently administered steroid regimen if it does not match the above.

ATRA will be administered in a divided dose of twice daily as an oral formulation at 35.5 mg/m2/day for the phase 1b portion, then escalated to 45mg/m2/day for 3 days. The first administration of ATRA will be given in the morning, two days before the scheduled Dara infusion. The last administration of ATRA will

be given in the evening of the day that Dara was administered (days -2, -1, and 0; day 0 is the day of Dara infusion).

Treatment repeats every 28 days for at least 8 cycles in the absence of disease progression or unacceptable toxicity. Patients achieving stable disease may continue to receive treatment in the absence of disease progression or unacceptable toxicity.

After completion of the study treatment, patients are followed up at 28 days and then every 3 months for up to 12 months. Subjects will be evaluated for disease response during each cycle and at the end of study.

Adverse events (secondary endpoint) will be recorded and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) (Version 5).

Tumor response, based on the investigator's assessment, will be evaluated according to the International Myeloma Working Group (IMWG) response criteria (Durie, 2006) and will be modified (mIMWG) to add criteria for MR (Kyle, 2009) (per Appendix B).

The phase 1b portion will estimate the maximum tolerated dose (MTD) by a standard 3+3 design using data collected in the dose escalation phase. MTD will be defined for each dosing level. A maximum of 2 dose levels are planned (35.5 mg/m2/day to 45 mg/m2/day). For phase 1b the maximum number of evaluable patients is planned to be 12.

The phase 2 portion will evaluate the clinical activity of Dara + Pom + Dex + ATRA. A Simon's two-stage minimax design will be used.

Analysis of biomarkers will also be explored in subjects who consent to participate in the exploratory biomarker study.

All subjects will be maintained on the Pomalidomide pregnancy prevention program (Appendix D) for the duration of the study.

For all subjects who enroll into this study, study visits and serial measurements of safety and efficacy will be performed as outlined in Table 1, Table of Events. The overall study design is depicted in Figure 1.

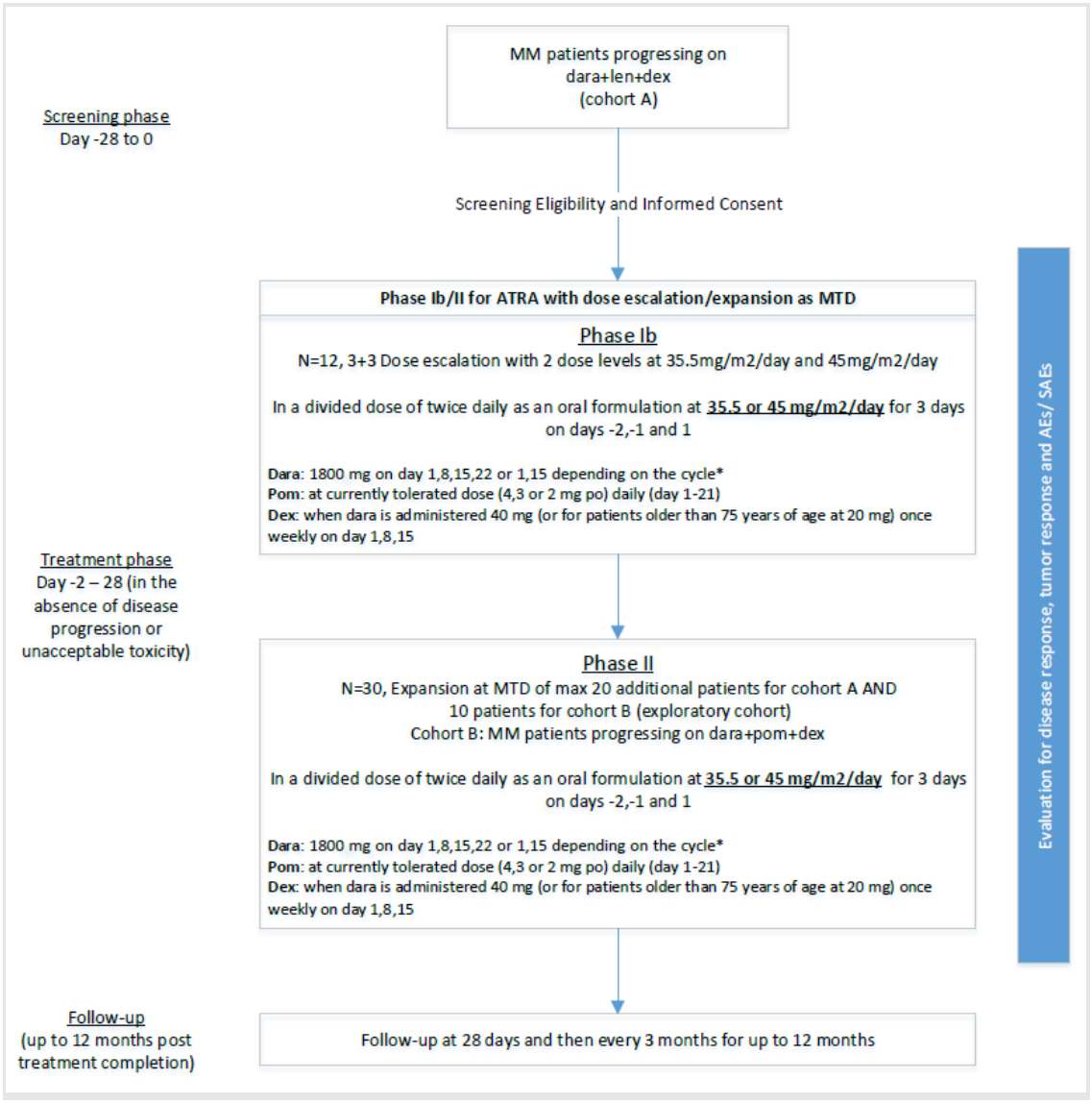
MM patients progressing on dara+len+dex (cohort A)
Screening phase
Day -28 to 0
Screening Eligibility and Informed Consent
Phase Ib/II for ATRA with dose escalation/expansion as MTD
Phase Ib
N=12, 3+3 Dose escalation with 2 dose levels at 35.5mg/m2/day and 45mg/m2/day
In a divided dose of twice daily as an oral formulation at 35.5 or 45 mg/m2/day for 3 days on days -2,-1 and 1
Dara: 1800 mg on day 1,8,15,22 or 1,15 depending on the cycle*
Pom: at currently tolerated dose (4,3 or 2 mg po) daily (day 1-21)
Dex: when dara is administered 40 mg (or for patients older than 75 years of age at 20 mg) once weekly on day 1,8,15
Treatment phase
Day -2 – 28 (in the absence of disease progression or unacceptable toxicity)
Phase II
N=30, Expansion at MTD of max 20 additional patients for cohort A AND 10 patients for cohort B (exploratory cohort)
Cohort B: MM patients progressing on dara+pom+dex
In a divided dose of twice daily as an oral formulation at 35.5 or 45 mg/m2/day for 3 days on days -2,-1 and 1
Dara: 1800 mg on day 1,8,15,22 or 1,15 depending on the cycle*
Pom: at currently tolerated dose (4,3 or 2 mg po) daily (day 1-21)
Dex: when dara is administered 40 mg (or for patients older than 75 years of age at 20 mg) once weekly on day 1,8,15
Evaluation for disease response, tumor response and AEs/ SAEs
Follow-up
(up to 12 months post treatment completion)
Follow-up at 28 days and then every 3 months for up to 12 months

Figure 1: Overall study design

Table 1: Table of events

	SCREENING	CYCLE 1					CYCLE 2+					END OF TREATMENT	FOLLOW UP
PROCEDURE	Day -28 to -1	Days -2, -1 (+/- 10 days)	Day 1 (+/- 10 days)	Day 8 (+/- 10 days)	Day 15 (+/- 10 days)	Day 22 (+/- 10 days)	Days -2, -1 (+/- 10 days)	Day 1 (+/- 10 days)	Day 8 (+/- 10 days)	Day 15 (+/- 10 days)	Day 22 (+/- 10 days)	28 days after last dose (+/- 28 days)	Q3 Months (+/- 28 days)
Informed Consent	X												
Inclusion/Exclusion Criteria	X												
Medical/Treatment History	X												
Vital Signs[h]	X	X	X	X	X		X	X	X	X	X	X	
Physical Exam	X	X	X	X	X		X	X	X	X	X	X	
Neurologic Exam	X		X					X					
Weight	X		X					X				X	
ECOG	X												
Patient reported outcomes – Quality of Life (QoL)	X		X					X				X	
PFT/FEV1 testing for patients with history of COPD/persistent asthma	X												
AE/SAE review		Continuous											
Medication evaluation	X	Continuous											
LOCAL LABS													
Venipuncture (Facility Fee)	X												
CBC (w/ platelet count)	X	X	X	X	X	X	X	X	X	X	X	X	
Serum Chemistry	X	X	X	X	X	X	X	X		X		X	
Hepatitis B (HBV) serology[e]	X												
HBV DNA testing[f]	X	Q12W during treatment, at the End of Treatment Visit, and Q12W for up to 6 months after the last dose of study treatment											
TSH, T3, Free T4, Coagulation	X												

	SCREENING	CYCLE 1					CYCLE 2+					END OF TREATMENT	FOLLOW UP
PROCEDURE	Day -28 to -1	Days -2, -1 (+/- 10 days)	Day 1 (+/- 10 days)	Day 8 (+/- 10 days)	Day 15 (+/- 10 days)	Day 22 (+/- 10 days)	Days -2, -1 (+/- 10 days)	Day 1 (+/- 10 days)	Day 8 (+/- 10 days)	Day 15 (+/- 10 days)	Day 22 (+/- 10 days)	28 days after last dose (+/- 28 days)	Q3 Months (+/- 28 days)
Thiamine testing	X		X					X					
Urinalysis	X												
Pregnancy Test	X		X					X					
Triglycerides	X		X	X	X	X		X	X	X	X		X
SPEP, UPEP, Serum/Urine Immunofix., Quant IgGs, 24Hr Urine, SFLC, B2 Micro	SOC		X					X					
CORRELATIVE SAMPLING													
Correlative Studies – peripheral blood collection, stool samples	X[b,d]	X[b,d]	X[b,d]					X[c,d]				X[c,d]	X[c,d]
Correlative Studies – bone marrow	X[b]	X[b]	X[b]									X	X[c]
CARDIOLOGY, PATHOLOGY, RADIOLOGY													
12-lead ECG	X[g]	X		X	X	X	X						
ECHO	X												
Bone Marrow Biopsy/Aspirate & Interp	SOC							X					X[i]
Radiological Assessments	SOC												
TREATMENT													
ATRA study drug (PO)		X	X				X	X					
Pomalidomide study drug (PO)		Pomalidomide will be administered on days 1-21 of cycle											
Dexamethasone study drug	X		X	X	X			X	X	X			
Dexamethasone Admin (IV)			X	X	X			X	X	X			
Daratumumab study drug	X		X[a]	X[a]	X[a]	X[a]		X[a]	X[a]	X[a]	X[a]		

	SCREENING	CYCLE 1					CYCLE 2+					END OF TREATMENT	FOLLOW UP
PROCEDURE	Day -28 to -1	Days -2, -1 (+/- 10 days)	Day 1 (+/- 10 days)	Day 8 (+/- 10 days)	Day 15 (+/- 10 days)	Day 22 (+/- 10 days)	Days -2, -1 (+/- 10 days)	Day 1 (+/- 10 days)	Day 8 (+/- 10 days)	Day 15 (+/- 10 days)	Day 22 (+/- 10 days)	28 days after last dose (+/- 28 days)	Q3 Months (+/- 28 days)
Daratumumab Admin (SC)			X[a]	X[a]	X[a]	X[a]		X[a]	X[a]	X[a]	X[a]		

[a] During 28-day treatment cycles, patients will receive Dara 1800 mg subcutaneous (SC) at their current dose upon enrollment onto the study depending on their cycle. They will receive Dara depending on the cycle they are in. If they are on cycles 1-2 then they will receive Dara 1800 mg SC on days 1,8,15,22; if they are on cycles 3-6 they will receive Dara 1800 mg SC on days 1 and 15; and if they are on cycle 7 or beyond they will receive Dara 1800 mg SC on day 1.

[b] Baseline correlative studies may be collected at screening, day -2/-1 or cycle 1 day 1.

[c] After baseline sample, correlative studies for peripheral blood and stool will be collected at cycle 2 day 1, end of treatment, and at time of relapse.

[d] Any time patients receive antibiotics while on study they should have stool and peripheral blood collected before starting antibiotics and upon completion of antibiotics (within a 7 day window). Patients should be provided with multiple stool kits prior to study so that they may collect stool even if antibiotics are prescribed by an outside physician.

[e] Local testing for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (Anti-HBs), and hepatitis B core antibody (Anti-HBc). Refer to Section 5.3.

[f] For subjects with serologic evidence of resolved HBV infection (i.e., positive Anti-HBs or positive Anti-HBc) at Screening, HBV DNA testing by PCR must be performed locally. Refer to Section 5.4.

[g] Prior to initiating therapy, the QTc interval should be assessed, pre-existing electrolyte abnormalities should be corrected, and medications known to prolong the QTc interval should be discontinued, if possible.

[h] Vital signs include systolic and diastolic blood pressure, pulse measurements, oxygen saturation, and body temperature. Vital signs should be assessed predose on the scheduled visit day, if possible. Blood pressure and pulse rate should be measured after the patient has been in a supine or sitting position for 5 minutes and assessed on the same arm throughout the study.

[i] To be performed at investigator discretion

4.2. Study Design Rationale

Pomalidomide + Dex has shown activity in several phase 1, phase 2 trials, and most recently in a randomized, phase 3 trial. The dose of 4 mg was established in a Phase 1 trial (CC-4047-MM-002, NCT00833833) which also achieved 42% minimal response or better, 21% partial response or better and 3% complete response in a heavily pretreated population (Richardson, 2013). In a Phase 2 trial following this Phase 1, response rates of at least PR of 34% were achieved as well as a median PFS of 4.6 months (Richardson, 2011a). A Phase 2 trial conducted by the IFM confirmed high efficacy of the combination of POM and Dex in subjects refractory to BTZ and LEN with response rates of 35% (Leleu, 2013). Recently, results of a Phase 3 trial comparing POM + Dex to high-dose Dex in subjects refractory and heavily pretreated patients, including LEN and BTZ pretreatment, have shown significant improvement in PFS as well as OS (Dimopoulos, 2012).

The present study is a multicenter, open-label, phase 2 study in the United States and Canada designed to further evaluate the efficacy and safety of combination POM + LD-Dex or POM+DARA+LD-Dex in the US, Canada and Japan in subjects with relapsed MM or refractory MM who received LEN-based therapy in the first or second line. Pomalidomide is efficacious in pretreated patients, especially those patients who are not only refractory to BTZ but also LEN and has shown statistically significant improvement in PFS. In a later line setting, the current treatment options are limited. Pomalidomide provides treatment control after LEN and BTZ, where there is still a high unmet medical need. The clinical efficacy of Pomalidomide in advanced relapsed and refractory MM does not appear to be affected by prior refractory disease status (Richardson, 2013). In the MM-002 clinical trial, response rates (25%-30%) and overall survival (OS; median 13.4-14.4 months) were similar for patients refractory to LEN, BTZ, LEN + BTZ, and the overall patient population. Similarly, the Mayo Clinic trial has demonstrated response rates between 32% to 38% in patients refractory to LEN and 26% to 29% in patients refractory to LEN + BTZ (Lacy, 2009). In the Japanese phase 2, MM-011 clinical trial, response rates (33% - 43%) were similar for patients' refractory to LEN and LEN+BTZ and the overall patient population (Ichinohe, 2016). Additionally, in the phase 3 MM-003 clinical trial, POM + Dex treatment of dual refractory patients (LEN and BTZ) significantly improved PFS (3.2 months, $P<0.001$; HR = 0.48) and OS (not reached, $P < 0.001$; HR = 0.53) compared with those treated with HiDex; 1.7 and 7.4 months, respectively). These phase 3 data met the primary PFS endpoint and crossed the upper boundary for superiority of OS (Dimopoulos, 2012).

Daratumumab is a human anti-CD38 IgG1κ monoclonal antibody with remarkable safety and activity as monotherapy in heavily treated relapsed and refractory multiple myeloma (MM) (Lokhorst, 2014; Lonial, 2016). In the GEN 501 clinical trial, response rates (36% - 44%) were similar in patients LEN, BTZ, LEN+BTZ and the overall patient population (Lokhorst, 2015; Iida, 2017). Daratumumab has demonstrated clinical activity in combination with LEN and Dex in relapsed or refractory MM and in Japanese subjects (Plesner, 2014; Dimopoulos, 2016; Suzuki, 2018). Daratumumab has also show clinical benefit in combination with BTZ and Dex in relapsed and/or refractory MM (Palumbo, 2016).

Recently an open label multi-center phase 1b clinical trial assessed the combination of POM+DARA+Dex in 103 patients with relapsed or refractory multiple myeloma. The combination demonstrated an ORR of

68% in a heavily pretreated patient population (median 4 prior lines of therapy) and ORR of 58% in double refractory (PI and IMiD). The toxicity profile of the three-drug combination was also well tolerated with most common Grade 3 toxicities being hematologic in nature including neutropenia (78%), anemia (28%), leukopenia (24%) and thrombocytopenia (19%) (Chari, 2017).

There have been no clinical trials evaluating the efficacy and safety of LEN following treatment with Pomalidomide. Preclinical data in mice suggest that Pomalidomide retains its antimyeloma activity in LEN-refractory disease to a much greater extent than LEN does in Pomalidomide-refractory disease. Investigators at the Mayo Clinic have reported outcomes for patients who relapsed after treatment with Pomalidomide. Only 7 out of 52 (13%) patients received LEN-based therapy as first salvage, and 2 out of 7 (29%) achieved a partial response or better; 5 out of 7 (71%) had SD or PD (Lacy, 2009).

Data support the idea that Pomalidomide provides consistent outcomes regardless of exposure to prior therapy. Results from the IFM 2009-02, MM-002, and Mayo Clinic trials demonstrated consistent responses across all subgroups (eg, LEN-refractory, BTZ refractory, and LEN/BTZ dual-refractory ± prior stem cell transplantation). Additionally, preclinical data in mice suggest that POM + Dex overcomes acquired resistance to LEN + Dex. Taken together, these results suggest minimal cross resistance for POM following LEN.

All-trans retinoic acid (ATRA) has been shown in both cell lines and primary MM samples to increase CD38 expression levels and also to reduce expression of the complement-inhibitory proteins CD55 and CD59(Nijhof et al, 2015). This resulted in significant enhancement of activity of Daratumumab in vitro and in humanized MM mouse models. Daratumumab and ATRA exhibit a strong synergy in MM cells derived from Dara-naïve patients and from patients with Dara-refractory disease, providing preclinical rationale for further evaluation of Daratumumab combined with ATRA in MM patients. Preliminary data from phase 1 trials combining Daratumumab and ATRA have shown that the combination is safe using ATRA 45 mg/m^2/day dose.

Second primary malignancies will be monitored as events of interest and will be reported as a serious adverse event (SAE) regardless of causal relationship to investigational product (IP). The multicenter nature as well as the inclusion of patients in Japan of the study provides reassurance that the results are likely to have general applicability and the size of the study allows accurate description of the nature, frequency, and severity of the AE profile. Subjects will receive study treatment until PD or discontinuation. In studies evaluating agents for subjects with refractory MM or relapsed and refractory progressing or relapsed malignant diseases, it is common practice to continue study treatment until PD or intolerable toxicity develops. All subjects will be followed for OS, subsequent anti-myeloma therapies and SPMs.

4.3. Study Duration

This study will consist of the following consecutive phases: Screening, Treatment and Follow-up.

The study will remain open to enrollment until the target subject enrollment of approximately 42 subjects has been reached. Given our current patient population we expect to complete enrollment in two years.

Each subject will be followed for up to 12 months after enrollment (unless the follow-up is shorter due to withdrawal of consent, loss to follow-up, or death).

4.4. End of Trial

The End of Trial is defined as either the date of the last visit of the last subject to complete the study, or the date of receipt of the last data point from the last subject that is required for primary, secondary and/or exploratory analysis, as pre-specified in the protocol and/or the Statistical Analysis Plan, whichever is the later date.

5. PROCEDURES

5.1. Study Entry

Prior to screening, subjects must sign an informed consent document. All screening assessments must be completed within 28 days prior to start of Cycle 1, with the exception of the skeletal survey, which may be performed within 60 days prior to initiation of study treatment.

Confirmation of diagnosis (including date of confirmed initial diagnosis and, if available, myeloma stage at time of initial diagnosis per the Salmon-Durie Criteria and/or the International Staging System, medical history, prior cancer and surgical history, and review of prior medications should be documented during the screening period. All prior radiotherapy, surgeries, and anti-myeloma therapies must be recorded in the electronic case report form (eCRF), including approximate dates for each therapy and the date of progression for each regimen. Results for any local cytogenetic testing (prefer fluorescence in situ hybridization [FISH] results), if available, as part of medical history, will be collected in the eCRF. See Table 1 (Table of Events) for a complete list of the required assessments during screening.

If the subject's safety and efficacy laboratory assessments performed at screening are within 7 days of enrollment into the study, they do not need to be repeated at Cycle 1 Day 1 and can be used as baseline results. The start of study drug dosing is designated as Cycle 1 Day 1. A 14-day wash-out period is required for any prior anti-myeloma therapy before study treatment is initiated.

5.2. Safety assessments

Adverse Events

All AEs should be assessed starting after the subject signs the informed consent document (ICD) until 30 days after treatment discontinuation. Adverse events that lead to study discontinuation should be followed until resolution or stabilization.

Serious Adverse Events

Serious adverse events, regardless of relationship to the IP (POM, DARA, or Dex), that occur from the time the subject signs the ICD to at least 30 days after treatment discontinuation and those made known to the investigator at any time thereafter that are suspected of being related to the IP (POM, DARA, or Dex) must be reported to Janssen Drug Safety within 24 hours of the investigator's knowledge of the event.

Echocardiography and Electrocardiography

An echocardiogram or multiple gated acquisition (MUGA) scan to assess baseline cardiac function and risk of cardiac dysfunction, including cardiomyopathy will be conducted during Screening. The decision to perform an echocardiogram or MUGA will be at the discretion of the Investigator. Additional echocardiograms or MUGA scans may be performed during subsequent visits if clinically appropriate, per Investigator discretion.

A standard 12-lead electrocardiogram (ECG) will be performed. Patients must rest for at least 5 minutes prior to the ECG recording. The Investigator will interpret the ECG using one of the following categories: normal, abnormal but not clinically significant, or abnormal and clinically significant. The date and time the ECG is performed and the following parameters will be recorded in the eCRF: heart rate, PR interval, QT interval, QRS interval, and QT corrected (QTc) using Bazett's formula.

Clinical Laboratory Tests

All safety laboratory assessments will be performed and analyzed at the site's local laboratory.

The following clinical laboratory tests will be performed and assessed at the local laboratory:

• Hematology (blood sample: whole blood) - EDTA tests including Hb, hematocrit, mean corpuscular volume, mean corpuscular Hb, mean corpuscular Hb concentration, WBC count, WBC differential, red blood cell (RBC) count, lymphocytes, monocytes, neutrophils, eosinophils, basophils, and platelets will be performed.

- WBC differential may be automated or manual as per institutional standards.

• Serum Chemistry (blood sample: serum)

- Complete Serum Chemistry will include sodium, potassium, chloride, bicarbonate (HCO3-), blood urea nitrogen (BUN), creatinine, glucose, calcium, phosphate, magnesium, ALT, AST, alkaline phosphatase, total bilirubin.

5.3. Minimal residual disease

We will evaluate the status of minimal residual disease (MRD) in patients who achieve sCR, CR, or nCR by 10-color multiparametric flow cytometry. When a patient achieves VGPR or biochemical CR, bone marrow confirmation will be performed to assess for MRD using bone marrow aspirate.

5.4. HBV Serology

All subjects will be tested locally for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (Anti-HBs), and hepatitis B core antibody (Anti-HBc) at Screening. HBV serology is not required at Screening if this was performed as part of standard of care within 3 months prior to first dose.

5.5. HBV DNA Tests

Subjects who are positive for Anti-HBc or Anti-HBs will undergo testing for hepatitis B DNA by PCR. Subjects with serologic findings suggestive of HBV vaccination (Anti-HBs positivity as the only serologic marker) and a known history of prior HBV vaccination do not need to be tested for HBV DNA by PCR. During and following study treatment, subjects who have history of HBV infection will be closely monitored for clinical and laboratory signs of reactivation of HBV as specified in the Time and Events

Schedule (Table 1). Where required by local law, the results of HBV testing may be reported to the local health authorities.

6. STUDY POPULATION

6.1. Number of participants

This is a multicenter, open label, phase 1b/2 study of patients with relapsed or refractory MM after treatment with Daratumumab (Dara)-based therapy in the second line setting. Patients must have been exposed to a PI, IMiD, and PI and must have had more than 2 or more prior lines of therapy.

This study is anticipated to enroll overall up to 42 patients who fulfill the eligibility criteria (20-32 subjects previously exposed to Dara + Len + Dex; 10-22 subjects previously exposed to Dara + Pom + Dex).

6.2. Inclusion criteria

Subjects must satisfy the following criteria to be enrolled in the study:

1. Documented multiple myeloma with prior exposure to an IMiD, PI, and CD-38 moAb.
2. Patients must have 2 or more prior lines of therapy.
3. Patients must have been previously exposed to:
    a. Dara+Len+Dex and must have achieved at least stable disease to this combination. or;
    b. Dara + Pom + Dex and must have achieved at least stable disease to this combination.
4. Histologically confirmed and relapsed multiple myeloma with measurable disease, defined by at least one of the following:
    a. Serum monoclonal protein ≥0.5 g/dL;
    b. Monoclonal protein in the urine on 24-hour electrophoresis ≥200 mg;
    c. Serum immunoglobulin free light chain (FLC) ≥10 mg/dL (100 mg/L) provided serum FLC ratio is abnormal;
    d. New or progressing biopsy proven plasmacytoma on exam or imaging; or
    e. Bone marrow plasma cells ≥20%;
5. Cycle 1 day 1 of study treatment must be within 3 months of last exposure to Daratumumab.
6. Life expectancy >3 months
7. ECOG PS 0-2
8. Age ≥18
9. Adequate organ function, including bone marrow, renal, hepatic, pulmonary, and cardiac function based on the last assessment performed within the Screening Period, defined as:
    a. Absolute neutrophil count (ANC) ≥1,000/µL;
    b. Platelet count ≥50,000/µL, (≥30,000/µL if bone marrow plasma cells are ≥50% of cellularity);
    c. Hemoglobin ≥7.5g/dL;
    d. Creatinine clearance ≥60 mL/min (assessed as glomerular filtration rate using the Cockcroft-Gault formula);

e. Alanine aminotransferase or aspartate aminotransferase ≤2.5 x upper limit of normal (ULN);
f. Total bilirubin ≤1.5 x ULN (except for patients with Gilbert's syndrome confirmed by UGT1A1 mutation);
g. Left ventricular ejection fraction ≥50% as assessed by echocardiography or multi-gated acquisition (MUGA) scan; and
h. Must have a minimum level of pulmonary reserve defined as Grade <2 dyspnea and pulse oxygenation ≥92% on room air;

10. Prior to first dose of study drug, a woman must be either:

- Not of childbearing potential: premenarchal; postmenopausal (>45 years of age with amenorrhea for at least 12 months or any age with amenorrhea for at least 6 months and a serum follicle stimulating hormone level >40 IU/L or mIU/mL]); permanently sterilized (eg, bilateral tubal occlusion [which includes tubal ligation procedures as consistent with local regulations], hysterectomy, bilateral salpingectomy, bilateral oophorectomy); or otherwise be incapable of pregnancy
- Of childbearing potential and practicing 2 highly effective method of birth control at time of informed consent and will continue through study and for at least one month after final dose of study drug. Must be consistent with local regulations regarding the use of birth control methods for subjects participating in clinical studies: e.g., established use of oral, injected or implanted hormonal methods of contraception; placement of an intrauterine device or intrauterine system; barrier methods: condom with spermicidal foam/gel/film/cream/suppository or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository; male partner sterilization (the vasectomized partner should be the sole partner for that subject); true abstinence (when this is in line with the preferred and usual lifestyle of the subject)

  Note: If the childbearing potential changes after start of the study (e.g., woman who is not heterosexually active becomes active, premenarchal woman experiences menarche)
- a woman must begin a highly effective method of birth control, as described above.

11. A woman of childbearing potential must have 2 negative serum (β human chorionic gonadotropin) or urine pregnancy tests during screening, the first one within 28 days prior to the first dose of study drug and the second within 24 hours prior to the first dose of study drug.
12. A man who is sexually active with a woman of childbearing potential and has not had a vasectomy must agree to use a barrier method of birth control e.g., either condom with spermicidal foam/gel/film/cream/suppository or partner with occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository, and all men must also not donate sperm during the study and for 3 months after receiving the last dose of study drug.
13. Subjects must be willing and able to adhere to the prohibitions and restrictions specified in this protocol and referenced in the informed consent form (ICF).

6.3. Exclusion Criteria

The presence of any of the following will exclude a subject from study enrollment:

1. Major concurrent illness or organ dysfunction
2. Active GVHD requiring systemic corticosteroids in a subject who previously received allogeneic-SCT.
3. Cord compression or CNS involvement

4. Recent/Prior active malignancy requiring active therapy 2 years prior to enrollment excluding non-melanoma skin cancer.
5. Prior life-threatening hypersensitivity to daratumumab or an IMiD
6. Plasma cell leukemia
7. Pregnant or lactating females
8. Men donating sperm during study
9. Seropositive for human immunodeficiency virus (HIV)
10. Seropositive for hepatitis B (defined by a positive test for hepatitis B surface antigen [HBsAg]). Subjects with resolved infection (ie, subjects who are HBsAg negative but positive for antibodies to hepatitis B core antigen [anti-HBc] and/or antibodies to hepatitis B surface antigen [anti-HBs]) must be screened using real-time polymerase chain reaction (PCR) measurement of hepatitis B virus (HBV) DNA levels. Those who are PCR positive will be excluded. EXCEPTION: Subjects with serologic findings suggestive of HBV vaccination (anti-HBs positivity as the only serologic marker) AND a known history of prior HBV vaccination, do not need to be tested for HBV DNA by PCR
11. Seropositive for hepatitis C (except in the setting of a sustained virologic response [SVR], defined as aviremia at least 12 weeks after completion of antiviral therapy)
12. Chronic obstructive pulmonary disease (COPD) with a Forced Expiratory Volume in 1 second (FEV1) less than 50% of predicted normal
13. Moderate or severe persistent asthma within the past 2 years, or uncontrolled asthma of any classification. Note that participants who currently have controlled intermittent asthma or controlled mild persistent asthma are allowed to participate
14. QTc > 480ms or ventricular arrythmia on screening EKG or history of ventricular arrythmia
15. Myocardial infarction within 6 months before randomization, or unstable or uncontrolled disease/condition related to or affection cardiac function (e.g., unstable angina, congestive heart failure, New York Heart Association Class III-IV)
16. Received any prior anti-myeloma therapy within 14 days of planned study treatment

7. DESCRIPTION OF STUDY TREATMENTS

7.1. Description of Investigational Product

The only investigational product we will receive for this study is Daratumumab.

Daratumumab Preparation – Subcutaneous

Daratumumab-SC will be provided as a fixed-dose (1800 mg), combination drug product containing rHuPH20 drug substance (2000 U/mL) and daratumumab drug substance (120 mg/mL) in a single vial.

Daratumumab Administration – Subcutaneous

[Daratumumab should be given according to product information: http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/DARZALEX+Faspro-pi.pdf]

Daratumumab (1800 mg) will be administered by SC injection by manual push over approximately 3 – 5 minutes in the abdominal subcutaneous tissues in the left/right locations, alternating between individual doses. The volume of the SC solution will be 15 mL for the 1800 mg dose. . Reasons for continued observation on subsequent daratumumab injection may include but are not limited to the following: subjects with a higher risk of respiratory complications (e.g., subjects with mild asthma or subjects with COPD who have an FEV1 < 80% at screening or developed FEV1 < 80% during the study without any medical history), subjects with IRR with the first injection of study drug, subject with decreased condition on day of dosing compared to prior dosing day. The dose of daratumumab will remain constant throughout the study.

Dara-SC Dosing:

Table 2: Dara-SC dosing schedule (whether in combination or monotherapy)

Weeks	**Schedule**
Weeks 1 to 8	Weekly (total of 8 doses)
Weeks 9 to 24[a]	Every two weeks (total of 8 doses)
Week 25 and onward until PD[b]	Every four weeks

[a] First dose of the every-2-week dosing schedule is given at Week 9

[b] First dose of the every-4-week dosing schedule is given at Week 25

All daratumumab administrations will be in an outpatient setting. Subjects will receive pre-injection medications and post-injection medication as outlined in Sections 7.2.

Vital signs should be monitored extensively on Cycle 1 Day 1 before, and after the first administration of daratumumab. For all other administrations, vital signs should be measured before the start of injection and at the end of the injection. If the subject experiences any significant medical event, then the investigator should assess whether the subject should stay overnight for observation. If the subject has

not experienced a significant medical event but is hospitalized overnight only for observation, then the hospitalization should not be reported as an SAE.

If an IRR develops, then the injection should be temporarily interrupted or slowed down. In the event of a life-threatening IRR (which may include pulmonary or cardiac events) or anaphylactic reaction, dara-SC should be discontinued, and no additional dara-SC should be administered to the participant. See Section 7.5 for instructions on the management of IRR and local ISRs.

7.2. Guidelines for Prevention and Management of Infusion Reactions:

All participants will receive the following medications 1 to 3 hours prior to each study drug administration:

- An antipyretic: paracetamol (acetaminophen) 650-1000 mg IV or PO
- An antihistamine: diphenhydramine 25-50 mg IV or PO or equivalent. Avoid IV use of promethazine.
    - After Cycle 6, if a participant has not developed an infusion-related reaction and is intolerant to antihistamines, modifications are acceptable as per investigator discretion.
- Corticosteroids (Long-acting or intermediate-acting):
        - Administer 20 mg dexamethasone (or equivalent) prior to every daratumumab infusion. When dexamethasone is the background regimen specific corticosteroid, the dexamethasone treatment dose will instead serve as pre-medication on daratumumab infusion days.
        - Dexamethasone is given orally or intravenously prior to the first daratumumab infusion and oral administration may be considered prior to subsequent infusions.
    - If the subject does not experience a major systemic administration-related reaction after the first 3 doses, consider discontinuing the administration of corticosteroids (excluding any background regimen-specific corticosteroid).

Pre-dose administration of a leukotriene inhibitor (montelukast 10 mg PO or equivalent) is optional in Cycle 1 Day 1 and can be administered up to 24 hours before infusion as per investigator discretion.

If necessary, all PO pre-infusion medications may be administered out of the clinic on the day of the infusion, provided they are taken within 3 hours before the infusion.

Post-dose Medication:

Administer post-infusion medication to reduce the risk of delayed infusion related reactions as follows:

- Consider administering low-dose methylprednisolone (≤ 20 mg) or equivalent, the day after the infusion. However, if a background regimen-specific corticosteroid (e.g. dexamethasone) is administered the day after the infusion, additional post-infusion steroids are not required, but may be considered by the investigator.
- For participants with a higher risk of respiratory complications (e.g. participants with mild asthma or participants with COPD who have an FEV1 < 80% at screening or

developed FEV1 < 80% during the study without any medical history) the following post-infusion medication should be considered:

- Antihistamine (diphenhydramine or equivalent)
- Leukotriene inhibitor (montelukast or equivalent)
- Short-acting β2 adrenergic receptor agonist such as salbutamol aerosol
- Control medications for lung disease (e.g. inhaled corticosteroids ± long-acting β2 adrenergic receptor agonists with asthma; long-acting bronchodilators such as tiotropium or salmeterol ± inhaled corticosteroids for participants with COPD)

- In addition, these at-risk participants may be hospitalized for monitoring for up to 2 nights after daratumumab administration. If participants are hospitalized, then an improvement in FEV1 should be performed and documented prior to discharge. If these participants are not hospitalized, then a follow-up telephone call should be made to monitor their condition within 48 hours after all infusions. If the participant has not experienced a significant medical event but is hospitalized overnight only for observation, then the hospitalization should not be reported as a serious adverse event. Investigators may prescribe bronchodilators, H1-antihistamines, and corticosteroids that are deemed necessary to provide adequate supportive care in the event a bronchospasm occurs after participants are released from the hospital/clinic. If an at-risk participant experiences no major infusion-related reactions, then these post-infusion medications may be waived after 4 doses at the investigator's discretion.
- Any post-infusion medication will be administered after the infusion has completed.

7.3. Definition of DLT

Toxicity will be evaluated according to the NCI CTCAE, Version 5.

Nonhematologic TEAEs of NCI CTCAE Grade ≥3 clearly unrelated to the underlying disease and occurring during the first cycle will be considered DLTs with the following exceptions:

- Asymptomatic laboratory changes (other than renal and hepatic laboratory values and Grade 4 lipase/amylase) that can be supplemented (reversion of Grade 4 events to Grade ≤2, reversion of Grade 3 events to Grade ≤1 or baseline) within 72h.
- Grade 3 nausea/vomiting that can be managed subsequently with anti-emetics (Grade 3 nausea or vomiting that persists beyond 48h with or without appropriately medical intervention will be considered a DLT).
- Grade 3 fatigue lasting for <72 hours.
- Grade 3 elevation of ALT or AST that resolves to Grade ≤1 or baseline) within 7 days.

The following hematologic TEAEs of Grade ≥3 clearly unrelated to the underlying disease and occurring during the first cycle will be considered DLTs:

- Grade ≥3 hemolysis.
- Grade 4 neutropenia lasting more than 7 consecutive days.

- Grade 4 thrombocytopenia of any duration.
- Grade 3 thrombocytopenia with clinically significant bleeding.
- Any other Grade ≥4 hematologic toxicity with the following exception: Grade 4 lymphopenia

An incomplete recovery from treatment-related toxicity causing a >3-week delay in the next scheduled infusion before the initiation of Cycle 2 will be considered a DLT.

For the purpose of dose escalation, DLTs are those events meeting the criteria above hat occur before Cycle 2 Day 1 administration. Related TEAEs meeting DLT definitions occurring in later cycles or in Phase 2 (DLT-like events) will determine the suitability of the MTD dose for future studies.

Dose modifications for toxicity are described in Section 7.5.

Intrapatient dose escalation will be permitted only when patients in the next dose level cohort have completed assessments for Cycle 1 and a decision has been made that this dose level does not exceed the MTD. Eligible patients for intrapatient escalation can also be changed to a different schedule if the conditions described above are met (for example a Dose Level 1 patient could be moved to the last cleared dose level).

7.4. Dose Escalation for ATRA and Study Stopping Rules

The phase 1b portion of the study will follow a 3+3 dose escalation design to evaluate Dose Level 1 (35.5 mg/m2/day) followed by Dose Level 2 (45 mg/m2/day) of ATRA in combination with Dara + Pom + dex for DLTs and to determine the MTD for further assessment in phase 2.

Patients will be enrolled in cohorts of 3 and assessed for DLTs over a 28-day period. In each dose level, the second and third patients can be dosed concurrently once the first patient in the cohort has gone uneventfully through the Day 8 visit. If it is necessary to enroll more than 3 patients in a cohort, and there have not been any TEAEs in the previously dosed patients in that cohort, these new patients can be enrolled concurrently.

If none of the patients in a cohort of 3 patients exhibits a DLT during the 28-day cycle, then the dose may be escalated for the next cohort of 3 patients. If 1 patient in a cohort of 3 patients exhibits a DLT, then that cohort will be expanded to a total of 6 patients. If 2 or more patients in a cohort of 3 patients exhibit a DLT, then that cohort will be deemed to have exceeded the MTD, and dose escalation will be stopped.

If the dose cohort below that at which the MTD is exceeded has enrolled only 3 patients, then 3 additional patients will be enrolled at that dose level. The MTD is defined as the highest dose with a cohort of 6 patients having no more than 1 patient with a DLT. For the cohort expansion, 3 patients will only be enrolled sequentially if a DLT observed in the initial cohort was life-threatening, it appeared before the Day 8 visit and/or the clinical team consider that based on the observed toxicity is prudent to stagger the enrollment. Sequential enrollment is no required in case of de-escalation or if no DLT was observed in the first 3 patients in a cohort.

During phase 1b dose escalation, patients who miss one or more schedule Cycle 1 doses of ATRA for reasons other than a DLT will be replaced.

Before initiating the dosing of the next cohort or opening a new schedule, when safety data are available for all patients in the current cohort, key safety data will be reviewed and evaluated by the study team consistent of investigators who will review the safety of all treated patients and make decisions regarding dose escalation. In addition, further changes to the dose escalation scheme may be considered. All decisions will be documented in writing. Any decision to modify the dose escalation scheme in a direction that increases the already approved frequency of administration or dose escalation steps, will be communicated to institutional review boards (IRBs) and the protocol amended accordingly.

7.5. Dose Modification

Management of Infusion-related Reactions and Local Injection-site Reactions of Daratumumab-SC

Infusion-related Reactions (IRRs)

Infusion-related reactions (IRRs) are systemic reactions related to daratumumab administration. Participants should be observed carefully during daratumumab administrations. Trained study staff at the clinic should be prepared to intervene in case of any IRRs, and resources necessary for resuscitation (e.g., agents such as epinephrine and aerosolized bronchodilator, medical equipment such as oxygen tanks, tracheostomy equipment, and a defibrillator) must be available at the bedside. Attention to staffing should be considered when multiple participants will be dosed at the same time. If an IRR develops during Dara SC administration, then the administration should be temporarily interrupted. Participants who experience AEs during Dara-SC administration must be treated for their symptoms. Participants should be treated with paracetamol (acetaminophen), antihistamine, or corticosteroids, as needed. Intravenous saline may be indicated. For bronchospasm, urticaria, or dyspnea, participants may require antihistamines, oxygen, corticosteroids, or bronchodilators. For hypotension, participants may require vasopressors. In the event of a life-threatening IRR (which may include pulmonary or cardiac events) or an anaphylactic reaction, Dara-SC should be discontinued.

Infusion-related Reactions Grade 1 or Grade 2:

If the investigator assesses a Grade 1-2 IRR to be related to administration of study intervention, then the Dara-SC administration should be interrupted. When the participant's condition is stable, Dara-SC administration may be restarted at the investigator's discretion. Refer to the SIPPM for further details regarding continuation of Dara-SC administration.

If the participant experiences a Grade 2 or higher event of laryngeal edema, or a Grade 2 or higher event of bronchospasm that does not respond to systemic therapy and does not resolve within 6 hours from onset, then the participant must be permanently discontinued from Dara-SC treatment.

Infusion-related Reactions Grade 3 or Higher:

For IRR AEs (other than laryngeal edema or bronchospasm) that are Grade 3, the Dara-SC administration must be stopped, and the participant must be observed carefully until resolution of the AE or until the intensity of the event decreases to Grade 1, at which point the Dara-SC administration may be restarted at the investigator’s discretion. Refer to the SIPPM for further details regarding continuation of Dara-SC administration.

If the intensity of the AE returns to Grade 3 after restart of the Dara-SC administration, then the participant must be permanently discontinued from Dara-SC treatment.

For IRR AEs that are Grade 4, the Dara-SC administration must be stopped, and the participant permanently discontinued from Dara-SC treatment.

Recurrent Infusion-related Reactions:

If a Grade 3 IRR (or Grade 2 or higher event of laryngeal edema, or a Grade 2 or higher event of bronchospasm) recurs during or within 24 hours after a subsequent Dara-SC administration, the participant must be permanently discontinued from Dara-SC treatment.

Injection Site Reactions:

In clinical studies, SC administration of daratumumab was associated with local injection site reactions, such as induration and erythema, in some subjects. The reactions usually resolved within 60 minutes. Local injection-site reactions should be managed per institutional standards.

Recommended Concomitant Therapy:

- Prophylaxis for Herpes Zoster Reactivation:

- Prophylaxis for herpes zoster reactivation is recommended during the Treatment Phase, as per institutional guidelines. Initiate antiviral prophylaxis to prevent herpes zoster reactivation within 1 week after starting study treatment and continue for 3 months following study treatment. Acceptable antiviral therapy includes acyclovir (eg 400 mg given orally 3 times a day, or 800 mg given orally 2 times a day or per institutional standards), famcyclovir (eg, 125 mg given orally, twice a day or per institutional standards), or valacyclovir (eg, 500 mg given orally, twice a day or per institutional standards), initiated within 1 week after the start of study drug.

- Management of Hepatitis B Virus Reactivation:

- Primary antiviral prophylaxis is permitted as per local standard of care. Per protocol, HBV DNA testing by PCR is mandatory for participants at risk for HBV reactivation.

In patients who develop reactivation of HBV while on study treatment, suspend treatment with study treatment and any concomitant steroids, chemotherapy, and institute appropriate treatment. Resumption of study treatment in patients whose HBV reactivation is adequately controlled should be discussed with physicians with expertise in managing HBV

Daratumumab Dose Modification

Individual dose modification of daratumumab is not permitted, but dose delay is recommended as the primary method for managing daratumumab-related toxicities, as described in Section 7.5.

Daratumumab-related Toxicity Management

Refer to Section 7.5 for details on management of daratumumab injection-related reactions.

<u>If any of the following criteria are met and the toxicity is more than expected for pomalidomide or underlying multiple myeloma, daratumumab injection must be held to allow for recovery from toxicity.</u> If attribution is unclear, then daratumumab should be held until recovery from toxicity as noted below.

The criteria for a dose delay are:

- Grade 4 hematologic toxicity, except for Grade 4 lymphopenia
- Grade 3 thrombocytopenia with bleeding
- Febrile neutropenia
- Grade 4 Neutropenia with infection, of any grade
- Grade 3 or higher non-hematologic toxicities with the following exceptions:
  - Grade 3 nausea that responds to antiemetic treatment within 7 days
  - Grade 3 vomiting that responds to antiemetic treatment within 7 days
  - Grade 3 diarrhea that responds to antidiarrheal treatment within 7 days
  - Grade 3 fatigue that was present at baseline or that lasts for <7 days after the last administration of daratumumab
  - Grade 3 asthenia that was present at baseline or that lasts for <7 days after the last administration of daratumumab

Administration of daratumumab may be restarted upon recovery from toxicity to Grade 2 or baseline, with the exception that Grade 2 laryngeal edema or Grade 2 bronchospasm must be fully recovered. Other than on Day 1 of a cycle, if any "within-cycle" daratumumab administration does not commence within the prespecified window of the scheduled administration date (Table 3), then the dose will be considered a missed dose. Administration may resume at the next planned dosing date.

Table 3: Daratumumab-related Toxicity Management

Daratumumab Dosing Frequency	**Dose Missed**	**Dosing Resumption**
Weekly	>3 days	Next planned weekly dosing date

Table 3: Daratumumab-related Toxicity Management

Daratumumab Dosing Frequency	Dose Missed	Dosing Resumption
Every 2 weeks	>7 days	Next planned every-2-weeks dosing date
Every 4 weeks	>21 days	Next planned every-4-weeks dosing date

A missed dose will not be made up. Delay of Day 1 drug dosing in any given cycle should not result in a skipped dose but should lead to a delay of the entire cycle instead. A minimum of 4 days between daratumumab doses must be observed.

If a dose is delayed, then the dates of all subsequent doses must be adjusted. If a dose delay occurs, then blood samples should be collected on the actual day of study drug administration, not on the original scheduled drug administration day. Any adverse event deemed to be related to daratumumab that requires a dose hold of more than 28 days will result in permanent discontinuation of daratumumab, unless, upon consultation with the sponsor and the review of safety and efficacy, continuation is agreed upon.

Daratumumab Interruption or Missed Doses

A daratumumab dose that is held for more than the permitted time (Table 3) from the per-protocol administration date for any reason other than toxicities suspected to be related to daratumumab should be brought to the attention of the sponsor at the earliest possible time. Patients whose dose is delayed or missed for 3 or more consecutive doses should be withdrawn from study treatment, unless, upon consultation with the sponsor and the review of safety and efficacy, continued treatment is agreed upon.

Pomalidomide related toxicities

Table 4: Dose Modification Instructions for Pomalidomide

Toxicity [a]	Dose Modification
Neutropenia Grade 4 neutropenia (ANC < 500/µL) or Febrile neutropenia (ANC < 1,000/µL with a single temperature of > 38.5 °C or a sustained temperature of ≥ 38 °C for more than one hour)	Withhold the dose and follow CBC weekly. If the subject was not receiving GCSF therapy, GCSF therapy may be started at the discretion of the treating physician. When dosing is resumed, the dose of POM may be maintained if neutropenia was the only POM-related toxicity requiring a dose modification and GCSF treatments are continued. Otherwise, decrease by one dose level. Note grade 4 neutropenia, ANC must be ≥ 500/ µL to restart dosing.

	For febrile neutropenia, ANC must be ≥ 1,000/µL to restart pomalidomide dosing at 1 mg less than the previous dose.
Thrombocytopenia Grade 4 thrombocytopenia (Platelets< 25,000/µL)	Withhold the dose and follow CBC weekly. Dosing may resume at one dose level lower once the platelet count has recovered to ≥ 50,000/µL.
Rash, Grade 3	Withhold dose for remainder of cycle. Decrease by one dose level when dosing restarted at next cycle (rash must resolve to ≤ Grade 1 before restarting dosing).
Rash, Grade 4 or Blistering	Discontinue subject from study treatment.
VTE ≥ Grade 3	Withhold dose for remainder of cycle. Assess anticoagulation treatment. Maintain dose level when dosing restarted at next cycle at discretion of treating physician. For Grade 4 VTE, discontinue pomalidomde treatment.
Other ≥ Grade 3 POM-related [b] adverse events	Withhold dose. Decrease by one dose level when dosing restarted (adverse event must resolve to ≤ Grade 1 before restarting dosing). For Grade 4 non-hematologic adverse events, discontinue pomalidomde treatment.

ANC = absolute neutrophil count; GCSF = granulocyte colony-stimulating factor; POM = Pomalidomide; VTE = venous thromboembolism.

[a] If recovery from toxicities is prolonged beyond 14 days, then the dose of POM will be decreased by one dose level when dosing is restarted.

[b] For Grade 3 or 4 AEs that are not considered to be related to study drug, the treating physician should consult with the sponsor institution for dose interruptions and reductions.

Table 5: Pomalidomide Dose Reduction Steps

Dose Level [a]	**Pom Dose reduction**
Starting dose	4 mg
Dose Level -1	3 mg
Dose Level -2	2 mg
Dose Level -3	1 mg

[a] The minimum permitted dose level for POM is 1.0 mg. No dose re-escalation is permitted for Pomalidomide.

Table 6: Dose Reductions for Dexamethasone-related Toxicities

Toxicity [a]	**Dex Dose Modification**
Dyspepsia = Grade 1-2	Maintain dose and treat with histamine (H2) blockers or equivalent. Decrease by one dose level if symptoms persist.

Dyspepsia ≥ Grade 3	Withhold dose until symptoms are controlled. Add H2 blocker or equivalent and decrease one dose level when dose restarted.
Edema ≥ Grade 3	Use diuretics as needed and decrease dose by one dose level.
Confusion or mood alteration ≥ Grade 2	Withhold dose until symptoms resolve. When dose restarted, decrease dose by one dose level.
Muscle weakness (steroid myopathy) ≥ Grade 2	Withhold dose until muscle weakness ≤ Grade 1. When dose restarted decrease dose by one dose level.
Hyperglycemia ≥ Grade 3	Decrease dose by one dose level. Treat with insulin or oral hypoglycemic agents as needed.
Acute pancreatitis	Discontinue subject from Dex treatment regimen.
Other ≥ Grade 3 Dex-related adverse Events	Stop Dex dosing until the adverse event resolves to ≤ Grade 2. Decrease by one dose level when Dex dosing is resumed.

[a] If recovery from toxicities is prolonged beyond 14 days, then the dose of Dex will be decreased by one dose level when dose is restarted.

Table 7: Dexamethasone Dose Reduction Steps

Dose Level	**≤ 75 years old**	**>75 years old**
Starting Dose	40 mg	20 mg
Dose Level -1	20 mg	12 mg
Dose Level -2	10 mg	8 mg

ATRA will be administered in a divided dose of twice daily as an oral formulation at 35 mg/m2/day for Phase with with dose escalation to 45mg/m2/day for 3 days. The dose expansion phase will be at the 45 mg/m2/day dose after safety and efficacy has been evaluated. The first administration of ATRA will be given in the morning, two days before the scheduled Dara infusion. The last administration of ATRA will be given in the evening of the day that Dara was administered (days -2, -1, and 1; day 1 is the day of Dara infusion).

ATRA-related toxicities

Subjects will be monitored for neurological symptoms and nutritional status. If Wernicke's encephalopathy is suspected, ATRA should be interrupted and parenteral thiamine should be initiated.

Pseudotumor cerebri

This complication has been mainly reported in patients aged <20 years and is characterized by presence of severe headache with nausea, vomiting, and visual disorders.

It is recommended to temporarily discontinue ATRA treatment and to administer opiates. As soon as the symptoms and the patient clinical conditions improve, the treatment with ATRA will be resumed at 50% of the previous dose during the first 7 days after the amelioration of pseudotumor cerebri. Thereafter, in absence of worsening of the previous toxicity, ATRA should be resumed at full dosage.

Table 8: ATRA Dose Reduction Steps

Dose Level	**ATRA Dose reduction**
Dose Level 2	45 (mg/m^2)
Dose Level 1 (Phase 1b starting dose)	35.5 (mg/m^2)
Dose Level -1	25 (mg/m^2)
Dose Level -2	20 (mg/m^2)

- ATRA will be discontinued for any Grade 4 non-hematologic toxicity.
- In the case of Grade 3 toxicity, ATRA should be held until the toxicity resolves to Grade ≤1 or baseline, at which time it may be resumed at a reduced dose.
- ATRA should be held for AST/ALT or alkaline phosphatase ≥5x ULN and/or elevation of serum total bilirubin ≥3x ULN. Upon resolution of hepatotoxicity, ATRA may be resumed at a reduced dose.

Treatment repeats every 28 days for at least 8 cycles in the absence of disease progression or unacceptable toxicity. Patients achieving stable disease may continue to receive treatment in the absence of disease progression or unacceptable toxicity.

After completion of the study treatment, patients are followed up at 28 days and then every 3 months for up to 12 months. Subjects will be evaluated for disease response during each cycle and at the end of study.

7.6. Criteria for Discontinuing ATRA and Discontinuation from Study

ATRA should be discontinued in patients experiencing an AE in Cycle 1 meeting criteria for a DLT for which the investigator considers that retreatment of the patient could be dangerous. For Grade 4 life threatening TEAEs, the subject will be permanently withdrawn from study, except when the investigator determines that the patient is receiving clinical benefit and there are chances to provide supportive care to mitigate the Grade 4 event to recur. In these circumstances, treatment may be restarted at the previously safe dose level or below when toxicity recovers to Grade ≤1 or baseline.

If the next cycle of treatment is delayed for >21 days because of ATRA-related toxicities, then the patient should have study treatment discontinued unless the investigator considers that the patient will receive benefit continuing in the study. If treatment discontinuation is determined, the end of study visit should be completed within 30-40 days after the last administration of ATRA.

7.7. Packaging and Labeling

The label for IP (Dara) will include manufacturer name, address and telephone number, the protocol number, IP name, dosage form, and strength amount of IP per container, lot number, expiry date (where

applicable), medication identification/kit number, dosing instructions, storage conditions, and required caution statements and/or regulatory statements as applicable. Additional information may be included on the label as applicable per local regulations.

7.8. Investigational Product Compliance

The investigator will document the number of capsules of POM issued to and returned by each subject at each study visit. The investigator will document the number of vials of DARA administered to each subject at each DARA administration visit. Overall, the investigator will also be responsible for documenting subject compliance for Dara, Pom and Dex.

8. CONCOMITANT MEDICATIONS AND PROCEDURES

8.1. Permitted Concomitant Medications and Procedures

Other therapies considered necessary for the subject's well-being may be administered at the discretion of the investigator. These therapies may include antibiotics, analgesics, antihistamines, or other medications and transfusions of RBC, platelets, or fresh frozen plasma given to assist in the management of complications associated with MM or its therapy. These therapies also include pre and post infusion medications required for the administration of DARA as per Section 8.2.

The prophylactic use of hematopoietic growth factors will be allowed throughout the study at the treating physician's discretion. Once allowed, the use of myeloid growth factors is encouraged when ANC is less than 1,000/µL at the discretion of the treating physician.

Subjects who met the ANC, hemoglobin, and platelet eligibility criteria due to growth factor treatment or platelet/blood transfusion received prior to the start of the screening period are acceptable. Platelet and RBC transfusions are also permitted during the study.

Adjunctive radiation therapy to a pathological fracture site or to treat bone pain is permitted. Subjects with myeloma-associated bone disease may receive bisphosphonate therapy prior to study entry, as well as other agents that may be used for myeloma-associated bone disease such as denosumab and teriparatide, unless such therapy is contraindicated. The use of bisphosphonates, as well as other agents for the treatment of myeloma-associated bone disease, is permitted throughout the study.

Thromboembolism prophylaxis: Low-dose aspirin, low molecular weight heparin, or other equivalent antithrombotic or anti-coagulant will be given to all subjects per Lenalidomide and Pomalidomide guidelines. The following therapies will be collected and recorded in the subject's Concomitant Medication eCRF page: Anti-infectious agents, anti-thrombotics, growth factors, and bisphosphonates or other agents used for the treatment of myeloma-associated bone disease. All procedures, including transfusions, will be collected and recorded in the subject's eCRF.

8.2. Prohibited Concomitant Medications and Procedures

Concomitant use of other approved or investigational anti-myeloma therapy within 14 days of Cycle 1 Day 1 or while the subject is taking study drug (study treatment phase) is prohibited. Subsequent anti-myeloma treatment should not be initiated prior to PD or study treatment discontinuation.

Chronic use of steroids (other than Dex) or any other immunosuppressive therapies is prohibited in this study without approval from the Medical Monitor.

Drugs known to prolong the QT corrected (QTc) interval should be avoided unless deemed medically necessary. See Appendix G for a comprehensive list of drugs known to prolong QTc.

8.3. Required Concomitant Medications and Procedures

Recent or active cancer is a recognized prothrombotic risk factor for increasing the risk of VTE.

Increased plasma viscosity related to monoclonal paraproteinemia has been implicated as a risk factor for VTE in MM subjects. Clinical studies have shown that thalidomide and Len in combination with Dex or other chemotherapeutic agents increase the risk of VTE (Baz, 2005; Weber, 2007). Aspirin has been reported to be effective in reducing the incidence of DVT in MM subjects treated with thalidomide or LEN (Baz, 2005).

For the current study, low-dose aspirin, low molecular weight heparin, or other equivalent antithrombotic or anti-coagulant will be given during the study to all subjects. Antithrombotic prophylaxis will be recorded on the eCRF.

Pre and post infusion medications required for the administration of Dara as per Section 8.2 will also be recorded on the eCRF. Subjects who develop symptomatic DVT will be assessed and diagnosed objectively by Doppler ultrasonography or a comparable method. Diagnostic algorithms are provided in Appendix A.

8.4. Management of Hepatitis B Virus Reactivation

Primary antiviral prophylaxis is permitted as per local standard of care. Per protocol, HBV DNA testing by PCR is mandatory for subjects at risk for HBV reactivation see Sections 5.4 and 5.5.

For subjects who are diagnosed with HBV reactivation while on treatment, study treatment should be interrupted until the infection is adequately controlled. If the benefits outweigh the risks, study treatment may be resumed with concomitant antiviral prophylaxis as per local standard of care. Consult a liver disease specialist as clinically indicated.

9. STATISTICAL ANALYSIS

9.1. Overview

In general, continuous data will be summarized by descriptive statistics, including number of patients, mean, standard deviation, median, minimum, and maximum. Categorical data will be summarized by the number and percentage of patients. Unless otherwise specified, data will be summarized by treatment arm. A detailed description of analysis methods will be provided in the statistical analysis plan.

9.2. Sample Size and Power Considerations

Phase 1b of the study will follow a standard 3 + 3 dose escalation design as described in Section 7.4. With two dose levels, the study will need between 3 and 12 patients depending on toxicities. Patients will be considered evaluable in phase 1b for MTD assessment provided that they have not missed any of their doses of ATRA in Cycle 1, or have had a DLT. Patients who are not considered evaluable as defined above will be replaced.

For the phase 2 portion:

Approximately 20 patients who fulfill the eligibility criteria of the protocol will be enrolled. The phase 2 study will use a Simon 2-stage minimax design, whereby 10 patients will be accrued in the first stage, and ORR assessed, before moving to the next stage. If ≥ 3 objective responses are observed in the first stage, the study will proceed to the next stage; and an additional 10 patients will be accrued. If there are 8 or

more responses among the 20 patients, the combination will be declared worthy for further evaluation. The null hypothesis that the true response rate is 25% or less will be tested against a one-sided alternative of 48% or higher at the one-sided type I error of 0.10. This design yields a type I error rate of 0.096 and power of 0.806 when the true response rate is 48%. The probability of early stopping due to futility is approximately 52.0%.

9.3. Efficacy Analysis

The primary efficacy parameter is ORR by IMWG criteria. The ORR will be evaluated using 2-sided 80% exact binomial confidence intervals. The rate variables such as CR, sCR, nCR, and VGPR will be evaluated using 2-sided 80% exact binomial confidence intervals.

The distribution of time-to-event response including DOR, TOS, PFS, and OS will be estimated by Kaplan-Meier methodology. The medians of these time-to-event efficacy responses, if available, and their 2-sided 95% CI, will be reported. In addition, the proportions of patients with events at selected time points, together with their 2-sided 95% CI will be presented. The calculations will be performed based on a fixed sample, single-stage design. Time to event analysis will be based on all data combined.

Exploratory endpoints including biomarkers, microbiome, blood variables, and exosome will be summarized descriptively.

9.4. Safety analysis

All safety analyses will be performed on subjects who take at least one dose of study treatment and summarized using descriptive statistics. A separate listing and summary of all AEs and SAEs will be provided.

Please refer to Section 7.4 regarding stopping rules for dose-escalation during Phase 1b.

For phase 2, the first safety analysis will be performed 3 months after the first 10 patients are enrolled and the second safety analysis will be performed 3 months after the next 10 patients are enrolled.

A threshold of fatal AEs related to ATRA of <10% is proposed. Any rate of fatal events related to ATRA clearly in excess of this will result in stopping of the trial. For the 20 patients expected to be treated between phase 1b and phase 2 with one specific dose, this means that the cohort will be stopped if 1 or more fatal TEAEs occur during the first stage of phase 2, and 2 or more fatal TEAEs occur in both stages.

This trial will also be stopped if the rate of TEAE, Grade 4 events, in any non-hematologic system organ class (SOC) exceeds 10% with the exception of Grade 4 asymptomatic laboratory abnormalities. This trial will also be stopped if events meeting the criteria of a DLT occur with an incidence of >40% at any point. The stop will result in an immediate halt in enrollment and may also necessitate the halting of treatment of ongoing patients, depending on the nature and severity of the safety data by the investigators.

The All-Subjects-as-Treated (ASaT) population will be employed for safety analyses. The ASaT population consists of all subjects who received at least one dose of trial treatment. Subjects who entered the study and did not take any of the study drug(s) and had this confirmed, will not be evaluated for safety.

Descriptive tables that summarize the number and percentage of subjects that experience adverse events as categorized in the NCI CTCAE Version 5 will be generated.

The severity of the toxicities will be graded according to the NCI CTCAE v5 whenever possible.

Of note, a death from an unrelated and unforeseen circumstance (i.e. car accident) will not be counted toward toxicity for the stopping rules.
A grade 3 unexpected AE in the first patient will not stop enrollment in the arm

9.5. Interim analysis

The first efficacy analysis for study futility will be assessed 3 months after 10 subjects are enrolled.

This study uses a Simon 2-stage minimax design. Interim analysis will be performed 3 months after 10 subjects are enrolled. If 2 or fewer of those 10 patients have a response, the study will be discontinued after Part 1 due to futility.

10. ADVERSE EVENTS

10.1. Monitoring, Recording and Reporting of Adverse Events

Any untoward medical event in a patient administered a pharmaceutical product which does not necessarily have to have a causal relationship with the treatment. An adverse event can be any unfavorable and unintended sign (including abnormal finding or lack of expected pharmacological action), symptom, or disease temporarily associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that (investigational or non-investigational) product. This includes any occurrence that is new in onset or aggravated in severity from the baseline condition, or abnormal results of any diagnostic procedures, including laboratory test abnormalities. A diagnosis or syndrome should be recorded on the AE page of the eCRF rather than the individual signs or symptoms of the diagnosis or syndrome.

Abuse, withdrawal, sensitivity or toxicity to an investigational product should be reported as an AE. Overdose, accidental or intentional, whether or not it is associated with an AE should be reported on the overdose CRF. Any sequela of an accidental or intentional overdose of an investigational product should be reported as an AE on the AE CRF. If the sequela of an overdose is an SAE, then the overdose and sequela must be reported on an SAE report form and on the AE CRF. In the event of overdose, the subject should be monitored as appropriate and should receive supportive measures as necessary. There is no known specific antidote for Pomalidomide, Daratumumab, or Dexamethasone overdose. Actual treatment should depend on the severity of the clinical situation and the judgement and experience of the treating physician.

All subjects will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or other appropriate tests and procedures.

All AEs will be recorded by the investigator from the time the subject signs informed consent to at least 30 days after the last dose of POM, DARA, or LD-Dex, and those SAEs made known to the investigator at any time thereafter that are suspected of being related to study IPs (POM, DARA, or LD-Dex). AEs and SAEs will be recorded on the AE page of the CRF and in the subject's source documents. All SAEs, Adverse Events of Special Interest and Special situations including pregnancy, suspected transmission of an infectious agent and those associated with an SAE must be reported to Janssen Drug Safety within 24 hours of the investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form.

As the sponsor of the Study designee, the Principal Investigator shall be solely responsible for complying, within the required timelines, any safety reporting obligation to competent Health Authorities, IRB/ECs and any participating sub-investigators, as defined in applicable laws and regulations. For the purposes of this section, safety data includes adverse events, product quality complaints (PQCs), and special situations including pregnancies.

The Principal Investigator will provide safety information to Janssen Scientific Affairs, LLC on adverse events, special situations including pregnancies and product quality complaints as defined within this section.

Management of Safety Data

This Study has been designated as an interventional study. As such, all adverse events for Janssen Medicinal Products regardless of causality and special situations excluding those from subjects not exposed to a Janssen Medicinal Product and product quality complaints with or without an adverse event as described in this Exhibit will be reported from the time a subject has signed and dated an Informed Consent Form (ICF) until completion of the subject's last study-related procedure (which may include contact for follow-up safety). Serious adverse events will be reported for 30 days after the last dose of study drug.

For the purposes of this study, the Janssen medicinal product is: DARZALEX Faspro®(daratumumab and hyaluronidase-fihj)

10.2. Evaluation of Adverse Events

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non- investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

10.3. Severity / Intensity

For both AEs and SAEs, the investigator must assess the severity / intensity of the event.

The severity of AEs will be graded based upon the subject's symptoms according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, Version 5);

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

Adverse events that are not defined in the NCI CTCAE should be evaluated for severity according to the following scale:

- 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, hospitalization is possible
- Grade 4 = Life threatening – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable
- Grade 5 = Death – the event results in death

The term “severe” is often used to describe the intensity of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is not the same as “serious” which is based on subject/event outcome or action criteria associated with events that pose a threat to a subject’s life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

10.3.1. Causality

The investigator must determine the relationship between the administration of IPs (POM, DARA, or LD-Dex) and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

Not suspected: Means a causal relationship of the adverse event to IP (POM, DARA, or LD-Dex) administration is unlikely or remote, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.

Suspected: Means there is a reasonable possibility that the administration of IP (POM, DARA, or LD-Dex) caused the adverse event.

‘Reasonable possibility’ means there is evidence to suggest a causal relationship between the IP and the adverse event.

Causality should be assessed and provided for every AE/SAE based on currently available information. Causality is to be reassessed and provided as additional information becomes available.

If an event is assessed as suspected of being related to a comparator, ancillary, or additional IP that has not been manufactured or provided by Janssen, please provide the name of the manufacturer when reporting the event.

10.3.2. Duration

For both AEs and SAEs, the investigator will provide a record of the start and stop dates of the event.

10.3.3. Action Taken

The investigator will report the action taken with IPs (POM, DARA, or LD-Dex) as a result of an AE or SAE, as applicable (eg, discontinuation or reduction of IP, as appropriate) and report if concomitant and/or additional treatments were given for the event.

10.3.4. Outcome

All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered, recovered with sequelae, not recovered (death due to another cause), or death (due to the SAE).

10.3.5. Abnormal Laboratory Values

An abnormal laboratory value is considered to be an AE if the abnormality:

- results in discontinuation from the study;
- requires treatment, modification/ interruption of IPs (POM, DARA, or LD-Dex) dose, or any other therapeutic intervention; or
- is judged to be of significant clinical importance.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a serious adverse event.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page/screen of the CRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE.

10.4. Adverse Events of Special Interest

Adverse events of special interest are events that Janssen Scientific Affairs, LLC is actively monitoring as a result of a previously identified signal (even if non-serious). These adverse events are:

- Infusion reactions: ≥ grade 3
- Infections: ≥ grade 4
- Cytopenias: ≥ grade 4
- Hepatitis B Reactivation
- Other malignancies

Any Adverse Event of Special Interest that is to be reported to the Janssen should be recorded on a Serious Adverse Event Report Form and be reported to the Janssen within **24 hours of knowledge of the event.**

10.5. Individual Case Safety Report (ICSR)

A valid ICSR must contain the four minimum criteria required to meet regulatory reporting requirements.

- an identifiable subject (but not disclosing personal information such as the subject's name, initials or address)
- an identifiable reporter (investigational site)

- a Janssen medicinal product
- an adverse event, outcome, or certain special situations

The minimum information required is:

- suspected Janssen medicinal product (doses, indication)
- date of therapy (start and end date, if available)
- batch or lot number, if available
- subject details (subject ID and country)
- gender
- age at AE onset
- reporter ID
- adverse event detail (AE verbatim in English), onset date, relatedness, causality, action taken, outcome, (if available)
- Janssen protocol ID

10.6. Serious Adverse Event (SAE)

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is medically important*

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

NOTE: DEATH FOR ANY REASON SHOULD BE REPORTED AS A SERIOUS ADVERSE EVENT.

10.6.1. Hospitalization

For reports of hospitalization, it is the sign, symptom or diagnosis which led to the hospitalization that is the serious event for which details must be provided.

Any event requiring hospitalization or prolongation of hospitalization that occurs during the study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (e.g., social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study. [Note: Hospitalizations that were planned before the start of data collection and where the underlying condition for which the hospitalization was planned has not worsened will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.]
- [For convenience the investigator may choose to hospitalize the subject for the duration of the treatment period.]

10.6.2. Life-Threatening Conditions

Disease progression should not be recorded as an adverse event or serious adverse event term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the serious adverse event definition.

10.7. Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For a medicinal product(s) with a marketing authorization, the expectedness of an adverse event will be determined by whether or not it is listed in the applicable product information.

http://www.darzalex.com/shared/product/darzalex/darzalex-prescribing-information.pdf

For DARZALEX Faspro (daratumumab and hyaluronidase-fihj), the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure.

10.8. Special Reporting Situations

Safety events of interest for a Janssen medicinal product that require expediting reporting and/or safety evaluation include, but are not limited to:

- Drug exposure during pregnancy (maternal and paternal)*
- Suspected transmission of any infectious agent via administration of a medicinal product*

*Reports of these events should be recorded on a Serious Adverse Event Report Form and be reported to Janssen Scientific Affairs, LLC **within 24 hours of becoming aware of the event.**

- Overdose of a Janssen medicinal product
- Exposure to a Janssen medicinal product from breastfeeding
- Suspected abuse/misuse of a Janssen medicinal product
- Inadvertent or accidental exposure to a Janssen medicinal product

- Any failure of expected pharmacological action (i.e., lack of effect) of a Janssen medicinal product
- Medication error involving a Janssen medicinal product (with or without patient exposure to the Janssen medicinal product, e.g., name confusion)
-
- Unexpected therapeutic or clinical benefit from use of a Janssen medicinal product

These safety events may not meet the definition of an adverse event; however, from a Janssen Scientific Affairs, LLC perspective, they are treated in the same manner as adverse events. Special situations should be recorded on the Adverse Event page of the CRF.

Any special situation that meets the criteria of a serious adverse event should be recorded on a Serious Adverse Event Report Form and be reported to Janssen Scientific Affairs, LLC **within 24 hours of becoming aware of the event.**

Maintenance of Safety Information

All safety data should be maintained in a clinical database in a retrievable format. The PRINCIPAL INVESTIGATOR shall provide all adverse events, both serious and non-serious, in report format. However, in certain circumstances more frequent provision of safety data may be necessary, e.g. to fulfill a regulatory request, and as such the data shall be made available within a reasonable timeframe at Janssen Scientific Affairs, LLC request.

Procedures for Reporting Safety Data and Product Quality Complaints (PQCs) for Janssen Medicinal Products to Janssen Scientific Affairs, LLC

All adverse events and special situations, whether serious or non-serious, related or not related, following exposure to a Janssen medicinal product are to be documented by the investigator and recorded in the CRF and in the subject's source records. Investigators must record in the CRF their opinion concerning the relationship of the adverse event to a Janssen medicinal product.

All (serious and non-serious) adverse events reported for a Janssen medicinal product should be followed up in accordance with clinical practice.

SAEs, Adverse Events of Special Interest and Special Reporting Situations

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct

- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

10.9. Pregnancy

All pregnancies or suspected pregnancies occurring in either a female subject or partner of a male subject are immediately reportable events and should be be recorded on a Serious Adverse Event Report Form and be reported to Janssen Scientific Affairs, LLC **within 24 hours of becoming aware of the event.**.

In the event of a pregnancy occurring in a female subject of childbearing potential or female partner of a male subject, Janssen will follow up with the clinical investigator each trimester of pregnancy and for 1 year following the birth of the infant (if applicable). Please reference the pregnancy information consent (permission) forms for data collection for additional information.

The exposure of any pregnant female (eg, caregiver or pharmacist) to Pomalidomide is also an immediately reportable event.

10.9.1. Females of Childbearing Potential:

Pregnancies and suspected pregnancies (including elevated beta human chorionic gonadotropin [βhCG] or positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on study treatment, or within 28 days of the subject's last dose of POM or LD-Dex or within 3 months of last dose of Daratumumab, are considered immediately reportable events. Investigational product is to be discontinued immediately and the subject instructed to return any unused portion of the IP to the investigator. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Janssen Drug Safety immediately by email, phone or facsimile, or other appropriate method, using the Initial Pregnancy Report Form, or approved equivalent form i.e. Clinical SAE Form. The female should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

The investigator will follow the female subject until completion of the pregnancy and must notify Janssen Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Follow-up Pregnancy Report Form or approved equivalent form.

If the outcome of the pregnancy was abnormal (eg, spontaneous or therapeutic abortion), the investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Janssen Drug Safety by facsimile, or other appropriate method, within 24 hours of the investigator's knowledge of the event using the SAE Report Form or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the investigator suspects is related to the in utero exposure to the POM or LD-Dex or within 3 months of last dose of Daratumumab should also be reported to Janssen Drug Safety by facsimile, or other appropriate method, within 24 hours of the investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

10.9.2. Male Subjects

If a female partner of a male subject taking investigational product Pomalidomide, Daratumumab or Dexamethasone becomes pregnant, the male subject taking IPs (POM, DARA, or LD-Dex) should notify the investigator, and the pregnant female partner should be advised to call their healthcare provider immediately. Reports of pregnancy in a partner of a male subject should be recorded on a Serious Adverse Event Report Form and be reported to Janssen Scientific Affairs, LLC **within 24 hours of becoming aware of the event.**

10.10. Reporting of Serious Adverse Events

Any AE that meets any criterion for an SAE requires the completion of an SAE Report Form in addition to being recorded on the AE page/screen of the CRF. All SAEs must be reported to Janssen Drug Safety within 24 hours of the investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form. This instruction pertains to initial SAE reports as well as any follow-up reports.

Second primary malignancies will be monitored as events of interest and must be reported as serious adverse events. This includes any second primary malignancy, regardless of causal relationship to IP (POM, DARA, or LD-Dex), occurring at any time for the duration of the study, from the time of signing the ICD for at least 5 years from the date the last subject is randomized into the study. Events of second primary malignancy are to be reported using the SAE report form and must be considered an "Important Medical Event" if no other serious criteria apply; these events must also be documented in the appropriate page(s) of the CRF (ie, AE and SPM CRF) and subject's source documents. Documentation of the diagnosis of the SPM must be provided at the time of reporting as a serious adverse event (eg, any confirmatory histology or cytology results, x-rays, CT scans, etc.).

The investigator is required to ensure that the data on these forms is accurate and consistent.

This requirement applies to all SAEs (regardless of relationship to IPs [POM, DARA, or LDDex]) that occur during the study (from the time the subject signs informed consent to at least 30 days after the last dose of IPs [POM, DARA, or LD-Dex]), and those made known to the investigator at any time thereafter that are suspected of being related to IPs (POM, DARA, or LD-Dex). SAEs occurring prior to treatment will be captured.

The SAE report should provide a detailed description of the SAE and include summaries of hospital records and other relevant documents. If a subject died and an autopsy has been performed, copies of the autopsy report and death certificate are to be sent to Janssen Drug Safety as soon as these become available. Any follow-up data will be detailed in a subsequent SAE Report Form, or approved equivalent form, and sent to Janssen Drug Safety.

Where required by local legislation, the investigator is responsible for informing the Institutional Review Board (IRB)/Ethics Committee (EC) of the SAE and providing them with all relevant initial and follow-up information about the event. The investigator must keep copies of all SAE information on file including correspondence with Janssen and the IRB/EC.

10.10.1. Safety Queries

Queries pertaining to SAEs will be communicated from Janssen Drug Safety to the site via facsimile or electronic mail. The response time is expected to be no more than 5 business days.

Urgent queries (eg, missing causality assessment) may be handled by phone.

10.11. Expedited Reporting of Adverse Events

In the United States, all suspected unexpected serious adverse reactions (SUSARs) will be reported in an expedited manner in accordance with 21 CFR 312.32.

Events of e.g. disease progression for the disease under study (including deaths due to disease progression for indications that are considered to be fatal) will be assessed as expected adverse events and will not be reported as expedited safety reports to regulatory authorities.

Where required by local legislation, the investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

The investigator must keep copies of all pertinent safety information on file including correspondence with Janssen and the IRB/EC.

11. REGULATORY CONSIDERATIONS

11.1. Good Clinical Practice

The study will be conducted according to the International Conference on Harmonization (ICH), Good Clinical Practice (GCP), the Declaration of Helsinki, Institutional Review Boards (IRB) and in accordance with the U.S. Code of Federal Regulations on Protection of Human Rights (21 CFR 50).

11.2. Institutional Review Board (IRB) Review

The final study protocol and consent form (and any other appropriate documents as applicable) will be approved by the Institutional Review Board (IRB) at Hackensack Meridian *Health*. Approval will be received in writing before initiation of the study.

Any changes to the study design will be formally documented in protocol amendments and will be approved by the IRB prior to implementation.

Any amendment to this protocol must also be approved by the Janssen Clinical Research Physician/Medical Monitor. The written signed approval from the IRB should specifically reference the investigator name, protocol number, study title and amendment number(s) that is applicable. Amendments that are administrative in nature do not require IRB approval but will be submitted to the IRB for information purposes.

The investigator must keep a record of all communication with the IRB and, if applicable, between a Coordinating investigator and the IRB. This statement also applies to any communication between the investigator (or Coordinating investigator, if applicable) and regulatory authorities.

Ongoing Information for IRB Committee

As required by legislation and local regulatory requirements, the investigator must submit to the IRB:

- Information on serious or unexpected adverse events as soon as possible;
- Annual reports on the progress of the study;
- Deviations from the protocol or anything that may involve added risk to subjects.

11.3. Data Safety Monitoring

The Georgetown Lombardi Comprehensive Cancer Center will be responsible for the data and safety monitoring of this multi-site trial. As this study is an investigator initiated Phase 1 or II study utilizing a non-FDA approved drug for which the PI holds the IND it is considered a high risk study which requires real-time monitoring by the PI and study team and reviewed quarterly by the LCCC Data and Safety Monitoring Committee (DSMC).

The Principal Investigator and the Co-Investigators will review the data including safety monitoring at their weekly institution based disease group meetings and on monthly disease group teleconferences.

All Serious Adverse Events (SAEs) are required to be reported to the IRB. Based on SAEs, the IRB retains the authority to suspend further accrual pending more detailed reporting and/or modifications to further reduce risk and maximize the safety of participating patients.

Progress on the trial and the toxicities experienced will be reviewed by the LCCC Data and Safety Monitoring Committee quarterly from the time the first patient is enrolled on the study. Results of the DSMC meetings will be forwarded to the IRB with recommendations regarding need for study closure.

DSMC recommendations should be based not only on results for the trial being monitored as well as on data available to the DSMC from other studies. It is the responsibility of the PI to ensure that the DSMC is kept apprised of non-confidential results from related studies that become available. It is the responsibility of the DSMC to determine the extent to which this information is relevant to its decisions related to the specific trial being monitored.

A written copy of the DSMC recommendations will be given to the trial PI and the IRB. If the DSMC recommends a study change for patient safety or efficacy reasons the trial PI must act to implement the change as expeditiously as possible. In the unlikely event that the trial PI does not concur with the DSMC recommendations, then the LCCC Associate Director of Clinical Research must be informed of the reason for the disagreement. The trial PI, DSMC Chair, and the LCCC AD for Clinical Research will be responsible for reaching a mutually acceptable decision about the study and providing details of that decision to the IRB. Confidentiality must be preserved during these discussions. However, in some cases, relevant data may be shared with other selected trial investigators and staff to seek advice to assist in reaching a mutually acceptable decision.

If a recommendation is made to change a trial for reasons other than patient safety or efficacy the DSMC will provide an adequate rationale for its decision. If the DSMC recommends that the trial be closed for any reason, the recommendation will be reviewed by the Associate Director for Clinical Research at G-LCCC. Authority to close a trial for safety reasons lies with the IRB, with the above described input from DSMC and the AD for Clinical Research.

11.4. Investigator Responsibilities

Investigator responsibilities are set out in the ICH Guideline for Good Clinical Practice and in the local regulations.

The investigator should ensure that all persons assisting with the study are adequately informed about the protocol, amendments, study treatments, as well as study-related duties and functions.

The investigator should maintain a list of Sub-Investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties. The investigator is responsible for keeping a record of all subjects who sign an informed consent document and are screened for entry into the study. Subjects who fail screening must have the reason(s) recorded in the subject's source documents.

The investigator, or a designated member of the investigator's staff, must be available during monitoring visits to review data, resolve queries and allow direct access to subject records (eg, medical records, office charts, hospital charts, and study-related charts) for source data verification. The investigator must ensure timely and accurate completion of CRFs and queries.

11.5. Subject Information and Informed Consent

The investigator must obtain informed consent of a subject and/or a subject's legal representative prior to any study related procedures.

Documentation that informed consent occurred prior to the study subject's entry into the study and of the informed consent process should be recorded in the study subject's source documents including the date. The original informed consent document signed and dated by the study subject and by the person consenting the study subject prior to the study subject's entry into the study, must be maintained in the investigator's study files and a copy given to the study subject.

In addition, if a protocol is amended and it impacts on the content of the informed consent, the informed consent document must be revised. Study subjects participating in the study when the amended protocol is implemented must be re-consented with the revised version of the informed consent document. The revised informed consent document signed and dated by the study subject and by the person consenting the study subject must be maintained in the investigator's study files and a copy given to the study subject.

11.6. Confidentiality

The patient charts, collected data, and all analysis of the data will adhere to HIPAA & institutional patient confidentiality requirements.

More specifically, a coding system will be used for which a unique identifier (study ID number) will be assigned to each patient name and contact details. Only the study number will be included in the data collection tool, data analysis software and potential publications. The list with the direct identifiers (for the purposes of linking data and keeping track of patients) will be stored separately in a secure server at each site.

Analytical datasets will be stored on secure servers that also limit access to the investigator team. Should results of the study be published or reported, individual names or other identifying information will not be used.

11.7. Retention of Records

Records will be retained in accordance with regulatory, organizational and sponsor requirements, but no less than six (6) years following the completion of the research. Disposal of records will be done in such a manner that no identifying information can be linked to research data.

11.8. Closure of the Study

Janssen reserves the right to terminate this study at any time for reasonable medical or administrative reasons. Any premature discontinuation will be appropriately documented according to local requirements (e.g., IRB, regulatory authorities).

In addition, the sponsor has the right to discontinue a single site at any time during the study for medical or administrative reasons such as:

- Unsatisfactory enrollment;
- GCP noncompliance;
- Inaccurate or incomplete data collection;
- Falsification of records;
- Failure to adhere to the study protocol.

12. DATA HANDLING AND RECORDKEEPING

12.1. Data/Documents

The investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the investigational product are complete, accurate, filed and retained. Examples of source documents include: hospital records; clinic and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiche; x-ray film and reports; and records kept at the pharmacy, and the laboratories, as well as copies of CRFs or CD-ROM.

12.2. Data Management

Data will be collected via electronic CRF (eCRFs). This data will be electronically verified through use of programmed edit checks specified by the clinical team. Discrepancies in the data will be brought to the attention of the clinical team, and investigational site personnel, if necessary. Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data.

12.3. Product Quality Complaint

A product quality compliant is defined as any suspicion of a product defect related to a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product, or delivery system. Not all PQCs involve a subject. Lot and batch numbers are of high significance and need to be collected whenever available.

Examples of PQC include but not limited to:

- Functional Problem: e.g., altered delivery rate in a controlled release product
- Physical Defect: e.g. abnormal odor, broken or crushed tablets/capsules
- Potential Dosing Device Malfunction: e.g., autoinjector button not working, needle detaching from syringe
- Suspected Contamination
- Suspected Counterfeit

If you become aware of a suspected PQC, you are obligated to report the issue immediately. You can do so by emailing IIS-BIO-VIRO-GCO@its.jnj.com or by contacting the Janssen Customer Care Center (1-888-423-5436).

13. QUALITY CONTROL AND QUALITY ASSURANCE

All aspects of the study will be carefully monitored by Sponsor Institution or its authorized representative for compliance with applicable government regulations with respect to current GCP and standard operating procedures.

13.1. Study Monitoring and Source Data Verification

Sponsor institution ensures that appropriate monitoring procedures are performed before, during and after the study. Before the study is initiated at a site visit or at an Investigator meeting, all aspects of the study are reviewed with the investigator and the staff. Prior to enrolling subjects into the study, a Janssen representative will review the protocol, CRFs, procedures for obtaining informed consent, record keeping, and reporting of AEs/SAEs with the investigator. Monitoring will include on-site visits with the investigator and his/her staff as well as any appropriate communications by mail, email, fax, or telephone. At each monitoring visit, the facilities, investigational product storage area, CRFs, subject's source documents, and all other study documentation will be inspected/reviewed by the Sponsor institution representative for accuracy, adherence to the protocol and Good Clinical Practice.

Accuracy will be checked by performing source data verification that is a direct comparison of the entries made onto the CRFs against the appropriate source documentation. Any resulting discrepancies will be reviewed with the investigator and/or his/her staff. Any necessary corrections will be made directly to the CRFs or via queries by the investigator and/or his/her staff. Monitoring procedures require that informed consents, adherence to inclusion/exclusion criteria and documentation of SAEs and their proper recording be verified. Additional monitoring activities may be outlined in a study-specific monitoring plan.

13.2. Audits and Inspections

In addition to the routine monitoring procedures, a Good Clinical Practice Quality Assurance unit exists within Janssen. Representatives of this unit will conduct audits of clinical research activities in accordance with Janssen SOPs to evaluate compliance with Good Clinical Practice guidelines and regulations.

The investigator is required to permit direct access to the facilities where the study took place, source documents, CRFs and applicable supporting records of study subject participation for audits and inspections by IRB/IECs, regulatory authorities (e.g., FDA, EMA, Health Canada, Pharmaceuticals and Medical Devices Agency) and company authorized representatives. The investigator should make every effort to be available for the audits and/or inspections. If the investigator is contacted by any regulatory authority regarding an inspection, he/she should contact Janssen immediately.

14. PUBLICATIONS

The results of this study may be published in a medical publication, journal, or may be used for teaching purposes. Additionally, this study and its results may be submitted for inclusion in all appropriate health authority study registries, as well as publication on health authority study registry websites, as required by local health authority regulations. Selection of first authorship will be based on several considerations, including, but not limited to study participation, contribution to the protocol development, and analysis and input into the manuscript, related abstracts, and presentations in a study.

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APPENDIX A: Research Biospecimen Sample Collection

Code for Correlative Studies	**(PtID) (Timepoint) (Date)**
Peripheral Blood Samples (7x Yellow top tubes (BD Vacutainer ACD Solution A Blood Collection tubes – 8.5ml) – 59.5ml 1 Streck Cell-Free DNA BCR tube	**Timepoint ID**
Screening/Cycle 1 Day 1 - to be collected prior drug administration	1
Cycle 2 Day 1 (+/-2 days)	2
End of Treatment Visit	EOT
Relapse	4 R

All Peripheral blood samples are to be kept at room temperature – no immediate processing needed.

Samples for HackensackUMC subjects are to be delivered via courier to lab. If sample is collected in the late afternoon, please store at room temperature on a shaker (slow speed) until delivered to Dr. Korngold's Laboratory the next day.

Samples for Georgetown University subjects are to be shipped via Fed Ex on the day of collection. The tubes are to be banded in sealed plastic bag and wrapped in bubble wrap. If sample is collected in the late afternoon, please store at room temperature on a shaker (slow speed) until next shipment day.

Please ship to:
Robert Korngold, PhD
Center for Discovery & Innovation, Hackensack Meridian Health
340 Kingsland St, Building 102
Nutley, NJ 07110
Tel: 201-880-3440
e-mail: Robert.Korngold@HMH-CDI.org

Any time patients receive antibiotics while on study they should have stool and peripheral blood collected before starting antibiotics and upon completion of antibiotics (within a 7 day window).

Bone Marrow Aspirate Samples (1x Yellow top tube) – first pull about 4 ml	**Timepoint ID**
Screening Visit or day 1, Cycle 1	S
Cycle 2 Day 1 (+/- 2 days)	2
End of Treatment Visit or Relapse	EOT

All Bone Marrow Aspirate samples are to be kept at room temperature – no immediate processing needed.

Samples for HackensackUMC subjects are to be delivered via courier to lab. If sample is collected in the late afternoon, please store at room temperature on a shaker (slow speed) until delivered to Dr. Korngold's Laboratory the next day.

Samples for Georgetown University subjects are to be shipped via Fed Ex on the day of collection. The tubes are to be banded in sealed plastic bag and wrapped in bubble wrap. If sample is collected in the late afternoon, please store at room temperature on a shaker (slow speed) until next shipment day.

Please ship to:
Robert Korngold, PhD
HMH Center for Discovery & Innovation
340 Kingsland St, Building 102
Nutley, NJ 07110
Tel: 201-880-3440
e-mail: Robert.Korngold@HMH-CDI.org

Stool Samples **To be collected up to 48 hours prior to clinic visit and *prior to drug administration**	**Timepoint ID**
Screening/Cycle 1 Day 1 - to be collected prior drug administration	1
Cycle 2 Day 1 (+/-2 days)	2
End of Treatment Visit	EOT
Relapse	4 R

All stool samples at HackensackUMC are to be kept at -80°C - no immediate processing needed.

Samples for HackensackUMC Subjects are to be delivered via courier to Center for Discovery & Innovation in an insulated container in dry ice.

Samples for Georgetown University subjects are to be shipped via Fed Ex on the day of collection. The tubes are to be placed in sealed plastic bag and shipped on dry ice. If sample is collected in the late afternoon, please store immediately at -20°C and ship on dry ice the following day.

Please ship to:
Rena Feinman, PhD
Center for Discovery & Innovation-Hackensack Meridian Health
340 Kingsland St, Building 102
Nutley, NJ 07110
Tel: 201-880-3440
e-mail: Rena.Feinman@hmh-cdi.org@HMH-CDI.org

Any time patients receive antibiotics while on study they should have stool and peripheral blood collected before starting antibiotics and upon completion of antibiotics (within a 7 day window). Patients should be provided with multiple stool kits prior to study so that they may collect stool even if antibiotics are prescribed by an outside physician.

APPENDIX B: International Myeloma Working Group Uniform Response Criteria 2016

Table 9: International Myeloma Working Group Uniform Response Criteria

Response Category	Response Criteria*
MRD response Criteria (requires a complete response)	
Sustained MRD-negative	MRD negativity in the marrow (NGF or NGS, or both) and by imaging as defined below, confirmed minimum of 1 year apart. Subsequent evaluations can be used to further specify the duration of negativity (eg, MRD-negative at 5 years) †
Flow MRD-negative	Absence of phenotypically aberrant clonal plasma cells by NGF‡ on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher
Sequencing MRD-negative	Absence of clonal plasma cells by NGS on bone marrow aspirate in which presence of a clone is defined as less than two identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using the LymphoSIGHT platform (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells§ or higher
Imaging plus MRD-negative	MRD negativity as defined by NGF or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT or decrease to less mediastinal blood pool SUV or decrease to less than that of surrounding normal tissue¶
Standard IMWG response criteria	
Stringent Complete Response (sCR)	Complete response (CR) as defined below, *plus* Normal serum free light chain (FLC) ratio** *and* Absence of clonal plasma cells by immunohistochemistry (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥100 plasma cells)††
Complete Response (CR)	Negative immunofixation of serum and urine *and* Disappearance of any soft tissue plasmacytomas *and* < 5% plasma cells in bone marrow aspirates In patients in whom the only measurable disease is by serum FLC levels: CR

	in such patients indicates a normal FLC ratio of 0.26 to 1.65 in addition to CR criteria listed above.
Very Good Partial Response (VGPR)	Serum and urine M-protein detectable by immunofixation but not on electrophoresis *or* 90% or greater reduction in serum M-protein plus urine M-protein level <100 mg per 24 hours In patients in whom the only measurable disease is by serum FLC levels: VGPR in such patients requires a > 90% decrease in the difference between involved and uninvolved FLC levels.

Table 9: International Myeloma Working Group Uniform Response Criteria (Continued)

Response Category	Response Criteria*
Partial Response (PR)	≥ 50% reduction of serum M-Protein and reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg per 24 hours If the serum and urine M-protein are not measurable, 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 unmeasurable, and the serum free light chain assay is also unmeasurable, a ≥ 50% reduction in plasma cells is required in place of M- protein, provided baseline bone marrow plasma cell percentage was ≥ 30% In addition to these criteria, if present at baseline, a ≥50% reduction in the size measured by sum of the products (SPD) §§ of the maximal perpendicular diameters of soft tissue plasmacytomas is also required
Stable Disease (SD)	Not meeting criteria for CR, VGPR, MR, PR, or progressive disease (PD)
Progressive disease (PD) ¶¶ ||||	Requires only one of the following: Increase of 25% from lowest response value in any of the following: ● Serum M-component (absolute increase must be ≥ 0.5 g/dL), and/or ● Urine M-component (absolute increase must be ≥ 200 mg/24 h), and/or Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be ≥ 10 mg/dL) Only in patients without measurable serum and urine M protein levels and without measurable disease by FLC levels, bone marrow plasma cell percentage (absolute increase must be ≥ 10%) Appearance of a new lesion(s), ≥ 50% increase from nadir in SPD§§ of > 1 lesion, or ≥ 50% increase in the longest diameter of a previous lesion > 1 cm in short axis; ≥ 50% increase in circulating plasma cells (minimum of 200 cells per μL) if this is the only measure of disease

Table 9: International Myeloma Working Group Uniform Response Criteria (Continued)

Response Category	Response Criteria*
Clinical Relapse	Clinical relapse requires one or more of the following criteria: Direct indicators of increasing disease and/or end organ dysfunction (CRAB features) related to the underlying clonal plasma-cell proliferative disorder. It is not used in calculation of time to progression or progression-free survival but is listed as something that can be reported optionally or for use in clinical practice; Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression); Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and ≥1 cm) increase as measured serially by the SPD§§ of the measurable lesion; Hypercalcaemia (> 11 mg/dL); Decrease in hemoglobin of ≥ 2 g/dL not related to therapy or other non-myeloma-related conditions; Rise in serum creatinine by 2 mg/dL or more from the start of the therapy and attributable to myeloma; Hyperviscosity related to serum paraprotein
Relapse from complete response (to be used only if the endpoint is disease-free survival)	Any one or more of the following criteria: Reappearance of serum or urine M-protein by immunofixation or electrophoresis; Development of ≥ 5% plasma cells in the bone marrow; Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcaemia see above)
Relapse from MRD negative (to be used only if the endpoint is disease-free	Any one or more of the following criteria: Loss of MRD negative state (evidence of clonal plasma cells on NGF or NGS, or positive imaging study for recurrence of myeloma); Reappearance of serum or urine M-protein by immunofixation or electrophoresis; Development of ≥ 5% plasma cells in the bone marrow; Appearance of any other sign of progression (ie, new plasmacytoma, lytic

survival)	bone lesion, or hypercalcaemia)
Minimal Response (MR)	≥ 25% but ≤ 49% reduction of serum M-protein and reduction in 24-hour urine M- protein by 50%-89% In addition to the above criteria, if present at baseline, ≥50% reduction in the size (SPD) §§ of soft tissue plasmacytomas is also required

Refer to IMWG criteria for specific details (Kumar, 2016).

For MRD assessment, the first bone marrow aspirate should be sent to MRD (not for morphology) and this sample should be taken in one draw with a volume of minimally 2 mL (to obtain sufficient cells), but maximally 4–5 mL to avoid haemodilution. IMWG = International Myeloma Working Group. MRD = minimal residual disease. NGF = next- generation flow. NGS = next-generation sequencing. FLC = free light chain. M-protein = myeloma protein. SPD = sum of the products of the maximal perpendicular diameters of measured lesions. CRAB features = calcium elevation, renal failure, anaemia, lytic bone lesions. FCM = flow cytometry. SUVmax = maximum standardised uptake value. MFC = multiparameter flow cytometry. ^{18}F-FDG PET = ^{18}F-fluorodeoxyglucose PET. ASCT = autologous stem cell transplantation.

* All response categories require two consecutive assessments made any time before starting any new therapy; for MRD there is no need for two consecutive assessments, but information on MRD after each treatment stage is recommended (eg, after induction, high-dose therapy/ASCT, consolidation, maintenance). MRD tests should be initiated only at the time of suspected complete response. All categories of response and MRD require no known evidence of progressive or new bone lesions if radiographic studies were performed. However, radiographic studies are not required to satisfy these response requirements except for the requirement of FDG PET if imaging MRD-negative status is reported.

† Sustained MRD negativity when reported should also annotate the method used (eg, sustained flow MRD-negative, sustained sequencing MRD-negative).

‡ Bone marrow MFC should follow NGF guidelines. The reference NGF method is an eight-colour two-tube approach, which has been extensively validated. The two-tube approach improves reliability, consistency, and sensitivity because of the acquisition of a greater number of cells. The eight-colour technology is widely available globally and the NGF method has already been adopted in many flow laboratories worldwide. The complete eight-colour method is most efficient using a lyophilised mixture of antibodies which reduces errors, time, and costs. 5 million cells should be assessed. The FCM method employed should have a sensitivity of detection of at least 1 in 10^5 plasma cells.

§ DNA sequencing assay on bone marrow aspirate should use a validated assay such as LymphoSIGHT (Sequenta).

¶ Criteria used by Zamagni and colleagues, and expert panel (IMPetUs; Italian Myeloma criteria for PET Use). Baseline positive lesions were identified by presence of focal areas of increased uptake

within bones, with or without any underlying lesion identified by CT and present on at least two consecutive slices. Alternatively, an SUVmax=2·5 within osteolytic CT areas >1 cm in size, or SUVmax=1·5 within osteolytic CT areas ≤1 cm in size were considered positive. Imaging should be performed once MRD negativity is determined by MFC or NGS. ||Derived from international uniform response criteria for multiple myeloma. Minor response definition and clarifications derived from Rajkumar and colleagues. When the only method to measure disease is by serum FLC levels: complete response can be defined as a normal FLC ratio of 0·26 to 1·65 in addition to the complete response criteria listed previously. Very good partial response in such patients requires a ≥90% decrease in the difference between involved and uninvolved FLC levels. All response categories require two consecutive assessments made at any time before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions or extramedullary plasmacytomas if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments do not need to be confirmed. Each category, except for stable disease, will be considered unconfirmed until the confirmatory test is performed. The date of the initial test is considered as the date of response for evaluation of time dependent outcomes such as duration of response.

** All recommendations regarding clinical uses relating to serum FLC levels or FLC ratio are based on results obtained with the validated Freelite test (Binding Site, Birmingham, UK).

†† Presence/absence of clonal cells on immunohistochemistry is based upon the κ/λ/L ratio. An abnormal κ/λ ratio by immunohistochemistry requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is κ/λ of >4:1 or <1:2.

‡‡ Special attention should be given to the emergence of a different monoclonal protein following treatment, especially in the setting of patients having achieved a conventional complete response, often related to oligoclonal reconstitution of the immune system. These bands typically disappear over time and in some studies have been associated with a better outcome. Also, appearance of monoclonal IgG κ in patients receiving monoclonal antibodies should be differentiated from the therapeutic antibody. §§Plasmacytoma measurements should be taken from the CT portion of the PET/CT, or MRI scans, or dedicated CT scans where applicable. For patients with only skin involvement, skin lesions should be measured with a ruler. Measurement of tumour size will be determined by the SPD.

¶¶ Positive immunofixation alone in a patient previously classified as achieving a complete response will not be considered progression. For purposes of calculating time to progression and progression-free survival, patients who have achieved a complete response and are MRD-negative should be evaluated using criteria listed for progressive disease. Criteria for relapse from a complete response or relapse from MRD should be used only when calculating disease-free survival.

|||| In the case where a value is felt to be a spurious result per physician discretion (eg, a possible laboratory error), that value will not be considered when determining the lowest value.

APPENDIX C: Global Pomalidomide Pregnancy Prevention Plan

1. POMALIDOMIDE PREGNANCY PREVENTION PLAN FOR SUBJECTS IN CLINICAL TRIALS

The Pregnancy Prevention Plan (PPP) applies to all subjects receiving pomalidomide within a clinical trial. The following PPP documents are included:

1. The Pomalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods document (Section 2) provides the following information:
   - Potential risks to the fetus associated with pomalidomide exposure
   - Definition of female of childbearing potential (FCBP)/female not of childbearing potential (FNCBP)
   - Requirements for counseling of all subjects receiving pomalidomide about pregnancy precautions and the potential risks of fetal exposure to pomalidomide
   - Acceptable birth control methods for both female subjects of childbearing potential and male subjects receiving pomalidomide in the study
   - Pregnancy testing requirements for subjects receiving pomalidomide who are FCBP
2. The Pomalidomide Education and Counseling Guidance Document for each gender (female and male; Section 3 and Section 4 respectively) must be completed and signed by a trained counselor at the participating clinical center prior to each dispensing of pomalidomide. A copy of this document must be maintained in the subject's records for each dispense.
3. The Pomalidomide Information Sheet (Section 5) will be given to each subject receiving pomalidomide. The subject must read this document prior to starting pomalidomide and each time the subject receives a new supply of pomalidomide.

2. POMALIDOMIDE RISKS OF FETAL EXPOSURE, PREGNANCY TESTING GUIDELINES AND ACCEPTABLE BIRTH CONTROL METHODS

2.1. Risks Associated with Pregnancy

Pomalidomide was teratogenic in both rats and rabbits when administered during the period of organogenesis. Pomalidomide is an analogue of thalidomide. Thalidomide is a known human teratogen that causes severe life-threatening human birth defects. If pomalidomide is taken during pregnancy, it can cause birth defects or death to an unborn baby.

The teratogenic effect of pomalidomide in humans cannot be ruled out. Therefore, a pregnancy prevention program must be followed.

2.1.1. Definition of Females of Childbearing Potential

A FCBP is a female who: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy or 3) 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 in the preceding 24 consecutive months).

2.1.2. Definition of Females Not of Childbearing Potential

Females who do not meet the above definition of FCBP should be classified as FNCBP.

2.2. Counseling

2.2.1. Females of Childbearing Potential

For a FCBP, pomalidomide is contraindicated unless all of the following are met (ie, all FCBP must be counseled concerning the following risks and requirements prior to the start of pomalidomide):

- She understands the potential teratogenic risk to the unborn child
- She understands the need for effective contraception, without interruption, 28 days before starting pomalidomide, throughout the entire duration of pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide
- She understands and agrees to inform the Investigator if a change or stop of method of contraception is needed
- She must be 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 pomalidomide as soon as it is dispensed following a negative pregnancy test

- She understands and accepts the need to undergo pregnancy testing based on the frequency outlined in this plan (Section 2.4) and in the Informed Consent
- She acknowledges that she understands the hazards pomalidomide can cause to an unborn fetus and the necessary precautions associated with the use of pomalidomide.

The Investigator must ensure that a FCBP:

- Complies with the conditions of the pregnancy prevention plan, including confirmation that she has an adequate level of understanding
- Acknowledges the aforementioned requirements.

2.2.2. Females Not of Childbearing Potential

For a FNCBP, pomalidomide is contraindicated unless all of the following are met (ie, all FNCBP must be counseled concerning the following risks and requirements prior to the start of pomalidomide):

- She acknowledges she understands the hazards pomalidomide can cause to an unborn fetus and the necessary precautions associated with the use of pomalidomide.

2.2.3. Males

The effect of pomalidomide on sperm development is not known and has not been studied. The risk to an unborn baby in females of child bearing potential whose male partner is receiving pomalidomide is unknown at this time. Therefore, male subjects taking pomalidomide must meet the following conditions (ie. all males must be counseled concerning the following risks and requirements prior to the start of pomalidomide):

- Understand the potential teratogenic risk if engaged in sexual activity with a pregnant female or a FCBP
- Understand 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 a FCBP
- Understand the potential teratogenic risk if the subject donates semen or sperm.

2.3. Contraception

2.3.1. Female Subjects of Childbearing Potential

Females of childbearing potential enrolled in this protocol must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) from heterosexual contact during the following time periods related to this study: 1) for at least 28 days before starting pomalidomide; 2) while taking pomalidomide; 3) during dose interruptions; and 4) for at least 28 days after the last dose of pomalidomide.

The two methods of reliable contraception must include one highly effective method and one additional effective (barrier) method. If the below contraception methods are not appropriate for the FCBP, she must be referred to a qualified provider of contraception methods to determine the medically effective contraception method appropriate to the subject. The following are examples of highly effective and additional effective methods of contraception:

- Examples of highly effective methods:
  - Intrauterine device (IUD)
  - Hormonal (birth control pills, injections, implants, levonorgestrel-releasing intrauterine system [IUS], medroxyprogesterone acetate depot injections, ovulation inhibitory progesterone-only pills [e.g. desogestrel])
  - Tubal ligation
  - Partner's vasectomy
- Examples of additional effective methods:
  - Male condom
  - Diaphragm
  - Cervical Cap

Because of the increased risk of venous thromboembolism in subjects with multiple myeloma taking pomalidomide and dexamethasone, combined oral contraceptive pills are not recommended. If a subject is currently using combined oral contraception the subject should switch to another one of the highly 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.

[Please note, the above highlighted text is applicable for protocols with dexamethasone-containing pomalidomide regimens.]

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 subjects with neutropenia.

2.3.2. Male Subjects

Male subjects must practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or agree to use a condom during sexual contact with a pregnant female or a FCBP while taking pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide, even if he has undergone a successful vasectomy.

2.4. Pregnancy Testing

Medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for FCBP.

Females of childbearing potential must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting pomalidomide. The first pregnancy test must be performed within 10 to 14 days prior to the start of pomalidomide and the second pregnancy test must be performed within 24 hours prior to the start of pomalidomide. The subject may not receive pomalidomide until the study doctor has verified that the results of these pregnancy tests are negative.

Females of childbearing potential with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while taking pomalidomide, at study discontinuation, and at Day 28 following the last dose of pomalidomide.

Females of childbearing potential with irregular menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 14 days while taking pomalidomide, at study discontinuation, and at Days 14 and 28 following the last dose of pomalidomide.

2.5. Pregnancy Precautions for Pomalidomide Use

2.5.1. Before Starting Pomalidomide

2.5.1.1. Female Subjects of Childbearing Potential

Females of childbearing potential must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting pomalidomide. The first pregnancy test must be performed within 10 to 14 days prior to the start of pomalidomide and the second pregnancy test must be performed within 24 hours prior to the start of pomalidomide. The subject may not receive pomalidomide until the study doctor has verified that the results of these pregnancy tests are negative.

Females of childbearing potential must use two reliable forms of contraception simultaneously, or practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) from heterosexual contact for at least 28 days before starting pomalidomide.

2.5.1.2. Male Subjects

Male subjects must agree to practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or agree to use a condom during sexual contact with a pregnant female or a FCBP while taking pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide, even if he has undergone a successful vasectomy.

2.5.2. During and After Study Participation

2.5.2.1. Female Subjects

- Females of childbearing potential with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while taking pomalidomide, at study discontinuation, and at Day 28 following the last dose of pomalidomide.
- Females of childbearing potential with irregular menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 14 days while taking pomalidomide, at study discontinuation, and at Days 14 and 28 following the last dose of pomalidomide.
- At each visit, the Investigator must confirm with the FCBP that she is continuing to use two reliable methods of birth control if not committing to complete abstinence, or confirm commitment to complete abstinence.
- If a FCBP considers the need to change or to stop a method of contraception, the Investigator must be notified immediately.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in a subject, pomalidomide must be immediately discontinued.
- Pregnancy testing and counseling must be performed if a subject misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Pomalidomide must be discontinued during this evaluation.
- Females must agree to abstain from breastfeeding while taking pomalidomide and for at least 28 days after the last dose of pomalidomide.

2.5.2.2. Male Subjects

- Must practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or use a condom during sexual contact with a pregnant female or a FCBP while receiving pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide, even if he has undergone a successful vasectomy.
- Must not donate semen or sperm while receiving pomalidomide, during dose interruptions or for at least 28 days after the last dose of pomalidomide.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days.

- If pregnancy or a positive pregnancy test does occur in the partner of a male subject while taking pomalidomide, the Investigator must be notified immediately.

2.5.3. Additional Precautions

- Subjects should be instructed to never give pomalidomide to another person.
- Subjects should be instructed to return any unused capsules to the study doctor.
- Subjects should not donate blood while receiving pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide.
- No more than a 28-day pomalidomide supply may be dispensed with each cycle of pomalidomide.

3. POMALIDOMIDE EDUCATION AND COUNSELING GUIDANCE DOCUMENT FOR FEMALE SUBJECTS

To be completed prior to each dispensing of pomalidomide.

Protocol Number:

Subject Name (Print): _____ DOB: _____/_____/_____ (dd/mmm/yyyy)

Check one risk category:

- ☐ FCBP (Female of childbearing potential): a female who: 1) has achieved menarche (first menstrual cycle) at some point. 2) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 3) 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

3.1. Female of Childbearing Potential:

1. I have verified and counseled the subject regarding the following:
   - ☐ Potential risk of fetal exposure to pomalidomide: A teratogenic potential of pomalidomide in humans cannot be ruled out. 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. Females of childbearing potential must agree not to become pregnant while taking pomalidomide.
   - ☐ That the required pregnancy tests performed are negative.
   - ☐ The subject confirmed that she is using TWO reliable methods of birth control at the same time, or complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) from heterosexual contact (at least 28 days prior to receiving pomalidomide, while receiving pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide).

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

     - Examples of highly effective methods:
       - Intrauterine device (IUD)
       - Hormonal (birth control pills, injections, implants, levonorgestrel-releasing intrauterine system [IUS], medroxyprogesterone acetate depot injections, ovulation inhibitory progesterone-only pills [e.g. desogestrel])

- Tubal ligation
- Partner's vasectomy

– Examples of additional effective methods:
  - Male condom
  - Diaphragm
  - Cervical Cap

☐ The subject confirmed that even if she has amenorrhea she must comply with advice on contraception.

☐ Pregnancy tests before, during administration of pomalidomide and at the last dose of pomalidomide, even if the subject agrees not to have reproductive heterosexual contact.

☐ Frequency of pregnancy tests to be done:

– Two pregnancy tests will be performed prior to receiving pomalidomide, one within 10 to 14 days, and a second within 24 hours of the start of pomalidomide.

– Every week during the first 28 days of this study and a pregnancy test every 28 days while the subject is taking pomalidomide if menstrual cycles are regular.

– Every week during the first 28 days of this study and a pregnancy test every 14 days while the subject is taking pomalidomide if menstrual cycles are irregular.

– If the subject missed a period or has unusual menstrual bleeding.

– When the subject is discontinued from the study and at Day 28 after the last dose of pomalidomide 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 the last dose of pomalidomide.

☐ The subject confirmed that she will stop taking pomalidomide immediately in the event of becoming pregnant and to call her study doctor as soon as possible.

☐ The subject confirmed that she has not and will not breastfeed a baby while taking pomalidomide and for at least 28 days after the last dose of pomalidomide.

☐ The subject has not and will never share pomalidomide with anyone else.

☐ The subject has not and will not donate blood while taking pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide.

☐ The subject has not and will not break, chew, or open pomalidomide capsules at any point.

☐ The subject confirmed that she will return unused pomalidomide capsules to the study doctor.

2. I have provided the Pomalidomide Information Sheet to the subject.

3.2. Female Not of Childbearing Potential (Natural Menopause for at Least 24 Consecutive Months, a Hysterectomy, or Bilateral Oophorectomy):

1. I have verified and counseled the subject regarding the following:
   - ☐ Potential risk of fetal exposure to pomalidomide: A teratogenic potential of pomalidomide in humans cannot be ruled out. If pomalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby.
   - ☐ The subject has not and will never share pomalidomide with anyone else.
   - ☐ The subject has not and will not donate blood while taking pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide.
   - ☐ The subject has not and will not break, chew, or open pomalidomide capsules at any point.
   - ☐ The subject confirmed that she will return unused pomalidomide capsules to the study doctor.
2. I have provided the Pomalidomide Information Sheet to the subject.

Do Not Dispense Pomalidomide if:

- **The subject is pregnant.**
- **No pregnancy tests were conducted for a FCBP.**
- **The subject states she did not use TWO reliable methods of birth control (unless practicing complete abstinence from heterosexual contact) at least 28 days prior to receiving pomalidomide, while receiving pomalidomide and during dose interruptions.**
- **The subject stated that she has or does not want to adhere to pregnancy precautions outlined within this PPP.**

Counselor Name (Print): _____

Counselor Signature: _____ Date: / / (dd/mmm/yyyy)

Maintain a copy of the Education and Counseling Guidance Document in the subject's records.

4. POMALIDOMIDE EDUCATION AND COUNSELING GUIDANCE DOCUMENT FOR MALE SUBJECTS

To be completed prior to each dispensing of pomalidomide.

Protocol Number:

Subject Name (Print): _____ DOB: _____/_____/_____ (dd/mmm/yyyy)

1. I have verified and counseled the subject regarding the following:
   - ☐ Potential risk of fetal exposure to pomalidomide: A teratogenic potential of pomalidomide in humans cannot be ruled out. If pomalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby.
   - ☐ The subject confirmed that he has practiced complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or used a condom when engaging in sexual contact (including those who have had a vasectomy) with a pregnant female or FCBP, while taking pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide.
   - ☐ The subject confirmed that he has not impregnated his female partner while in the study.
   - ☐ The subject confirmed that he will notify his study doctor if his female partner becomes pregnant and the female partner of a male subject taking pomalidomide confirmed that she will call her healthcare provider immediately if she becomes pregnant.
   - ☐ The subject has not and will never share pomalidomide with anyone else.
   - ☐ The subject confirmed that he has not donated and will not donate semen or sperm while taking pomalidomide or during dose interruptions and that he will not donate semen or sperm for at least 28 days after the last dose of pomalidomide.
   - ☐ The subject has not and will not donate blood while taking pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide.
   - ☐ The subject has not and will not break, chew, or open pomalidomide capsules at any point.
   - ☐ The subject confirmed that he will return unused pomalidomide capsules to the study doctor.
2. I have provided the Pomalidomide Information Sheet to the subject.

Do Not Dispense Pomalidomide if:

- **The subject stated that he has or does not want to adhere to pregnancy precautions outlined within this PPP.**

Counselor Name (Print): _____

Counselor Signature: _____ Date: _____/_____/_____(dd/mmm/yyyy)

Maintain a copy of the Education and Counseling Guidance Document in the subject's records.

5. POMALIDOMIDE INFORMATION SHEET

For subjects enrolled in clinical research studies

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?

1. **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. Pomalidomide was found to cause birth defects when tested in pregnant rats and rabbits.

   If you are a female who is able to become pregnant:

   - **Do not take pomalidomide if you are pregnant or plan to become pregnant**
   - **You must practice complete abstinence from sexual contact with a male or use two reliable, separate forms of effective birth control at the same time:**
     - for 28 days before starting pomalidomide
     - while taking pomalidomide
     - during breaks (dose interruptions) of pomalidomide
     - for at least 28 days after the last dose of pomalidomide
   - **You must have pregnancy testing done at the following times:**
     - within 10 to 14 days prior to the first dose of pomalidomide
     - 24 hours prior to the first dose of pomalidomide
     - weekly for the first 28 days
     - if you have regular menstrual periods: every 28 days after the first month
     - if you have irregular menstrual periods: every 14 days after the first month
     - 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 while taking pomalidomide**
     - If you suspect you are pregnant at any time during the study, you must stop pomalidomide immediately and immediately inform your study doctor. Your study doctor will report all cases of pregnancy to Celgene Corporation.

- **Do not breastfeed while taking pomalidomide and for at least 28 days after the last dose of pomalidomide**
- The study doctor will be able to advise you where to get additional advice on contraception.

If you are a female not able to become pregnant:

In order to ensure that an unborn baby is not exposed to pomalidomide, your study doctor will confirm that you are not able to become pregnant.

If you are a male:

The effect of pomalidomide on sperm development is not known and has not been studied. The risk to an unborn baby in females whose male partner is receiving pomalidomide is unknown at this time.

- Male subjects (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 breaks (dose interruptions) of pomalidomide
  - For at least 28 days after the last dose of pomalidomide
- **Male subjects should not donate sperm or semen** while taking pomalidomide, during breaks (dose interruptions) and for at least 28 days after the last dose of 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 Celgene Corporation. Your partner should call their healthcare provider immediately if they become pregnant.**

2. **All subjects:**

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

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