TITLE: A PHASE II STUDY OF DARATUMUMAB, CLARITHROMYCIN, POMALIDOMIDE AND DEXAMETHASONE (D-ClaPd) IN MULTIPLE MYELOMA PATIENTS PREVIOUSLY EXPOSED TO DARATUMUMAB

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Protocol Summary

Full Title:	**A PHASE II STUDY OF DARATUMUMAB, CLARITHROMYCIN, POMALIDOMIDE AND DEXAMETHASONE (D-ClaPd) IN MULTIPLE MYELOMA PATIENTS PREVIOUSLY EXPOSED TO DARATUMUMAB**
Short Title:	D-ClaPd IN REL/REF MULTIPLE MYELOMA
Clinical Phase:	2
Principal Investigator:	Mateo Mejia Saldarriaga, MD
Study Description:	This single-arm phase 2 study will test the hypothesis that in patients with previous daratumumab exposure, daratumumab in combination with ClaPd will yield higher ≥VGPR rates in historical pomalidomide/dexamethasone.
Sample Size:	N= 40
Enrollment:	This study will enroll 40 subjects and screen up to 44 subjects.
Study Population:	Patients will be over 18 years of age with relapsed/refractory multiple myeloma. Patients who have received 1 or more prior lines of therapy which must include daratumumab and may include ASCT are eligible. The patient must have received both an IMiD and PI in prior lines. Prior pomalidomide exposure in 1 or more previous lines of therapy allowed if PR or better achieved. No disease progression may have occurred within 60 days of receiving pomalidomide. Patient may be daratumumab refractory (i.e less than a PR) achieved on prior daratumumab-based therapy or have exhibited progression within 60 days of receiving daratumumab.
Study Design:	This is a single-center single-arm phase 2 study in which 40 patients will receive daratumumab in combination with clarithromycin/pomalidomide/dexamethasone until PD or unacceptable toxicity, whichever comes first. Patients will be treated for 8 cycles of therapy with continuation of maintenance daratumumab/pomalidomide if evidence of PR or better.
Facilities Enrolling	

Participants:	Weill Cornell Medical College-NewYork Presbyterian Hospital (WCMC/NYPH), Brooklyn Methodist Hospital (BMH), and NewYork-Presbyterian Queens (NYPQ)

Participant Duration:	Time it will take for each individual participant to complete all participant visits in the induction phase is 8 months. Patients who complete all 32 cycles of treatment for the entire study, if have not progressed or started new treatment, will be followed with disease evaluations every 90 days (+/- 30 days) until confirmed disease progression or for total duration of 24 months from last EOT visit, whichever comes first, and for survival for up to 10 years from date of enrollment or until death.
Study Agent/Device Name	
Intervention Description:	**Induction Phase (Cycles 1-8,** q28 day cycles): • Daratumumab 1800 mg SC weekly x 8 wks, 1800 mg SC q2wk days 1 and 15 (cycles 3-6) 1800 mg SC q4wk day 1 (cycles 7-8) • Clarithromycin 500mg PO bid continuous until VGPR or 8 cycles, whichever occurs first • Pomalidomide 4 mg PO days 1-21 • Dexamethasone 20 mg IV as premed days 1 and 8 (cycle 1); 20 mg PO days 2 and 9 (cycle 1); 40 mg PO as premed days 15 and 22 (cycle 1); 40 mg PO qwk (cycles 2-6); 20 mg PO qwk (cycles 7-8) **Maintenance Phase (Cycle 9+):** up to 24 months q28 day cycles • Daratumumab 1800 mg SC day 1 • Pomalidomide 4 mg PO days 1-21 • Dexamethasone 20 mg PO qwk
Primary Objective:	PRIMARY: To determine best response rate within 8 cycles of induction therapy.
Secondary Objectives:	SECONDARY: To determine median PFS and OS, time to response (TTR), time to progression (TTP), response duration, time to next therapy (TTNT), time to ≥VGPR, ORR, CR or better rate, MRD negativity rate after 8 and 32 months, AEs in induction and maintenance phases, clinical response in high-risk groups.
Exploratory Objectives:	Assessment of MRD by multiparameter flow cytometry (MFC), FISH, NGS, PET/MRI imaging studies at best response. MFC-based tests of BM aspirates of both CD138-isolated clonal plasma cells and immune cells from marrow and tissue will be studied for various immune-based and daratumumab-based markers; dose-intensity analyses (mean relative dose intensity of dexamethasone); QoL assessments.
Endpoints:	*Primary Endpoint:*

The primary endpoint is the ≥ VGPR response proportion; A 95% confidence interval will be estimated for the ≥ VGPR response proportion via binomial proportions.
Secondary endpoints: include median PFS, OS, time to response and progression, DoR, TTNT, ORR, VGPR rate, CR or better rate, and MRD negativity rate. Median PFS/OS, including survival curves, will be estimated using Kaplan-Meier methodology. Greenwood's formula will be used to calculate 95% confidence intervals for the Kaplan-Meier survival estimates.

SCHEDULE OF STUDY PROCEDURES

	Screening Phase Day-28 to 0	Treatment (Cycle is 28 days) +/- 3 days for Cycle 1 and 2, +/- 7 days for Cycles 3-30	End of Treatm At 1 year (+/- 7 days) & 90 days after last dose of study drug (+/-7 days)	Post-Treatment Observation Phase Each cycle is 90 days, +/- 30 days for 24 months or until progression
Informed consent[a]	X			
Inclusion/exclusion criteria review	X			
Demography/Medical history	X			
Physical Exam	X	X[b] (every cycle)	X	
Vital signs[c]	X	X[d] (every cycle)	X	
Weight	X	X (every cycle)	X	
ECOG status	X	X (every cycle)	X	
ECG	X			
Echocardiogram	X		X	
Pulmonary function testing[e]	X[e]		X[e]	
Chest x-ray[f]				
NYHA classification	X	X (cycle 1 only)	X	
Patient Diary[g]	X	X (every cycle)	X	
Concomitant medications	Continuous from time of ICF until 30 days of last treatment			
Adverse events	Continuous from time of ICF until 30 days of last treatment			
Study Drug Administration				
Daratumumab 1800 mg SC dosing[h]		Daratumumab 1800 mg SC on Days 1, 8, 15, and 22 of Cycles 1 and 2 (weekly dosing), on Days 1 and 15 of Cycles 3 to 6 (every 2 weeks dosing), and on Day 1 of Cycle 7 and subsequent cycles (every 4 weeks dosing)		

Clarithromycin		500 mg PO bid continuous days 1-28 of cycles 1-8 only		
Pomalidomide		Pomalidomide 4 mg PO days 1-21		

Dexamethasone		Dexamethasone (Cycle 1 D1 & 8): 20 mg IV Cycle 1 D2 & D9: 20mg PO Cycle 1 D15 & D22: 40mg PO Cycles 2- 6: 40 mg PO qwk Cycles 7- 8: 20mg PO qwk Cycle 9+: 20mg PO qwk		
Prophylactic Medications				
Varicella Zoster Prophylaxis		Valacyclovir 500mg PO qd (or equivalent, renally dosed-adjusted)		
Gastrointestinal Prophylaxis		Pantoprazole 40 mg PO daily, or other		
Laboratory Assessments				
Pregnancy test[i]	X	X	X	
Blood typing/indirect antiglobulin test	X			
Hematology (CBC) with differential	X	On Days 1, 8, 15, and 22 for Cycles 1 and 2; On Days 1 and 15 for Cycles 3 through 6; D1 from Cycle 7 onward and as clinically indicated	X	
Serum chemistry[j]	X	On Days 1, 8, 15, and 22 for Cycle 1-2, Day 1, 15 for cycles 3-6 and day 1 of each subsequent cycle	X	
Hepatitis B and C screening[k]	X	HBV DNA monitoring q12weeks	X	X[j]
Disease Assessments				
Serum β2-microglobulin	X			
Serum free light chains	X	X (every cycle)	X	X (every cycle)

SPEP and IFE	X	X (every cycle)	X	X (every cycle)
24-hour UPEP and IFE	X	X (every cycle)	X	X (every cycle)
PB/Urine for mass spec[l]		X[l] (only if ≥VGPR achieved)		X[l] (every cycle)
Quantitative Immunoglobulins	X	X (every cycle)	X	X (every cycle)
NT-proBNP, BNP, Troponin T & I[m]	X	X (every cycle)	X	X (every cycle)
Skeletal survey or CT scan	X			
Bone marrow biopsy[n,o]	X	X[n] (to confirm CR only)	X[n]	
Correlative Studies				
BM aspirate for MFC and NGS[o]	X	X[o] (only if ≥VGPR achieved)	X[0]	
PET/MRI[p]	X	X[p] (only if ≥VGPR achieved)	X[p]	

a. Patients must sign the informed consent form before any study-specific procedures are performed
b. During Cycle 1, patients will have clinic visit with physical exam with physician or advanced practice provider on Day 8, 15, and 22.
c. Vital signs include temperature, heart rate, blood pressure
d. On daratumumab infusion days on Day 1 and 8 of Cycle 1, vital signs will be measured before, during, and after daratumumab infusions. For all other infusions, vital signs will be measured before the infusion start and at the end of the infusion.
e. Only if history of respiratory disease or active symptoms. Must include measurement forced expiratory volume at one second (FEV1)
f. Not required if PET or chest CT scan has been obtained
g. Diaries will be provided to patients to record self-administered pomalidomide and dexamethasone dosed at home. At Screening, the patient will receive instructions on how to complete the diary and it will subsequently be reviewed at each visit to evaluate compliance with pomalidomide and dexa methasone.
h. See section 6.2.1.3 for pre- and post- daratumumab infusion medications
i. Pregnancy test will be performed in female patients of childbearing potential at the following timepoints: 10-14 days before the first dose on C1D1; 24 hours before the first dose on C1D1; weekly for first 4 weeks of C1; monthly thereafter beginning with C2; EOT visit (serum or urine β-hCG). Non-child-bearing potential is defined as female patients who are permanently sterile or are post-menopausal (no menses in 12 consecutive months without an alternative medical cause).
j. Serum chemistries: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
k. Hepatitis B screening includes hepatitis B core antibody (HBcAb) and hepatitis B surface antigen (HBsAg) and antibody (Anti-HBs) testing. If evidence of chronic HBV with positive anti-HBc or anti-HBs at screening, then must perform hepatitis B DNA test quantitative viral load q12w during treatment, at End of Treatment Visit, and q12w for up to 6 months after the last dose of study treatment. Hepatitis C screening includes hepatitis C antibody. If hepatitis C antibody reactive, then must perform hepatitis C RNA quantitative viral load.
l. PB for mass spectrometry (MALDI-TOF MS), obtain at screening and day 1 of each cycle (only when in ≥VGPR), at EOT visits and D1 of each post-treatment observation phase cycle until PD or 24 months, whichever occurs first.
m. If TTE is abnormal or clinical history of hypertension or heart disease
n. Bone marrow assessment should include morphologic review, flow cytometry, conventional cytogenetics, and myeloma fluorescence in situ hybridization (FISH) panel. A repeat bone marrow biopsy may be performed if patient achieves a hematologic complete remission to assess for minimal residual disease.
o. For research only: BM aspirate for correlative studies (3.3.1 - 3.3.3), obtain at screening and at best response (only if ≥VGPR achieved) and at 1 year: EDTA (DNA) and EDTA (MFC).
p. For research only: PET/MRI for correlative studies (3.3.4), obtain at screening and at best response (only if ≥VGPR achieved) and at 1 year

TABLE OF CONTENTS

Protocol Summary 2
SCHEDULE OF STUDY PROCEDURES 6
TABLE OF CONTENTS 9
LIST OF TABLES AND FIGURES 11
LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS 12
1. BACKGROUND AND STUDY RATIONALE 16
1.1 Scientific Background and Study Rationale 16
1.2 Disease Under Treatment 19
1.3 Daratumumab 19
1.3.1 Preclinical Experience 19
1.3.2 Clinical Experience 19
1.3.3 Pharmacokinetics and Drug Metabolism 28
1.4 Pomalidomide 29
1.4.1 Preclinical Experience 30
1.4.2 Clinical Experience 30
2. STUDY OBJECTIVES 35
2.1 Primary Objectives 35
2.2 Secondary Objectives 35
3. STUDY ENDPOINTS 35
3.1 Primary Endpoints 35
3.2 Secondary Endpoints 35
3.3 Exploratory Endpoints and Correlative Studies 36
4. STUDY DESIGN 37
4.1 Overview of Study Design 37
4.2 Number of Patients 38
4.3 Duration of Study 38
5. STUDY POPULATION 40
5.1 Inclusion Criteria 40
5.2 Exclusion Criteria 41
6. STUDY DRUG 42
6.1 Description of Investigational Agents 42
6.1.1 Daratumumab 42
6.1.2 Pomalidomide Capsules 43
6.2 Study Drug Administration 43
6.2.1 Daratumumab Administration 43
6.2.2 Pomalidomide Administration 45
6.2.3 Clarithromycin (Biaxin®) 46
6.2.4 Dexamethasone Administration 46
6.3 Dose-Modification Guidelines 47
6.3.1 Criteria for Beginning or Delaying a Subsequent Treatment Cycle 47
6.3.2 Daratumumab Dose Modifications and Delays 48
Table 6-1 Daratumumab Dose Delay Schedule 48
6.3.3 Pomalidomide Dose Adjustments and Delays 49
Table 6-2 Pomalidomide Dose Levels 49
6.3.4 Clarithromycin Dose adjustments 52

6.3.5 Dexamethasone Dose adjustments 52
Table 6-4 Dexamethasone Dose Levels 52
Table 6-5 Dexamethasone Dose Adjustments for Adverse Events 54
6.4 Excluded Concomitant Medications and Procedures 55
6.5 Permitted Concomitant Medications and Procedures 55
6.6 Precautions and Restrictions 56
6.7 Management of Clinical Events 57
6.8 Preparation, Reconstitution, and Dispensing 60
6.9 Packaging and Labeling 60
6.10 Storage, Handling, and Accountability 60
6.11 Termination of Treatment and/or Study Participation 61
7. STUDY PROCEDURES 63
7.1 Screening 63
7.2 Treatment Period 63
7.3 End of Treatment Visit 63
7.4 Post-Treatment Observation Phase 63
7.5 High-Dose Chemotherapy and Autologous Stem Cell Transplantation 63
8. STATISTICAL AND QUANTITATIVE ANALYSES 65
8.1 Statistical Methods 65
8.1.1 Determination of Sample Size 65
8.1.2 Randomization and Stratification 65
8.1.3 Populations for Analysis 66
8.1.4 Procedures for Handling Missing, Unused, and Spurious Data 66
8.1.5 Safety Analysis 66
8.1.6 Efficacy Analysis 67
8.1.7 Futility Analysis and Stopping Rules 67
9. ADVERSE EVENTS 69
9.1 Overview 69
9.1.1 Adverse Event Definition 69
9.1.2 Serious Adverse Event Definition 69
9.2 Procedures for Reporting Serious Adverse Events 71
9.2.1 Janssen SOP for Reporting Serious Adverse Events 71
9.2.2 Report of Adverse Events to the Institutional Review Board 77
10. Data Safety and Monitoring Committee (DSMC) 77
11. REFERENCES 78
12. APPENDICES 80
12.1 Eastern Cooperative Oncology Group (ECOG) Scale for Performance Status 80
12.2 Cockcroft-Gault Equation 80
12.3 List of common QT prolonging drugs 80
12.4 CYP3A4 Inducers 81

LIST OF TABLES AND FIGURES

Tables

Table 6-1 Daratumumab Dose Delay Schedule

Table 6-2 Pomalidomide Dose Levels

Table 6-3 Pomalidomide Dose Adjustments for Toxicities

Table 6-4 Dexamethasone Dose Levels

Table 6-5 Dexamethasone Dose Adjustments for Adverse Events

Figures

Figure 1. Completed and Ongoing Clinical Studies with Daratumumab

LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Common abbreviations used in oncology protocols are provided below. Program-specific or protocol-specific abbreviations must be added to this list, and unnecessary abbreviations removed, as applicable. Abbreviations that are retained should not be changed.

Abbreviation	Term
ADR	adverse drug reaction
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
$AUC_{24\ hr}$	area under the plasma concentration versus time curve from zero to 24 hours
AUC_{inf}	area under the plasma concentration versus time curve from zero to infinity
AUC_{τ}	area under the plasma concentration versus time curve from zero to next dose
BCRP	breast cancer resistance protein
βhCG	beta-human chorionic gonadotropin
BID	bis in die; twice a day
BM	bone marrow
BSA	body surface area
BUN	blood urea nitrogen
CBC	complete blood count
CL	clearance, IV dosing
CL_P	plasma clearance
CL_{Total}	total clearance
C_{max}	single-dose maximum (peak) concentration
CNS	central nervous system
CO_2	carbon dioxide
CR	complete response
CRM	continual reassessment method
CT	computed tomography
C_{trough}	single-dose end of dosing interval (trough) concentration
CV	coefficient of variation
CYP	cytochrome P_{450}
DId	Daratumumab, Ixazomib, dexamethasone

Abbreviation	Term
DDI	drug-drug interaction
DLT	dose-limiting toxicity
DME	drug metabolizing enzymes
DNA	deoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
EOS	End of Study (visit)
EOT	End of Treatment (visit)
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
GGT	gamma glutamyl transferase
GI	Gastrointestinal
GLP	Good Laboratory Practices
GM-CSF	granulocyte macrophage-colony stimulating factor
GMP	Good Manufacturing Practice
Hb	Hemoglobin
Hct	Hematocrit
HDPE	high-density polyethylene
HIV	human immunodeficiency virus
IB	Investigator's Brochure
IC_{50}	concentration producing 50% inhibition
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IRB	institutional review board
ITT	intent-to-treat
IV	intravenous; intravenously
K_i	inhibition constant
LDH	lactate dehydrogenase
LFT	liver function test(s)

Abbreviation	Term
MedDRA	Medical Dictionary for Regulatory Activities
Millennium	Millennium Pharmaceuticals, Inc., and its affiliates
MM	Multiple Myeloma
MRI	magnetic resonance imaging
MRU	medical resource utilization
MTD	maximum tolerated dose
MUGA	multiple gated acquisition (scan)
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NPO	nothing by mouth
NT-proBNP	N-terminal pro b-type natriuretic peptide
NYHA	New York Heart Association
OS	Overall survival
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	progressive disease (disease progression)
PFS	Progression free survival
Pgp	P-glycoprotein
PK	pharmacokinetic(s)
PO	*per os*; by mouth (orally)
PR	partial remission ***or*** partial response *choose one*
PRO	patient-reported outcome
QD	*quaque die*; each day; once daily
QID	*quater in die;* 4 times a day
QOD	*quaque altera die*; every other day
QOL	quality of life
QTc	rate-corrected QT interval (millisec) of electrocardiograph
RBC	red blood cell
SAE	serious adverse event
SC	Subcutaneous
SD	stable disease
SmPC	Summary of Product Characteristics
$t_{1/2}$	terminal disposition half-life
TEAE	treatment-emergent adverse event

Abbreviation	Term
TGI	tumor growth inhibition
T_{max}	single-dose time to reach maximum (peak) concentration
ULN	upper limit of the normal range
US	United States
V_z	volume of distribution in the terminal phase
VGPR	Very good partial response
WBC	white blood cell
WHO	World Health Organization

1. BACKGROUND AND STUDY RATIONALE

1.1 Scientific Background and Study Rationale

Multiple Myeloma (MM) is a neoplastic disorder characterized by abnormal proliferation of plasma cells producing excess quantities of single immunoglobulin protein isotype (M-protein). It is estimated that 19,000 new cases of myeloma are diagnosed in the US each year[1], accounting for approximately 1% of all cancers and 10-15% of all hematological malignancies.[2] The disease is twice as common in blacks as whites.[3] MM usually occurs in older individuals with a median age of 69 years old.

The overall median survival for patients with MM is 36 months, with stage I, II, and III patients surviving a median of >60, 41, and 23 months respectively.[4] Several prognostic factors have been identified. An elevated serum level of beta-2 micro-globulin (ß2M), a component of the class I HLA molecule, is a powerful prognostic indicator of shortened survival.[5] Since ß2M is excreted by the kidney, renal insufficiency will increase serum levels of ß2M. The plasma cell labeling index (PCLI) identifies the percentage of proliferating plasma cells in S phase of the cell cycle and is powerful independent predictor of progression and survival.[6] An elevated serum lactate dehydrogenase (LDH) predicts an aggressive course with lymphoma like features.[7] Chromosomal abnormalities, such as translocations t(4;14) and t(14;16) confer poor prognosis.[8]

Patients who have previously been treated for myeloma and have relapsed, or patients that have MM that is refractory to therapy, are known to have a worse overall prognosis in terms of survival, likelihood of response to other chemotherapeutics, as well as duration of response to salvage therapies.[9] MM is still an incurable disease and all patients eventually relapse or become refractory to treatment. There are few salvage therapies available, so it is imperative to investigate new treatment options for the MM patients with relapsed or refractory disease.

The emergence of immunomodulatory drugs (IMiDs), such as thalidomide, lenalidomide and pomalidomide, as effective therapies have altered the therapeutic paradigm for MM. Following the approval and establishment of thalidomide-containing regimens, such as melphalan, prednisone and thalidomide (MPT) as the standard first-line therapy for newly diagnosed MM (NDMM), lenalidomide in combination with standard high-dose dexamethasone (RD) was approved for the treatment of patients with previously treated and NDMM. Pomalidomide is an analogue of thalidomide that, among other anti-tumor properties, on an equimolar basis *in vitro*, displays equivalent anti-angiogenic activity, about 8-fold greater activity in stimulation of apoptosis, at least 10-fold greater activity in inhibition of cellular COX-2 production and over 4,000-fold greater activity in inhibition of cellular TNF-alpha production relative to thalidomide[9,10]. Pomalidomide has also been shown to stimulate antibody-dependent cytotoxic T-cell activity (ADCC)[9].

However, even with the newly approved agents including thalidomide, lenalidomide and proteasome inhibitors such as bortezomib and carfilzomib, MM remains an incurable disease and most patients will eventually relapse and progress after multiple lines of different therapeutic regimens.

At tolerated doses (MTD = 2 mg QD and 5 mg QOD), pomalidomide has been shown to be active in subjects with relapsed or refractory MM (study CC-4047-00-01)[9,11,12]. In 45 subjects who received doses of pomalidomide ranging, by cohort, up to 10 mg daily, the most commonly occurring dose-limiting toxicity (DLT) was reversible neutropenia. As with other IMiDs administered to subjects receiving concomitant systemic steroids, deep vein thrombosis (DVT) was seen[9,13]. Pivotal phase 2 and 3 studies of pomalidomide/ dexamethasone in relapsed/refractory MM yielded ORRs of 33% and 31%, respectively[14,15]. In a randomized phase 2 study, pomalidomide with/without low-dose dexamethasone in patients with relapsed/refractory multiple myeloma was assessed. Patients who had received ≥2 prior therapies including lenalidomide and bortezomib were randomized to POM (4 mg/day on days 1-21 of each 28-day cycle) with/without dexamethasone (40 mg/week). In the pomalidomide/ dexamethasone arm, median PFS was 4.2 months, ORR was 33%, CR 3%, median response duration was 8.3 and median overall survival 16.5. Grade 3-4 neutropenia occurred in 41%; no grade 3-4 peripheral neuropathy was reported. In a phase 3 study (5 median prior lines, 100% lenalidomide/ bortezomib exposed, 95% lenalidomide refractory and 75% double-refractory), ORR 31%, ≥VGPR 6% and ≥CR 1%. At a median f/u of 10 mos, median PFS 4 mos and median OS 12.7 mos. The most common grade 3-4 haematological adverse events in the pomalidomide plus low-dose dexamethasone was neutropenia 48%, anaemia 33%, and thrombocytopenia 22%. Grade 3-4 non-haematological adverse events in the pomalidomide plus low-dose dexamethasone included pneumonia 13%, bone pain 7%, and fatigue 5%. There were 4% treatment-related adverse events leading to death in the pomalidomide plus low-dose dexamethasone group.

Daratumumab, both as monotherapy and in combination, appears safe and highly effective in heavily pretreated MM and is approved as a single agent for patients who have received at least three prior lines of therapy including a proteasome inhibitor and an immunomodulatory drug or who are double-refractory to a proteasome inhibitor and an immunomodulatory drug. In an open-label, international, phase 2 trial (SIRIUS), 106 patients with relapsed MM (median of five prior therapies) were treated with daratumumab (16 mg/kg, weekly for eight weeks and then every two weeks for 16 weeks). Infusion reactions, mostly mild, were common with the first infusion (37 %) and occurred in 6% of subsequent infusions. The ORR was 29 % (≥VGPR 12%, CR 3%) with a median time to first response of one month. The estimated median PFS and OS rates were 3.7 and 17.5 months, respectively[16].

A favorable toxicity profile makes daratumumab a particularly good combination agent. The safety of an IMiD with daratumumab, even in patients previously exposed yields very low toxicity and good efficacy. Combination studies of lenalidomide and pomalidomide with daratumumab at various dose levels has been studied in the daratumumab naïve relapsed/refractory myeloma setting. Daratumumab 16 mg/kg plus pomalidomide (4 mg days 1-21) and dexamethasone 40 mg weekly (DPd) in a 28-day cycle was evaluated in 103 relapsed/refractory myeloma patients with median of 4 prior therapies[17]. ORR was 60%,

≥VGPR 42%, and MRD$^-$ was 29% in the CR patients. Median PFS was 8.8 mos. Aside from increased neutropenia (grade ≥3 neutropenia 78% without increased infection rate), the safety profile of DPd was consistent with that of the individual therapies.

Pomalidomide and daratumumab combination have been shown to potentiate clinical efficacy in myeloma even when the disease has developed resistance to the individual agents. Patients with pomalidomide and/or daratumumab-refractory disease were identified who were treated with daratumumab-pomalidomide/dexamethasone. Of the 11 refractory to either daratumumab or pomalidomide, the ORR and CBR were 54·6% (all PRs) and 63·6%. Of the 8 refractory to both daratumumab and pomalidomide in separate lines of therapy, ORR and CBR were 12·5% (all PRs) and 50·0%[18]. Nooka *et al* also reported an ORR with daratumumab-pomalidomide of 36·8% in patients with daratumumab or pomalidomide-refractory disease and 33·3% for those with daratumumab and pomalidomide-refractory disease[19].

Biaxin®, or clarithromycin, is a semi-synthetic macrolide antibiotic indicated for the treatment of mild to moderate infections caused by susceptible strains of microorganisms. Pre-clinical studies have shown that Biaxin® has immunomodulatory properties mediated in part by suppression of Interleukin-6 and other cytokines and slows hepatic clearance of dexamethasone leading to greater corticosteroid exposure.[20] Based upon these properties, the group at Cedars Sinai Comprehensive Cancer Center began a trial using Biaxin® 500mg bid for the treatment of newly diagnosed and relapsed/refractory MM patients.[21] Of the 30 patients treated, 6 patients achieved a CR, 7 achieved a PR, 6 patients had SD, 4 had a mixed response and 7 patients were too early to evaluate. Follow up studies by other groups in Canada and France have failed to duplicate these promising results.

A phase II study of clarithromycin (500mg twice daily), lenalidomide (25mg daily for 21 days out of a 28 day cycle), and dexamethasone (40mg weekly) called the BiRD regimen was conducted at this institution. We achieved an overall response rate of 91%, and CR rate of 30%[22]. The BiRD study evaluated the efficacy of the combination of Biaxin®, lenalidomide, and dexamethasone in treatment-naïve MM patients and proved to be a powerful regimen.

In the relapsed/refractory setting, a Phase 2 study of Biaxin®, pomalidomide, and dexamethasone (ClaPd) was studied in 120 patients with median of 5 prior lines (84% lenalidomide refractory). An ORR of 60% with ≥VGPR 23%, median PFS and DoR 7.7 and 9.3 mos, respectively and median OS 19.3 mos was seen. No influence on PFS was seen with lenalidomide or lenalidomide/bortezomib refractoriness nor significant differences in PFS/OS between low and high-risk patients. The most common gr 3/4 AEs were neutropenia 47% (gr 4 14%), lymphopenia 37% (gr 4 6%) and thrombocytopenia 33% (gr 4 16%) with no grade 5 events and a discontinuation rate of 3%[23,24].

This study is intended to investigate the combination of daratumumab, clarithromycin (Biaxin®), pomalidomide and dexamethasone [D-ClaPd] in multiple myeloma patients who have relapsed or refractory MM and have been previously exposed to daratumumab. Primary

endpoint will be response rate to treatment. Secondary endpoints will include toxicity of the combination, time to maximum response, and time to disease progression.

1.2 Disease Under Treatment

Multiple Myeloma

1.3 Daratumumab

Daratumumab, a CD38 antagonist, is approved in multiple myeloma. The active ingredient, daratumumab, is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody (mAb) that binds CD38 expressing cells with high affinity in a variety of hematological malignancies, including myeloma, lymphomas, and leukemias, as well as other cell types and tissues with various expression levels.

1.3.1 Preclinical Experience

Please refer to the current daratumumab Investigator's Brochure (IB) and Safety Management Attachment (SMA).

1.3.2 Clinical Experience

As of 29 Jun 2018, 34 company-sponsored studies in hematologic diseases/malignancies, solid tumors, and healthy volunteers have been initiated in the daratumumab clinical development program. These studies characterized the safety, efficacy, pharmacokinetics, and pharmacodynamics of daratumumab.

Daratumumab as IV monotherapy has been administered to approximately 717 patients in Studies GEN501, MMY1002, MMY2002, SMM2001, LYM2001, and MMY3010. Daratumumab as combination therapy has been administered to approximately 1310 patients in Studies GEN503, MMY1001, MMY1005, MMY3003, MMY3004, MMY3007, and MMY3008. Daratumumab as SC monotherapy has been administered to 45 patients in Study MMY1004.

An overview of ongoing studies, patient populations, and doses investigated is shown in Figure 1. Please refer to current daratumumab Investigator's Brochure for most recent updates from ongoing daratumumab trials.

Sponsor-Initiated Studies for Daratumumab Monotherapy and Combination Therapy

Study	Subject Population	Regimen	No. of Subjects Treated with Daratumumab as Mono or Combination Therapy (N)[f]
Multiple Myeloma			
Daratumumab IV Monotherapy			**N=1106**
54767414MMY2002[a,c]	R/R MM	Dara	124
GEN501[a,c]	R/R MM	Dara	104
54767414MMY1002[a,c]	R/R MM	Dara	9
54767414SMM2001[e]	Smoldering MM	Dara	122
54767414MMY3010[a,e]	R/R MM	Dara	692
54767414MMY1003[b,e]	R/R MM	Dara	22
54767414MDS2002[e]	MDS	Dara	33
Daratumumab IV Combination Therapy			**N=1761**
GEN503[c]	R/R MM	DRd	45
54767414MMY1001[b]	R/R MM	Dara+ various background	240
54767414MMY3003[b]	R/R MM	DRd vs Rd	283
54767414MMY3004[b]	R/R MM	DVd vs Vd	243
54767414MMY1005[c]	R/R MM	DVd	8
54767414MMY2036	R/R MM	Dara+JNJ-6372383 vs JNJ-6372383	9
54767414MMY3007[b]	Previously untreated MM	Dara-VMP vs VMP	346
54767414MMY3008[e]	Previously untreated MM	DRd vs Rd	364[g]
54767414MMY1006[e]	Newly diagnosed MM	DRd	7
54767414MMY2004	Newly diagnosed MM	D-RVD vs RVD	116
54767414MMY2012	Newly diagnosed & Relapsed MM	Dara-CyBorD	100
Daratumumab SC Monotherapy			**N=543**
54767414MMY1004[e]	R/R MM	Dara	
Part 1		Dara-MD	53
Part 2		Dara-CF (also known as Dara SC)	25
54767414MMY1008[e]	R/R MM	Dara-CF	6
54767414MMY3012	R/R MM	Dara SC vs Dara IV	459
Daratumumab SC Combination Therapy			**N=75**
54767414AMY3001	AL Amyloidosis		
Safety Run-in		Dara SC+CyBorD	28
Randomized		CyBorD±Dara SC	10
54767414MMY2040	Newly diagnosed MM, R/R MM	Dara SC+VMP or VRd or Rd	37
NHL and Leukemia			
Daratumumab IV Monotherapy			**N=57**
54767414LYM2001[b]	R/R DLBCL, MCL, FL	Dara	36
54767414NKT2001	R/R NKTCL	Dara	20
Daratumumab IV Combination Therapy			
54767414ALL2005	Pediatric and young adult ALL/LL	Dara+vincristine, prednisone, methotrexate (B cell cohort); Dara+vincristine, prednisone, doxorubicin, PEG-asparaginase, methotrexate	1

1.3.2.1 Daratumumab IV Monotherapy Studies

Among the 156 patients treated with a therapeutic dose of daratumumab 16 mg/kg administered intravenously as monotherapy in Studies GEN501, MMY2002, and MMY1002:

- 6 patients (4%) discontinued daratumumab treatment due to a treatment emergent adverse event (TEAE), none of which were considered by the investigator to be related to daratumumab.
- 3 patients (2%) died due to TEAEs within 30 days after the last dose of study drug.
- The most frequently reported TEAEs were fatigue (40%); nausea and anemia (28% each); back pain (26%); cough (24%), neutropenia (23%); pyrexia (22%), upper respiratory tract infection (22% each), and thrombocytopenia (21%).
- SAEs were reported in 33% of patients, the most frequently reported SAEs were pneumonia (6%) and pyrexia, hypercalcemia, and general physical health deterioration (3% each).
- Grade 3 or 4 TEAEs were reported in 56% of patients; most commonly these were anemia (17%), thrombocytopenia (14%), neutropenia (12%), lymphopenia (6%), leukopenia, pneumonia, and hypertension (5% each).

TEAEs of infection were reported in 59% of patients. The most frequently reported were upper respiratory tract infection (22%), nasopharyngitis (15%), pneumonia (9%), sinusitis (7%), and urinary tract infection (6%). Grade 3 and 4 TEAEs of infections or infestations were reported in 10% and 1% of patients, respectively.

1.3.2.2 Daratumumab IV Combination Studies

The safety profile of daratumumab in combination with standard background regimens (bortezomib, lenalidomide, pomalidomide, dexamethasone, melphalan, prednisone, thalidomide, carfilzomib) is consistent with those of the background regimens and single agent daratumumab. With the exception of IRRs and neutropenia/thrombocytopenia, the safety profiles of daratumumab in combination with Rd, Vd, or Pom-dex were similar to those of the background regimens. In particular, among the 318 patients treated with 16 mg/kg of daratumumab in combination with lenalidomide and dexamethasone in Study MMY3003 and Phase 2 of Study GEN503:

- TEAEs leading to discontinuation of study treatment were reported in 27 patients (9%).
- 17 patients (5%) died within 30 days of last dose due to an AE.
- The most frequently reported TEAEs (reported in ≥25% of patients) were neutropenia (63%), diarrhea (48%), fatigue (36%), anemia (33%), cough (32%), upper respiratory tract infection (32%), muscle spasms (30%), constipation (29%), thrombocytopenia (28%), nasopharyngitis (27%), and nausea (26%). No TEAEs of tumor lysis syndrome, hemolysis, or transfusion reaction were reported.
- SAEs were reported in 174 patients (55%); the most frequently reported SAEs were pneumonia (9%), influenza (4%), febrile neutropenia (4%), pyrexia (3%), bronchitis (3%), pulmonary embolism (3%), lower respiratory tract infection (2%), and diarrhea (2%).
- Grade 3 or 4 TEAEs were reported in 267 patients (84%); the most frequently reported Grade 3 or 4 TEAEs were neutropenia (56%), anemia (14%), and thrombocytopenia (14%).
- Infections or infestations were reported in 87% of patients. The most frequently reported were upper respiratory tract infection (32%), nasopharyngitis (27%), bronchitis (17%), pneumonia (15%), and respiratory tract infection (11%).

Among the 243 patients treated in Study MMY3004 with daratumumab in combination with bortezomib and dexamethasone:

- TEAEs leading to discontinuation of study treatment were reported in 22 patients (9%).
- Fourteen deaths (6%) were reported within 30 days after the last dose. Twelve patients died due to TEAEs and 2 patients died due to disease progression.
- The most frequently reported TEAEs (reported in ≥25% of patients) were thrombocytopenia (60%), peripheral sensory neuropathy (49%), diarrhea (34%), upper respiratory tract infection (30%), anemia (28%), and cough (27%).
- SAEs were reported in 118 patients (49%); the most frequently reported was pneumonia (21 patients; 9%), anemia, bronchitis, thrombocytopenia, atrial fibrillation, upper respiratory tract infection (3% each), and pyrexia (2%).
- Grade 3 or 4 TEAEs were reported in 193 patients (79%); the most frequently reported Grade 3 or 4 TEAEs were thrombocytopenia (45%), anemia (15%), and neutropenia (13%).
- Infections or infestations were reported in 73% of patients. The most frequently reported were upper respiratory tract infection (30%), pneumonia (14%), and bronchitis (13%).

Among the 103 patients treated in Study MMY1001 with daratumumab in combination with pomalidomide and dexamethasone:

- TEAEs leading to discontinuation of study treatment were reported in 15 patients (15%).
- Nine deaths (9%) were reported during study treatment or within 30 days after the last dose. Six patients died due to TEAEs; 2 patients died due to disease progression; and 1 patient died due to unknown reason.
- The most frequently reported TEAEs (reported in ≥25% of patients) were neutropenia (80%), anemia (54%), fatigue (52%), diarrhea (43%), thrombocytopenia (42%), cough (38%), dyspnea (32%), pyrexia (30%), leukopenia (37%), constipation (34%), nausea (31%), upper respiratory tract infection (28%), back pain (28%), and muscle spasms (27%).
- SAEs were reported in 55 patients (53%); the most frequently reported were pneumonia (9 patients; 9%), sepsis, febrile neutropenia (5% each), fall (4%), anemia, and dyspnea (3% each)
- Grade 3 or 4 TEAEs were reported in 102 patients (99%). The most frequently reported Grade 3 or 4 TEAEs were neutropenia (77%), anemia (28%), thrombocytopenia (19%), lymphopenia (14%), and fatigue (12%).

- Infections or infestations were reported in 72% of patients. The most frequently reported were upper respiratory tract infection (28%), pneumonia (15%), sinusitis (14%), and bronchitis (12%).

Daratumumab SC Monotherapy Study MMY1004- Relapsed/Refractory MM

Daratumumab SC Monotherapy

Safety data in subjects with relapsed/refractory multiple myeloma demonstrate a favorable safety profile for daratumumab in combination with rHuPH20 when administered subcutaneously at doses up to 1800 mg. A maximum tolerated dose (MTD) has not been established. Preliminary efficacy data are promising and support further evaluation of daratumumab co-formulated with rHuPH20 in Phase 3 studies.

Study MMY3012 – Relapsed/Refractory MM

As of 29 Jun 2018, 459 subjects have been treated in ongoing Study MMY3012. The most frequently (≥10%) reported TEAEs in the Dara-SC and Dara-IV treatment arms combined were anemia (17%), thrombocytopenia (13%), and neutropenia (12%).

Grade 3 or 4 TEAEs were reported for 127 (28%) subjects. The most frequently reported Grade 3 or 4 TEAEs were anemia and thrombocytopenia (9% each), and neutropenia (7%).

SAEs were reported for 71 (16%) subjects. The most common SAEs (>5 subjects [1%]) were pneumonia (2%), anemia, pyrexia, influenza, lung infection, and septic shock (1% each).

Daratumumab SC Combination Therapy Pharmacokinetics

The PK of daratumumab SC (1800 mg) combined with cyclophosphamide, bortezomib, and dexamethasone (CyBorD) was available for the safety run-in (n=10) cohort of Study AMY3001. The median primary PK endpoint of C3D1 Ctrough values in Study AMY3001 (Dara + CyBorD) are similar to the monotherapy data observed in dara SC cohort of Study MMY1004 (682 and 799 µg/mL, respectively). The mean (SD) C3D1 Ctrough value in Study AMY3001 was 699.32 (151) µg/mL (n=9), compared with 932 (394) µg/mL for the dara SC cohort (n=22) in Study MMY1004. The range of C3D1 Ctrough observations in Study AMY3001 is within the range observed in dara SC cohort of Study MMY1004, and the variability for AMY3001 appeared to be lower than the dara SC cohort in Study MMY1004. The observed C1D4 (1st dose Cmax) median value was 191.11 µg/mL for AMY3001 (n=10), which is comparable with 193.78 µg/mL for the dara SC cohort in MMY1004 (n=17).

These data indicate that the PK of daratumumab SC was similar following monotherapy and combination therapies.

Daratumumab Subcutaneous Combination Therapy Studies

Study AMY3001 – AL Amyloidosis

Study AMY3001 is reported in 2 parts, a safety run-in, and a randomized portion. As of 29 Jun 2018, 28 subjects have been treated with Dara-SC+CyBorD in the safety run-in portion of the study, and a total of 21 subjects have been treated in the randomized portion of the study.

Safety Run-In

TEAEs were reported for all subjects in the safety run-in (Appendix 3 TSFAE01S_AMY). The most frequently (≥20%) reported TEAEs were diarrhea (57%), fatigue (46%), nausea, edema peripheral (43% each), lymphopenia (39%), constipation, anemia (36%), hyperglycemia, dizziness (32% each), dyspnea, insomnia (29% each), hypoalbuminemia, upper respiratory tract infection (25% each), decreased appetite, dysgeusia, headache, cough, rash maculo-papular (21% each).

Grade 3 or 4 TEAEs were reported for 17 (61%) subjects. The most frequently reported Grade 3 or 4 TEAEs were fatigue (18%), lymphopenia and diarrhea (11% each).

SAEs were reported for 8 (29%) subjects. All SAEs were reported in 1 subject each, except for cellulitis and pneumonia (2 subjects [7%] each) (Appendix 3 TSFAE05S_AMY). No deaths were reported in the safety run-in.

Randomized Study
As of 29 Jun 2018, 9 subjects have experienced SAEs in the randomized portion of the study (Appendix 3 LSFAE03_AMY). One subject in the CyBorD arm died in the randomized portion of the study.

Part 1 Daratumumab Mix-and-Deliver SC Formulation

Data from the 53 subjects who received dara-MD administered subcutaneously are presented in the following section.

Overview of Treatment Emergent Adverse Events

An overview of TEAEs, as of a 3 August 2017 date, is provided in the IB. A total of 8 subjects received dara-MD 1200 mg and 45 subjects received dara-MD 1800 mg. Among the 53 subjects treated, the most frequently reported TEAEs (≥20% of all subjects) were upper respiratory tract infection (1200 mg: 38%; 1800 mg: 22%), insomnia (1200 mg: 38%; 1800 mg: 11%), decreased appetite (1200 mg: 38%; 1800 mg: 7%), thrombocytopenia (1200 mg: 38%; 1800 mg: 18%), viral upper respiratory tract infection (1200 mg: 25%; 1800 mg: 13%), vomiting (1200 mg: 25%; 1800 mg: 13%), hyperuricaemia (1200 mg: 25%; 1800 mg: 2%), hypokalaemia (1200 mg: 25%; 1800 mg: 4%), blood creatinine increased (1200 mg: 25%; 1800 mg: 4%), anemia (1200 mg: 25%; 1800 mg: 33%), fatigue (1200 mg: 25%; 1800 mg: 20%) pyrexia (1200 mg: 25%; 1800 mg: 27%), diarrhea (1200 mg: 25%; 1800 mg: 22%), headache (1200 mg: 25%; 1800 mg: 18%), cough (1200 mg: 25%; 1800 mg: 13%), epistaxis (1200 mg: 25%; 1800 mg: 4%), hypertension (1200 mg: 25%; 1800 mg: 7%), rhinitis allergic (1200 mg: 25%; 1800 mg: 2%), nasal congestion (1200 mg: 25%; 1800 mg: 2%), rectal hemorrhage (1200 mg: 25%; 1800 mg: 0%), and asthenia

(1200 mg: 13%; 1800 mg: 20%).

Grade 3 or 4 Treatment Emergent Adverse Events

Grade 3 or 4 TEAEs were reported in 63% and 49% of subjects in the 1200 mg and 1800 mg cohorts, respectively. The most frequently reported Grade 3 or 4 TEAEs were in the Blood and Lymphatic System Disorders System Organ Class (SOC), reported in 38% and 31% of subjects in the 1200 mg and 1800 mg cohorts, respectively. Two of 8 (25%) subjects in the 1200 mg cohort and 4% in the 1800 mg cohort had Grade 3 or 4 hypertension.

Treatment Emergent Adverse Events Leading to Discontinuation

No subject discontinued study treatment due to a TEAE.

Serious AEs

SAEs were reported in 26% of all subjects: 50% and 31% of subjects in the 1200 mg and 1800 mg cohorts, respectively. The most frequently reported serious TEAEs (≥5% at SOC level) were in the Infections and Infestations SOC (1200 mg: 38%, 1800 mg: 16%), the Nervous System Disorders SOC (1200 mg: 13%, 1800 mg: 4%), and the Respiratory, thoracic and mediastinal disorders (1200 mg: 13%, 1800 mg: 2%), At the preferred term level, no serious TEAEs were reported in ≥5% of subjects in the 1800 mg cohort.

Deaths

One subject in the dara-MD 1800 SC cohort died within 30 days of the last dose of study drug from progressive disease.

Injection-site Reactions AEs

For subjects receiving dara-MD, the incidence of all-grade IRRs was 13% and 24% in the 1200 mg and 1800 mg cohorts, respectively).

IRRs were mostly Grade 1 or 2 and included chills, pyrexia, non-cardiac chest pain, edema of the tongue, nausea, vomiting, dyspnea, wheezing, flushing, hypertension, hypotension, oropharyngeal pain, rash, paresthesia and pruritus. Only 1 subject (in the 1200 mg cohort) developed Grade 3 dyspnea; no Grade 4 IRR was reported in either cohort.
All IRRs developed during or within 6 hours of the start of the first dara-MD infusion and were controlled with antihistamine, corticosteroid, or bronchodilator treatment and did not result in treatment discontinuation. No IRRs were reported on subsequent infusions.

Part 2 Daratumumab-CF SC Formulation

Preliminary safety data for the 25 subjects treated with at least 1 dose dara-CF, also referred to as dara SC, administered subcutaneously as of the clinical data cutoff (3 August 2017) are presented in the following section.

Overview of Treatment Emergent Adverse Events

An overview of TEAEs is provided in the IB. Overall, 21 (84%) subjects in the Dara-CF cohort experienced TEAEs. The most frequently reported TEAEs (≥3 [12%] subjects) were lymphopenia (32%); thrombocytopenia, pyrexia, fatigue, asthenia, back pain, nausea, headache, insomnia (16% each); and leukopenia, anemia, chills, and diarrhea (12% each).

Grade 3 or 4 Treatment Emergent Adverse Events

Grade 3 or 4 TEAEs were experienced by 9 (36%) of the 25 subjects. The most frequently reported Grade 3 or 4 TEAEs (≥2 [8%] subjects) were lymphopenia (16%), and thrombocytopenia (8%).

Treatment Emergent Adverse Events Leading to Discontinuation

No subject discontinued study treatment due to a TEAE.

Serious AEs

SAEs were experienced by 2 (8%) of the 25 subjects. The SAEs were pyrexia, asthenia, fatigue, hyponatremia, febrile neutropenia, leukopenia, and thrombocytopenia.

Deaths

No deaths were reported during the Treatment Phase for subjects reeving dara-CF 1800 mg SC.

Injection-site Reactions AEs

Adverse events in relation to SC injection in the periumbilical area were reported in 3 of 25 subjects treated with dara-CF and consisted of Grade 1 injection site discoloration/injection site induration (although no measurable induration was reported in this

subject), Grade 1 hematoma, and Grade 1 erythema.

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
- HBV Reactivation
- Other malignancies

Any adverse event of special interest should be recorded on a Serious Adverse Event Report Form and be reported to the COMPANY **within 24 hours of becoming aware of the event.**

1.3.3 Pharmacokinetics and Drug Metabolism

1.3.3.1 Daratumumab Subcutaneous Monotherapy Pharmacokinetics

Preliminary pharmacokinetic data are available from subjects in Part 1 and Part 2 of Study MMY1004. In Part 1, a fixed dose of 1200 or 1800 mg of daratumumab was mixed with rHuPH20 and administered subcutaneously (60 mL infusion and 90 mL infusion, respectively) following the approved monotherapy dosing schedule (weekly for 8 weeks, every 2 weeks for 16 weeks, and then every 4 weeks thereafter). In Part 2, a fixed dose of 1800 mg of daratumumab co-formulated with rHuPH20 (dara-CF, also referred to as dara SC) was administered. As expected with subcutaneous administration, concentration-time curves following administration in all cohorts indicate a later Tmax of approximately 72h post-dose, compared with IV administration when Tmax occurs at or near the end of infusion.

The primary PK endpoint of C3D1 C_{trough} mean value was 904.42 µg/mL for the dara-CF cohort (n=18) compared with 754.62 µg/mL for the 1800 mg daratumumab mix-and-deliver (dara-MD) cohorts (n=38), 617.17 µg/mL in Study GEN501 Part 2 (n=27), and 573.49 µg/mL in Study MMY2002 (n=73). The median C3D1 C_{trough} values for dara-CF are similar to the 1800 mg daratumumab mix-and-deliver (dara-MD formulations (798.9 and 795.5 µg/mL, respectively), and slightly higher than the 16 mg/kg IV median values from Studies MMY2002 and GEN501 (559.6 and 713.9 µg/mL, respectively). The range of C3D1 C_{trough} observations for the SC cohort is within the range observed following 16 mg/kg IV dosing, and the variability appeared to be similar for the daratumumab SC and 16 mg/kg IV cohorts.

The observed mean C_{max} values following the last (8^{th}) weekly dose for the dara-CF cohort was 1012.4 µg/mL, similar to the mean C_{max} of 914.9 µg/mL observed after the

C3D1 (9^{th}) dose for daratumumab IV in Study MMY2002. The C3D1 C_{max} was selected for this comparison as the C_{max} was not captured following the last weekly (8^{th}) dose in Study MMY2002. The observed C_{max} values from the daratumumab SC cohort is within the range observed for dara-MD and daratumumab 16 mg/kg IV.

These data indicate that an 1800 mg dose of dara-CF would be anticipated to result in a similar or greater Cycle 3 Day 1 trough concentration compared to 16 mg/kg IV.

1.3.3.2 Drug-Drug Interactions

No formal clinical drug-drug interaction studies were performed, and no interactions with concomitant medications are expected.

The calculated PK parameters of bortezomib, thalidomide and pomalidomide were derived by non-compartmental analysis based on data from Study MMY1001. Due to the limited sampling timepoints over 24 hours, only the parameters of AUC0-24h, Cmax, and Tmax were estimated. Despite the small sample size, the results observed indicate a lack of clinically relevant drug-drug interactions between daratumumab and small molecule drugs bortezomib, thalidomide, and pomalidomide when administered in a variety of combinations.

Daratumumab peak and trough concentrations at similar timepoints are comparable across monotherapy and combination therapy studies, including across different regimens within the same study (MMY1001), indicating that the regimen difference has no impact on the concentration of daratumumab.

1.3.3.3. Immunogenicity

Immunogenicity data are available for Part 1 of Study MMY1004; 1 (2.4%) of 42 evaluable subjects who received daratumumab pre-mixed with rHuPH20 subcutaneously was positive for anti-daratumumab antibodies.

1.4 Pomalidomide

Pomalidomide, in combination with dexamethasone, is indicated for patients with multiple myeloma 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 is an immunomodulatory antineoplastic agent. The chemical name is (RS)-4-Amino-2-(2,6-dioxopiperidin-3-yl)-isoindoline-1,3-dione. The empirical formula for pomalidomide is C13H11N3O4 and the gram molecular weight is 273.24.

Pomalidomide is a yellow solid powder. It has limited to low solubility into organic solvents and it has low solubility in all pH solutions (about 0.01 mg/mL). Pomalidomide has a chiral carbon atom which exists as a racemic mixture of the R(+) and S(-) enantiomers.

Pomalidomide is available in 1-mg, 2-mg, 3-mg, and 4-mg capsules for oral administration. Each capsule contains pomalidomide as the active ingredient and the following inactive ingredients: mannitol, pregelatinized starch, and sodium stearyl fumarate. The 1-mg capsule shell contains gelatin, titanium dioxide, FD&C blue 2, yellow iron oxide, white ink, and black ink. The 2-mg capsule shell contains gelatin, titanium dioxide, FD&C blue 2, yellow iron oxide, FD&C red 3, and white ink. The 3-mg capsule shell contains gelatin, titanium dioxide, FD&C blue 2, yellow iron oxide, and white ink. The 4-mg capsule shell contains gelatin, titanium dioxide, FD&C blue 1, FD&C blue 2, and white ink.

Pomalidomide is an analogue of thalidomide with immunomodulatory, antiangiogenic, and antineoplastic properties. Cellular activities of pomalidomide are mediated through its target cereblon, a component of a cullin ring E3 ubiquitin ligase enzyme complex. In vitro, in the presence of drug, substrate proteins (including Aiolos and Ikaros) are targeted for ubiquitination and subsequent degradation leading to direct cytotoxic and immunomodulatory effects. In in vitro cellular assays, pomalidomide inhibited proliferation and induced apoptosis of hematopoietic tumor cells. Additionally, pomalidomide inhibited the proliferation of lenalidomide resistant multiple myeloma cell lines and synergized with dexamethasone in both lenalidomide-sensitive and lenalidomide-resistant cell lines to induce tumor cell apoptosis. Pomalidomide enhanced T cell- and natural killer (NK) cell-mediated immunity and inhibited production of pro-inflammatory cytokines (e.g., TNF-α and IL-6) by monocytes. Pomalidomide demonstrated anti-angiogenic activity in a mouse tumor model and in the in vitro umbilical cord model.

1.4.1 Preclinical Experience

Please refer to the current pomalidomide Investigator's Brochure (IB).

1.4.2 Clinical Experience

In Trial 1 in MM, data were evaluated from 219 patients (safety population) who received treatment with pomalidomide + low-dose dex (112 patients) or pomalidomide alone (107 patients). Median number of treatment cycles was 5. Sixty-seven percent of patients in the study had a dose interruption of either drug due to adverse reactions. Forty-two percent of patients in the study had a dose reduction of either drug due to adverse reactions. The discontinuation rate due to adverse reactions was 11%.

The table below summarizes the analysis results of overall response rate (ORR) and duration of response (DOR), based on assessments by the Independent Review Adjudication Committee for the treatment arms in Trial 1. ORR did not differ based on type of prior antimyeloma therapy.

	Pomalidomide (m=108)	Pomalidomide + Low-dose Dex (n=113)
Response	8 (7.4)	33 (29.2)

Overall Response Rate, %	(3.3, 14.1)	(21.0, 38.5)
Complete Response Rate %	0 (0.0)	1 (0.9)
Partial Response %	8 (7.4)	32 (28.3)
Duration of Response (DOR) Median, months	NE	7.4
95% CI for DOR (months)	NE	(5.1, 9.2)

In Trial 2, data were evaluated from 450 patients (safety population) who received treatment with pomalidomide + low-dose dex (300 patients) or high-dose dexamethasone (high-dose dex) (150 patients). The median number of treatment cycles for the pomalidomide + low-dose dex arm was 5. In the pomalidomide + low-dose dex arm, 67% of patients had a dose interruption of pomalidomide, the median time to the first dose interruption of pomalidomide was 4.1 weeks. Twenty-seven percent of patients had a dose reduction of pomalidomide, the median time to the first dose reduction of pomalidomide was 4.5 weeks. Eight percent of patients discontinued pomalidomide due to adverse reactions.

The table below summarizes the progression free survival (PFS) and overall response rate (ORR) based on the assessment by the Independent Review Adjudication Committee (IRAC) review at the final PFS analysis and overall survival (OS) at the OS analysis. PFS was significantly longer with POMALYST + Low-dose Dex than High-dose Dex: HR 0.45 (95% CI: 0.35-0.59 $p < 0.001$). OS was also significantly longer with POMALYST + Low-dose Dex than High-dose Dex: HR 0.70 (95% CI: 0.54-0.92 $p = 0.009$). The Kaplan-Meier curves for PFS and OS for the ITT population are provided in Figures 1 and 2, respectively.

	Pomalidomide (m=302)	Pomalidomide + Low-dose Dex (n=153)
Progression Free Survival Time		
Median	3.6 [3.0, 4.6]	1.8 [1.6, 2.1]
Hazard ratio	0.45 [0.35, 0.59]	
Overall Survival Time		
Complete Response	1 (0.3)	0
Very Good Partial Response	8 (2.6)	1 (0.7)
Partial Response	62 (20.5)	5 (3.3)

1.4.3 Pharmacokinetics and Drug Metabolism

Pomalidomide is primarily metabolized by CYP1A2 and CYP3A4. Pomalidomide is also a substrate for Pglycoprotein (P-gp).

CYP1A2 inhibitors: In healthy volunteers, co-administration of fluvoxamine, a strong CYP1A2 inhibitor, increased Cmax and AUC of pomalidomide by 24% and 125% respectively. Increased pomalidomide exposure increases the risk of exposure related

toxicities. Avoid co-administration of strong CYP1A2 inhibitors (e.g. ciprofloxacin and fluvoxamine) and Clinical Pharmacology. If co-administration is unavoidable, reduce the pomalidomide dose.

In patients with multiple myeloma who received pomalidomide 4 mg daily alone or in combination with dexamethasone, pomalidomide steady-state drug exposure was characterized by AUC of 860 ng·h/mL (CV% =37%) and Cmax of 75 ng/mL (CV% = 32%).

Absorption: Following administration of single oral doses of pomalidomide, the maximum plasma concentration (Cmax) for pomalidomide occurs at 2 and 3 hours postdose.

Effect of Food Co-administration of pomalidomide with a high-fat meal (approximately 50% of the total caloric content) and high-calorie meal (approximately 800 to 1000 calories) (the meal contained approximately 150, 250, and 500 to 600 calories from protein, carbohydrates, and fat, respectively) delays the Tmax by 2.5 hours, decreased mean plasma Cmax and AUC in healthy volunteers by about 27% and 8%, respectively.

Distribution: Pomalidomide has a mean apparent volume of distribution (Vd/F) between 62 and 138 L at steady state. Pomalidomide is distributed in semen of healthy subjects at a concentration of approximately 67% of plasma level at 4 hours postdose (~Tmax) after 4 days of once-daily dosing at 2 mg. Human plasma protein binding ranges from 12% to 44% and is not concentration dependent. Pomalidomide is a substrate for P-gp.

Elimination: Pomalidomide has a mean total body clearance (CL/F) of 7-10 L/h. Pomalidomide is eliminated with a median plasma half-life of approximately 9.5 hours in healthy subjects and approximately 7.5 hours in patients with multiple myeloma.

Metabolism: Pomalidomide is primarily metabolized in the liver by CYP1A2 and CYP3A4. Minor contributions from CYP2C19 and CYP2D6 were also observed in vitro.

Following a single oral administration of [14C]-pomalidomide to healthy subjects, approximately 73% and 15% of the radioactive dose was eliminated in urine and feces, respectively, with approximately 2% and 8% of the radiolabeled dose eliminated unchanged as pomalidomide in urine and feces.

Specific Populations

Age (61 to 85 years old), sex and race had no clinically significant effect on the systemic exposure of pomalidomide. The pharmacokinetics of pomalidomide is unknown in pediatric patients.

Renal Impairment: Pomalidomide pharmacokinetic parameters were not significantly affected in patients with moderate (30 mL/min ≤ CrCL< 60 mL/min) or severe (15 mL/min ≤ CrCL< 30 mL/min) renal impairment relative to patients with normal renal function (CrCL ≥ 60 mL/min). Mean exposure (AUC) to pomalidomide increased by 38% in patients with severe renal impairment requiring dialysis (CrCL< 30 mL/min requiring dialysis) and 40% in patients with end stage renal disease (CrCL< 15 mL/min) on non-dialysis days. In patients with severe renal impairment requiring dialysis, the estimated dialysis clearance is approximately 12 L/h which is higher than pomalidomide total body clearance, indicating hemodialysis will remove pomalidomide from the blood circulation.

Hepatic Impairment: Mean exposure (AUC) increased by 51%, 58% and 72% in subjects with mild, moderate or severe hepatic impairment as defined by Child-Pugh criteria, respectively.

Drug Interaction Studies

Co-administration of pomalidomide with the following drugs did not increase pomalidomide exposure to a clinically significant extent: ketoconazole (a strong CYP3A4 and P-gp inhibitor), carbamazepine (a strong CYP3A4 inducer) and dexamethasone (a weak to moderate inducer of CYP3A4). Co-administration of pomalidomide with drugs that are CYP1A2 inducers has not been studied.

CYP1A2 Inhibitors: Co-administration of fluvoxamine (a strong CYP1A2 inhibitor) with pomalidomide increased mean [90% confidence interval] pomalidomide exposure by 125% [98% to 157%] compared to pomalidomide alone in healthy subjects. Co-administration of fluvoxamine in the presence of ketoconazole (a strong CYP3A4 and P-gp inhibitor) with pomalidomide increased mean pomalidomide exposure by 146% [126% to 167%] compared to pomalidomide administered alone in healthy subjects, indicating the predominant effect of CYP1A2 inhibition in the increase of pomalidomide exposure.

Strong CYP3A4 and P-gp Inhibitors: Co-administration of ketoconazole (a strong CYP3A4 and P-gp inhibitor) in 16 healthy male subjects increased AUC of pomalidomide by 19% compared to pomalidomide administered alone.

Drugs that Induce Pomalidomide Metabolism

Strong CYP1A2 Inducers: Co-administration of pomalidomide with drugs that are CYP1A2 inducers has not been studied and may reduce pomalidomide exposure.

Strong CYP3A4 Inducers: Co-administration of carbamazepine to 16 healthy male subjects decreased AUC of pomalidomide by 20% with a 90% confidence interval [13% to 27%] compared to when pomalidomide was administered alone.

Dexamethasone: Co-administration of multiple doses of 4 mg pomalidomide with 20 mg to 40 mg dexamethasone (a weak to moderate inducer of CYP3A4) to patients with multiple myeloma had no effect on the pharmacokinetics of pomalidomide compared to when pomalidomide was administered alone.

Smoking: In 14 healthy male subjects who smoked 25 cigarettes per day for a total of 10 days, after single oral dose of 4 mg pomalidomide, Cmax of pomalidomide increased 14% while AUC of pomalidomide decreased 32%, compared to that in 13 healthy male volunteers who were non-smokers.

In Vitro Studies

Pomalidomide does not inhibit or induce CYP450 enzymes or transporters in vitro.

2. STUDY OBJECTIVES

2.1 Primary Objectives

- To determine best response within 8 cycles of treatment with daratumumab, clarithromycin, pomalidomide, and dexamethasone (D-ClaPd) in patients with multiple myeloma.

2.2 Secondary Objectives

To determine:

- Median PFS
- Overall survival
- Time to response
- Time to progression
- Duration of response
- Time to next therapy
- Overall response rate
- Complete response rate
- VGPR response rate
- Exploratory Endpoints and Correlative Studies (see Section 3.3)

3. STUDY ENDPOINTS

3.1 Primary Endpoints

- ≥ VGPR response proportion as best response within 8 cycles of induction treatment

3.2 Secondary Endpoints

- PFS
- Overall survival
- Time to response
- Time to progression
- Duration of response
- Time to next therapy
- Complete response rate or better
- Overall response rate (responses ≥ PR)
- VGPR response rate or better
- MRD negativity rate
- Improvement in response rate during maintenance therapy

3.3 Exploratory Endpoints and Correlative Studies

There will be numerous correlative studies incorporated into the main study as exploratory endpoints. These will include monitoring for response assessment by imaging studies as well as MRD by multiparameter flow cytometry (MFC), FISH, and NGS. MFC-based tests of immune cells from marrow will be studied for various immune-based and daratumumab-based markers (see below). Samples obtained for correlative studies will be retained and may be stored for potential future use. The samples will be collected and stored in a de-identified manner, and only individuals associated with the protocol will have access to and/or handle the samples. The samples will be analyzed and/or stored at the main study site.

3.3.1 MFC of bone marrow aspirate at diagnosis and at best response for MRD using Euroflow-based panel (both time points)

3.3.2 NGS at diagnosis and at best response for MRD using NGS assays

3.3.3 MFC at diagnosis and at best response of bone marrow aspirate for immune cells and daratumumab-based markers (M1/M2, CD36, CD38, NK; CD55/59)

3.3.4 Imaging (PET/MRI) at diagnosis and at best response/MRD

3.3.5 Dose intensity analysis (mean relative dose intensity of dexamethasone)

4. STUDY DESIGN

4.1 Overview of Study Design

This is a single center, single-arm phase 2 study that will be conducted at Weill Cornell Medical College to evaluate the best response within 8 cycles of induction in relapsed/refractory multiple myeloma compared to historical pomalidomide/dexamethasone. Patients will receive daratumumab/clarithromycin/ pomalidomide/dexamethasone (D-ClaPd) for 8 cycles of induction followed by daratumumab/pomalidomide/dexamethasone for maintenance until PD or unacceptable toxicity, whichever comes first. Patients will be treated for up to 24 months of maintenance if evidence of PR or better after induction.

D-ClaPd has potential for synergistic activity with good tolerability/safety in relapsed/refractory myeloma.
In patients with previous daratumumab exposure, the following hypotheses will be tested:

- D-ClaPd will yield higher ≥VGPR rates in relapsed/refractory myeloma than historical pomalidomide/dexamethasone (≥VGPR 9%) in this setting.
- Daratumumab retreatment in combination with ClaPd in early relapse will have higher ORR than ClaPd (ORR 60%).

Patient participation will include a screening phase and a treatment phase. The screening phase will be up to 28 days prior to first dose of study drug. The Treatment Phase begins on the date of the first study treatment and ends on the date the patient and the investigator agree that the patient will no longer continue study treatment.

During the treatment phase, daratumumab, clarithromycin, pomalidomide, and dexamethasone will be administered as per the following schedule.

Cycle 1 (28-day cycle)

- Daratumumab 1800 mg SC on days 1, 8, 15, and 22
- Clarithromycin 500 mg PO bid continuous 1-28 days until VGPR achieved
- Pomalidomide 4 mg PO on days 1-21 of 28-day cycle
- Dexamethasone 20 mg IV will be administered as a premedication prior to daratumumab injection on days 1 and 8, 20 mg PO will be administered the day after daratumumab dosing on days 2 and 9 (total of 40 mg/week)**, 40 mg PO will be administered as a premedication prior to daratumumab injection on days 15 and 22

Cycles 2-6 (28-day cycle)

- Daratumumab 1800 mg SC on days 1, 8, 15, and 22 for Cycle 2 and Daratumumab 1800 mg SC q2wk days 1 & 15 Cycles 3-6
- Clarithromycin 500 mg PO bid continuous days 1-28 (if <VGPR and discontinued if VGPR achieved)
- Pomalidomide 4 mg PO on days 1-21 of 28-day cycle

- Dexamethasone 40 mg PO will be administered as a premedication prior to daratumumab injection weekly for Cycle 2 and biweekly for Cycles 3-6
- Dexamethasone 40 mg PO weekly on non-daratumumab treatment days (Cycles 3-6)

Cycles 7-8 (28-day cycle)

- Daratumumab 1800 mg SC q4wks on Day 1
- Clarithromycin 500 mg PO bid days continuous 1-28 (if <VGPR and discontinued if VGPR achieved)
- Pomalidomide 4 mg PO on Days 1-21 of 28-day cycle
- Dexamethasone 20 mg PO will be administered as a premedication prior to daratumumab injection on day 1 of daratumumab (Cycles 7-8)
- Dexamethasone 20 mg PO weekly on non-daratumumab treatment days

Cycles 9-30 Maintenance (28-day cycle)

- Daratumumab 1800 mg SC q4wks on Day 1
- Pomalidomide 4 mg PO on Days 1-21 of 28-day cycle
- Dexamethasone 20 mg PO will be administered as a premedication prior to daratumumab injection on day 1 of daratumumab.
- Dexamethasone 20 mg PO weekly on non-daratumumab treatment days

During the study, assessments will be performed as shown in the Study Calendar and as clinically indicated.

**Dexamethasone dosing if ≥ 70 year old- decrease dex dose by 50% in induction:
10 mg IV as premed on days 1 and 8 and 20mg PO on days 15 and 22 (Cycle 1) 10 mg PO the day after daratumumab on day 2 and 9 for Cycle 1 (total 20 mg/week)
20 mg PO as premedication weekly for cycle 2
20 mg PO weekly (cycles 3-6); 10 mg PO weekly (cycles 7+)

4.2 Number of Patients

Approximately 40 patients will be enrolled and treated on study.

4.3 Duration of Study

Patients will receive D-ClaPd at a dose defined by the treatment plan for up to 30 cycles, unless one of the following occurs:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s) defined as:

Occurrence of an AE that is related to treatment with the study drug which, in the judgment of the investigator, compromises the patient's ability to continue study-specific procedures, or is considered to not be in the patient's best interest.

Persistent AE requiring a delay of therapy for more than 4 weeks (28 days).

- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Patient becomes pregnant
- Patient loses the ability to freely provide consent through imprisonment or involuntary incarceration for treatment of a psychiatric or physical illness
- Patient achieves complete remission (CR), and the patient and investigator feel that discontinuation is in the patient's best interests, or
- Patient achieves a level of response that qualifies him or her for another therapy, such as high dose therapy with autologous stem cell transplantation, and the patient and investigator feel that discontinuation is in the patient's best interests

Follow-up

At the completion or early discontinuation of treatment, patients will be followed for an additional 90 days after the last administration of treatment or up until the initiation of the next line of treatment, whichever comes first. Patients with adverse events will be followed until the event has resolved or the condition has stabilized

Post Treatment Observation Phase

Patients who discontinue study treatment before disease progression has been observed, will undergo disease evaluations every 90 days (+/- 30 days) as specified in the Post-Treatment Observation Phase in the Study Calendar for a duration of 24 months or until confirmed hematologic disease progression, whichever comes first.

5. STUDY POPULATION

5.1 Inclusion Criteria

Each patient must meet all inclusion criteria listed below to enroll in study:

1. Subject must voluntarily sign and understand written informed consent.
2. Age ≥ 18 years at the time of signing the consent form.
3. Histologically confirmed MM
4. Relapsed and/or refractory myeloma defined as follows:

    i. Relapse or progressive disease after at least one previous line of therapy which must include prior daratumumab. At least 8 doses of daratumumab in a previous line must be administered either as monotherapy or in combination with a daratumumab-free interval of ≥3 months AND
    ii. Patient may be daratumumab refractory defined as less than a partial remission (PR) achieved on prior daratumumab-based therapy or have exhibited progression within 60 days of receiving daratumumab. If previous therapy was autologous stem cell transplant (SCT), ≥ 3 months must have elapsed after SCT.

5. Measurable disease as defined by > 0.5 g/dL serum monoclonal protein, >0.1 g/dL serum free light chains, > 0.2 g/24h urinary M-protein excretion, and/or measurable plasmacytoma(s).
6. Must have received prior treatment with both an immunomodulatory drug and proteasome inhibitor in the same or separate lines of therapy.
7. ECOG performance status ≥2 (Appendix 12.1)
8. Females of childbearing potential(FCBP)† must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL within 10 – 14 days prior to and again within 24 hours of prescribing pomalidomide (prescriptions must be filled within 7 days) and must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, at least 4 weeks before she starts taking pomalidomide FCBP must also agree to ongoing pregnancy testing. Men must agree to use a latex condom during sexual contact with females of child-bearing potential even if they have had a successful vasectomy. Females must agree not to donate eggs (ova, oocytes) and men not to donate sperm for the purpose of assisted reproduction during the study and for 4 weeks after the last dose of pomalidomide and for 3 months after the last dose of daratumumab. †A female of childbearing potential is a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).
9. Able to take aspirin daily as prophylactic anticoagulation (patients intolerant to ASA may use warfarin or low molecular weight heparin).
10. Life expectancy ≥ 3 months
11. Subjects must meet the following laboratory parameters:

i. Absolute neutrophil count (ANC) ≥750 cells/mm^3 (.75 x 10^9/L)
ii. Platelets count ≥ 50,000/mm3 (50 x 10^9/L)
iii. Serum SGOT/AST ≤ 2.0 x upper limits of normal
iv. Serum SGPT/ALT <3.0 x upper limits of normal (ULN)
v. Serum CrCl ≥ 30 mL/min
vi. Total bilirubin ≤ 1.5 x ULN (Total bilirubin ≥ 1.5 x ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).

12. All study participants must be registered into the mandatory POMALYST REMS™ program and be willing and able to comply with the requirements of the POMALYST REMS™ program.

5.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study:

1. Prior exposure to non-daratumumab anti-CD38 monoclonal antibodies. Prior pomalidomide exposure in 1 or more previous lines of therapy allowed if partial remission (PR) or better achieved. No disease progression may have occurred within 60 days of receiving pomalidomide.
2. Clinically significant cardiac disease defined by any of the following criteria:
    1. New York Heart Association (NYHA) Class III or IV heart failure
    2. Unstable cardiac arrhythmia
    3. Unstable angina
    4. Myocardial infarction within the past 6 months.
3. Baseline prolongation of the QT interval (men >450 ms; women >470 ms), on concurrent drugs known to prolong the QT interval (see Appendix 12.3), or with ongoing proarrhythmic conditions.
4. Severe obstructive airway disease defined by forced expiratory volume at one second (FEV1) < 50%.
5. Planned high-dose chemotherapy and autologous stem cell transplantation within 6, 28-day treatment cycles after starting on treatment.
6. Female patients who are lactating or have a positive serum pregnancy test during the screening period.
7. Failure to have fully recovered (ie, ≤Grade 1 toxicity) from the reversible effects of prior chemotherapy.
8. Major surgery within 14 days before enrollment.
9. Radiotherapy within 14 days before enrollment. If the involved field is small, 7 days will be considered a sufficient interval between treatment and study drug administration.
10. Infection requiring systemic intravenous antibiotic therapy or other serious infection within 14 days before study enrollment.
11. Systemic treatment, within 14 days before the first dose, with strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital, see Appendix 12.4), or use of Ginkgo biloba or St. John's wort.
12. Ongoing or active systemic infection including

    - Seropositive for human immunodeficiency virus (HIV)

- 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
- 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).

13. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.
14. Known allergy to any of the study medications, their analogues, or excipients in the various formulations of any agent.
15. Known GI disease or GI procedure that could interfere with the oral absorption or medication tolerance including difficulty swallowing.
16. Diagnosed or treated for another malignancy within 2 years before study enrollment or previously diagnosed with another malignancy and have any evidence of residual disease. Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.
17. Patient has ≥ Grade 3 peripheral neuropathy, or Grade 2 with pain on clinical examination during the screening period.
18. Participation in other clinical trials, including those with other investigational agents not included in this trial, within 30 days of the start of this trial and throughout the duration of this trial.
19. History of thromboembolic event within the past 6 months prior to enrollment.

6. STUDY DRUG

6.1 Description of Investigational Agents

6.1.1 Daratumumab

Daratumumab SC drug product for oncology/hematology is a colorless to yellow liquid. The final daratumumab SC product is daratumumab at a target concentration of 120 mg/mL co-formulated with rHuPH20 in a 25R vial at a nominal fill to deliver 15 mL. As a bridging strategy, administration of daratumumab by the SC route was after mixing the daratumumab IV drug product with rHuPH20 in polypropylene syringes. Refer to the Halozyme rHuPH20 Investigator's Brochure for details.

Daratumumab SC drug product for oncology/hematology is co-formulated at a concentration of 120 mg/mL daratumumab with 2000 U/mL rHuPH20 in an isotonic buffer consisting of histidine, sorbitol, methionine, NaCl and polysorbate 20 at pH 5.6.

For additional details, please see the daratumumab package insert.

6.1.2 Pomalidomide Capsules

Pomalidomide is supplied as dark blue opaque cap and yellow opaque body, imprinted "POML" on the cap in white ink and "1 mg" '2 mg" "3 mg" or "4 mg"on the body in black ink.

Store at 20°C-25°C (68°F-77°F); excursions permitted to 15°C-30°C (59°F-86°F). [see USP Controlled Room Temperature].

Care should be exercised in handling of pomalidomide. Pomalidomide capsules should not be opened or crushed.
If powder from pomalidomide contacts the skin, wash the skin immediately and thoroughly with soap and water. If pomalidomide contacts the mucous membranes, flush thoroughly with water. Follow procedures for proper handling and disposal of anticancer drugs.

6.2 Study Drug Administration

All protocol-specific criteria for administration of study drug must be met and documented before drug administration. Study drugs will be administered or dispensed only to eligible patients under the supervision of the investigator or identified sub-investigator(s). Patients should be monitored for toxicity, as necessary, and doses of daratumumab, pomalidomide, and dexamethasone should be modified or delayed as needed to accommodate patient tolerance to treatment (See Section 6.3).

6.2.1 Daratumumab Administration

The daratumumab vials should be stored in the original carton in a refrigerator at 2ºC to 8ºC and must not be utilized after the expiry date printed on the label. The product must be protected from light and must not be frozen. Since daratumumab does not contain preservatives, any unused portion remaining in the vial must be discarded.

Refer to the Halozyme rHuPH20 Investigator's Brochure for details on storage and handling of rHuPH20.

Daratumumab 1800 mg SC is to be administered as described in the Study Calendar.

Injections may be performed as outpatient or inpatient visits, depending on local clinical practice. Patients will receive pre-medications and post-medications as outlined in Section

6.2.1.3. Daratumumab (1800 mg) will be administered by SC injection by manual push over approximately 3 - 5 minutes in the abdominal subcutaneous tissues in left/right locations, alternating between individual doses. The volume of the SC solution will be 15 mL for the 1800 mg dose. Refer to the Investigational Product Preparation Instructions (IPPI) for additional guidance on SC administration of Dara-SC. Vital signs should be monitored before, during, and after the first injection of daratumumab on Cycle 1 Day 1 and Cycle 1 Day 8. For all other doses, vital signs should be measured immediately before and after the injection. The median time to onset of IRRs for daratumumab SC is over 3 hours. Thus, all subjects must be observed for at least 6 hours after the end of the SC injection during Cycle 1 Day 1 and, if deemed necessary by the investigator, after subsequent injections. Reasons for continued observation on subsequent daratumumab injections may include but are not limited to the following: subjects with a higher risk of respiratory complications (eg, 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 first injection of study drug, subject with a decreased condition on day of dosing compared to prior dosing day. The dose of daratumumab will remain constant throughout the study.

6.2.1.1 Management of Daratumumab Reactions

For reactions of any grade/severity, management may include but is not limited to treatment with acetaminophen, antihistamine, or corticosteroids. Intravenous saline may be indicated. For bronchospasm, urticaria, or dyspnea, patients may require antihistamines, oxygen, corticosteroids, or bronchodilators. For hypotension, patients may require vasopressors.

Management of reactions may further require treatment discontinuation of daratumumab as outlined below.

- Grade 1-2 (mild to moderate): Once reaction symptoms resolve, resume dosing at next scheduled dose interval.
- Grade 3 (severe): Once reaction symptoms resolve, resume dosing at next scheduled dose interval. Permanently discontinue daratumumab upon the third occurrence of a Grade 3 or greater infusion reaction.
- Grade 4 (life threatening): Permanently discontinue daratumumab treatment.

6.2.1.2 Concomitant Medications

<u>Pre-injection Medications</u>

Administer the following premedications to reduce the risk of reactions to all patients 1-3 hours prior to every SC injection of daratumumab.

- Dexamethasone 20 mg IV or PO. Dexamethasone must be given intravenously prior to the first daratumumab dosing and oral administration may be administered prior to subsequent injections.

- Antipyretic (oral acetaminophen 650 mg to 1000 mg)

- Antihistamine (oral or intravenous diphenhydramine 25-50 mg IV)

- Leukotriene receptor antagonist (oral montelukast 10 mg)

- If FEV1 ≤ 80% at baseline, strongly consider administering **β**2-adrenergic agonist inhaler (e.g. albuterol)

Post-injection Medication
Patients will be administered pre- and post-medications for the prevention and management of IRRs.

Consider administering low-dose oral methylprednisolone (≤20 mg) or equivalent day after daratumumab injection.

For patients with a higher risk of respiratory complications (eg, patients with mild asthma or patients with COPD who have an FEVI <80% during screening or developed FEVI <80% during the study without any medical history), the following medications should be considered following SC daratumumab injection:

- Antihistamine (diphenhydramine or equivalent)
- Short-acting β2-adrenergic receptor agonist such as salbutamol
- Control medications for lung disease (eg, inhaled corticosteroids ± long acting β2-adrenergic receptor agonist for patients with asthma; long-acting bronchodilators such as tiotropium or salmeterol ± inhaled corticosteroids for patients with COPD).

Please note that concomitant medications will be recorded in the medical record only.

6.2.2 Pomalidomide Administration

Pomalidomide will be administered only to eligible patients under the supervision of the investigator or identified sub-investigator(s). Patients should be monitored for toxicity, as necessary, and doses of pomalidomide should be modified as needed to accommodate patient tolerance to treatment; this may include symptomatic treatment, dose interruptions, and adjustments of pomalidomide dose (see Section 6.3).

Pomalidomide will not be supplied for the study and will be obtained commercially.

Pomalidomide should be taken once daily at about the same time each day and may be taken with or without food.

The capsules should not be opened, broken, or chewed. Pomalidomide should be swallowed whole with water.
If a dose is missed, it may still be taken up to 12 hours after the time they would normally take it. If more than 12 hours have elapsed, they should be instructed to skip the dose for that day. The next day, they should take pomalidomide at the usual time. Warn patients not to take 2 doses to make up for the one that they missed.

6.2.3 Clarithromycin (Biaxin®)

Clarithromycin is a semi-synthetic macrolide antibiotic and is active in vitro against a variety of aerobic and anaerobic gram-positive and gram-negative microorganisms. Biaxin® is indicated for the treatment of mild to moderate infections caused by susceptible strains of microorganisms. It is administered as 500 mg tablets (Abbott Laboratories) to be taken orally. It is rapidly absorbed after oral administration and distributes widely into most body tissue with the exception of the CNS. Peak serum concentrations within 2 hours with a Tmax of 2-4 hours. The elimination half-life is about 3 to 4 hours and has primarily renal excretion.

Commercial clarithromycin will be used. Subjects will receive a prescription from the investigator. 500 mg tablets for oral administration will be obtained from the subject's local pharmacy.

6.2.4 Dexamethasone Administration

For Cycle 1, 20mg IV dexamethasone will be administered as a premedication on days 1 and 8 and 20 mg PO will be administered on days 2 and 9 (40mg weekly)**; 40mg PO will be administered as premedication on days 15 and 22.
For Cycles 2-6, 40 mg PO dexamethasone will be administered weekly.
For Cycles 7-8, 20mg PO dexamethasone will be administered weekly.
For Cycle 9+, 20mg PO dexamethasone will be administered weekly.
When dexamethasone is administered on daratumumab treatment days, dexamethasone should be administered as a premedication prior to daratumumab injection.

**Dexamethasone dosing if $\geq$ 70 years old- decrease dex dose by 50% in induction:
10 mg IV as premed on days 1 and 8 and 20mg PO on days 15 and 22 (Cycle 1)
10 mg PO the day after daratumumab on days 2 and 9 for Cycle 1 (total 20 mg/week)
20 mg PO as premedication weekly for cycle 2
20 mg PO weekly (cycles 3-6); 10 mg PO weekly (cycles 7+)

When taken orally, dexamethasone should be taken with food or milk to avoid gastrointestinal side effects. Missed doses can be taken as soon as the patient remembers if the next scheduled dose is 72 hours or more away. A double dose should not be taken to make up for a missed dose. If the patient vomits after taking a dose, the patient should not repeat the dose but should resume dosing at the time of the next scheduled dose.

6.2.4.1 Prophylactic and Supportive Medications

6.2.4.1.1. Valacyclovir 500 mg PO daily (or equivalent antiviral, renally dosed-adjusted), continuing for the duration of treatment (additional prophylaxis is at the Investigator's discretion) for varicella zoster prevention while on daratumumab and pomalidomide.

6.2.4.1.2 Aspirin 162 mg PO daily while on pomalidomide

6.2.4.1.3 Pantoprazole 40 mg PO daily, or other oral proton-pump inhibitor to prevent peptic disease for the duration of treatment with dexamethasone

6.2.4.1.4 IgG level will be checked monthly and IVIG (400 mg/kg) will be administered for IgG levels <500.

6.3 Dose-Modification Guidelines

No daratumumab dose modification (increase or decrease) is permitted during the study. Guidelines for pomalidomide and dexamethasone dose modifications are provided in Sections 6.3.3 and 6.3.4, respectively, although are only guidelines and not intended to supersede the clinical judgment of the treating physician.

6.3.1 Criteria for Beginning or Delaying a Subsequent Treatment Cycle

Treatment with Daratumumab, Pomalidomide, and Dexamethasone will use a cycle length of 28 days. For a new cycle of treatment to begin, the patient must meet the following criteria:

- ANC must be ≥ 1,000/mm^3.
- Platelet count must be ≥ 75,000/mm^3
- All other nonhematologic toxicity must have resolved to ≤ Grade 2 or to the patient's baseline condition for cardiac toxicities (See Table 6.4 for definition of cardiac toxicities).

If the patient fails to meet the above-cited criteria for initiation of the next cycle of treatment, dosing should be delayed for 1 week. At the end of that time, the patient should be re-evaluated to determine whether the criteria have been met. If the patient continues to fail to meet the above-cited criteria, delay therapy and continue to reevaluate. The maximum delay before treatment should be discontinued will be 4 weeks or at the discretion of the Principal Investigator.

6.3.2 Daratumumab Dose Modifications and Delays

No daratumumab dose modification (increase or decrease) is permitted.

During each cycle, the daratumumab dose must be held if any of the following criteria are met, to allow for recovery from toxicity.

- Grade 4 hematologic toxicity, or Grade 3 or higher thrombocytopenia with bleeding;
- Grade 3 or higher non-hematologic toxicities with the following exceptions:
  - Grade 3 nausea or Grade 3 vomiting that responds to antiemetic treatment,
  - Grade 3 diarrhea that responds to antidiarrheal treatment,
  - isolated Grade 3 γ-glutamyltransferase elevation, or
  - Grade 3 fatigue or asthenia that was present at baseline or that lasts for <7 days after the last administration of daratumumab.

Daratumumab treatment should be resumed when the toxicity has resolved to ≤ Grade 2. If the daratumumab administration does not commence within the prespecified window of the scheduled administration date as per Table 6-1, then the dose will be considered a missed dose. Administration may resume at the next planned dosing date.

Table 6-1 Daratumumab Dose Delay Schedule

Cycles	Frequency	Dose Miss	Dosing Resumptio
1-2	Weekly (q1wk)	>3 days	next planned weekly dosing date
3-6	Every 2 weeks (q2wk)	>7 days	next planned dosing date
7-12	Every 4 weeks (q4wk)	>14 days	next planned monthly dosing date

A missed dose will not be made up. Doses of daratumumab given in Cycle 7 and onwards may be delayed up to 4 weeks. If a dose is delayed, then the dates of all subsequent doses must be adjusted. 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.

Patients whose dose is held for more than 28 days or are missing ≥3 consecutive planned doses of daratumumab for reasons other than toxicity should be withdrawn from study drug, unless, upon consultation with the PI and the review of safety and efficacy, continuation is agreed upon.

6.3.3 Pomalidomide Dose Adjustments and Delays

Pomalidomide dose levels are outlined in Table 6-2, and dose adjustments for hematologic and nonhematologic toxicities are outlined in Table 6-3.

Table 6-2 Pomalidomide Dose Levels

Dose Level	Dose (mg)
Starting Dose	4 mg
-1	3 mg
-2	2 mg
-3	1 mg

Table 6-3: Dose Modifications Guidelines for Pomalidomide:		
NCI CTC Toxicity Grade	**Onset Day 2-14 of Cycle**	**Onset ≥ Day 15 of Cycle**
Grade 3 neutropenia associated with fever (temperature ≥ 38.5° C) or Grade 4 neutropenia	• Hold (interrupt) pomalidomide. • Follow CBC weekly. • If neutropenia has resolved to ≤ grade 2 prior to Day 21, restart at next lower dose level and continue through Day 21. If neutropenia is the only toxicity for which a dose reduction is required G-CSF may be used and the dose maintained	• Omit pomalidomide for remainder of cycle • See Instructions for Initiation of a New Cycle (6.3.1) and reduce the dose by 1 dose level. If neutropenia is the only toxicity for which a dose reduction is required. G-CSF may be used and the dose maintained for the next cycle at the investigators discretion.
Thrombocytopenia ≥Grade 3 (platelet count < 50,000/mm³)	• Hold (interrupt) pomalidomide. • Follow CBC weekly. • If resolves to ≤ grade 2 prior to Day 21, restart at next lower dose level and continue through Day 21.	• Omit pomalidomide for remainder of cycle • See Instructions for Initiation of a New Cycle (6.3.1) and reduce the dose by 1 dose level.
Non-blistering rash **Grade 3** **Grade 4**	• If Grade 3, hold (interrupt) pomalidomide. Follow weekly. • If the toxicity resolves to ≤ grade 1 prior to Day 21, restart at next lower dose level and continue the cycle through Day 21. • Discontinue and remove from study.	• Omit pomalidomide for remainder of cycle. • See Instructions for Initiation of a New Cycle (6.3.1) and reduce the dose by 1 dose level. • Discontinue pomalidomide. Remove patient from study.
Desquamating (blistering) rash- any Grade	• Discontinue pomalidomide. Remove patient from study.	• Discontinue pomalidomide. Remove patient from study.
Neuropathy **Grade 3**	• Hold (interrupt) Pom. Follow at least weekly. • If the toxicity resolves to ≤ grade 1 (or to baseline at study entry) prior to Day 21, restart at next lower dose	• Omit pomalidomide for the remainder of the cycle. • See Instructions for Initiation of a New Cycle (6.3.1) and reduce the dose by 1 dose level.

Table 6-3: Dose Modifications Guidelines for Pomalidomide:		
NCI CTC Toxicity Grade	**Onset Day 2-14 of Cycle**	**Onset ≥ Day 15 of Cycle**
Grade 4	level and continue the cycle through Day 21. • Discontinue pomalidomide. Remove patient from study.	• Discontinue pomalidomide. Remove patient from study.
Venous thrombosis/embolism ≥ Grade 3	• Hold (interrupt) pomalidomide and start anticoagulation; restart at investigator's discretion (maintain dose level).	• Omit pomalidomide for remainder of cycle and start anticoagulation .
Hyperthyroidism or hypothyroidism	• Omit pomalidomide for remainder of cycle, evaluate etiology, and initiate appropriate therapy. • See Initiation of a New Cycle (6.3.1) and reduce dose by 1 dose level.	• Omit pomalidomide for remainder of cycle, evaluate etiology, and initiate appropriate therapy. • See Initiation of a New Cycle (6.3.1) and reduce dose by 1 dose level.
other non-hematologic toxicity (non cardiac) ≥ Grade 3	• Hold (interrupt) pomalidomide. Follow at least weekly. • If resolves to ≤ grade 2 prior to Day 21, restart at next lower dose level and continue through Day 21.	• Omit pomalidomide for remainder of cycle. • See Instructions for Initiation of a New Cycle (6.3.1) and reduce the dose by 1 dose level.
Grade 3 dyspnea, cardiac edema, arrhythmias OR any increase in NYHA class or NTproBNP ≥ 30% **Grade 4**	• Hold Pom. Follow biweekly. If resolves to baseline prior to Day 21, restart at next lower dose and continue through Day 21. If does not resolve to baseline by day 21, hold Pom for remainder of cycle. CC-4047 at next lower dose level and continue through Day 21. • Discontinue pomalidomide.	• Omit pomalidomide for remainder of cycle. • See Instructions for Initiation of a New Cycle (6.3.1) and reduce the dose by 1 dose level. • Discontinue pomalidomide.

Dosage Adjustment for Strong CYP1A2 Inhibitors
Avoid concomitant use of pomalidomide with strong inhibitors of CYP1A2. Alternative treatments must be used.

Dosage Adjustment for Patients with Hepatic Impairment
For patients with mild or moderate hepatic impairment (Child-Pugh classes A or B), the recommended starting dose is 3 mg daily (25% dose reduction). For patients with severe hepatic impairment (Child-Pugh class C), the recommended dose is 2 mg (50% dose reduction)

Permanently discontinue pomalidomide for angioedema, skin exfoliation, bullae, or any other severe dermatologic reaction.

For other Grade 3 or 4 toxicities, hold treatment and restart treatment at 1mg less than previous dose when toxicity has resolved to ≤ to Grade 2 at the physician's discretion.

If pomalidomide is discontinued for toxicity, the patient may continue on study receiving daratumumab per study schedule with dexamethasone alone without pomalidomide.

Once pomalidomide is reduced for any toxicity, the dose may not be re-escalated.

6.3.4 Clarithromycin Dose adjustments

Clarithromycin will be dose reduced by 50% to 250mg PO bid for CrCl <30 mL/min during treatment as there is 20-40% renal excretion.

6.3.5 Dexamethasone Dose adjustments

Dexamethasone dose levels are outlined in Table 6-4, and dose adjustments for adverse events are outlined in Table 6-5.

Table 6-4 Dexamethasone Dose Levels

Dose Level	Dose (mg)
Starting Dose (weekly)	40 mg
-1	20 mg
-2	12 mg
-3	8 mg

NOTE: The 20 mg dose of dexamethasone premedication must still be given before the injection on the day of each daratumumab administration regardless of any dexamethasone dose reductions. Therefore, the -2 and -3 dose level weekly dexamethasone dose adjustments only apply to dexamethasone doses on non-daratumumab administration weeks.

Table 6-5 Dexamethasone Dose Adjustments for Adverse Events

Adverse Event	Recommended Action
Dyspepsia, gastric or duodenal ulcer, gastritis Grade 1–2 (requiring medical management)	Treat with H2 blockers, sucralfate, or pantoprazole If symptoms persist despite above measures, decrease dexamethasone dose by 1 dose level.
> Grade 3 (requiring hospitalization or surgery)	Hold dexamethasone until symptoms controlled. Restart at 1 dose decrement along with concurrent therapy with pantoprazole. If symptoms persist despite above measures, discontinue dex permanently.
Acute pancreatitis	Discontinue dexamethasone permanently.
Edema > Grade 3 (limiting function and unresponsive to therapy or anasarca)	Diuretics as needed, and restart dexamethasone at 1 dose decrement; if edema persists despite above measures, decrease dose another level. Discontinue dexamethasone permanently if symptoms persist despite second reduction.
Confusion or mood alteration > Grade 2 (interfering with function +/– interfering with activities of daily living)	Hold dexamethasone until symptoms resolve. Restart dexamethasone at 1 dose decrement. If symptoms persist despite above measures, reduce by another dose decrement.
Muscle weakness > Grade 2 (symptomatic and interfering with function +/– interfering with activities of daily living)	Decrease dexamethasone by 1 dose level. If weakness persists, decrease dose by 1 more dose level. Discontinue dexamethasone permanently if symptoms persist.
Hyperglycemia ≥ Grade 3	Treatment with insulin or other hypoglycemic agents as needed. If uncontrolled despite above measures, decrease dose by 1 dose level until levels are satisfactory.
Other nonhematologic Toxicity ≥ Grade 3 felt related to dexamethasone	Hold dexamethasone dose. Resume at 1 dose decrement when toxicity has resolved to Grade 2 or less or to baseline. If toxicity recurs, discontinue dexamethasone permanently.

6.4 Excluded Concomitant Medications and Procedures

The following medications and procedures are prohibited during the study.

Systemic treatment with concurrent drugs known to prolong the QT interval (see Appendix 12.3)

Systemic treatment with any of the following metabolizing enzyme inducers should be avoided, unless there is no appropriate alternative medication for the patient's use:

- Strong CYP3A inducers: rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, and phenobarbital. For a more comprehensive list of CYP3A inducers, please refer to Appendix 12.4.

The following medicinal products and procedures are prohibited during the study.

- Excluded foods and dietary supplements include St. John's wort and Ginkgo biloba.
- Any antineoplastic treatment with activity against MM, other than study drugs
- Radiation therapy (note that, in general, the requirement for local radiation therapy indicates disease progression)
- Platelet transfusions to help patients meet eligibility criteria are not allowed within 3 days prior to study drug dosing for any dosing day

6.5 Permitted Concomitant Medications and Procedures

The following medications and procedures are permitted during the study:

- Antiemetics, including 5-HT3 serotonin receptor antagonists, may be used at the discretion of the investigator.
- Loperamide or other antidiarrheal should be used for symptomatic diarrhea at discretion of the investigator. The dose and regimen will be according to institutional guidelines. IVF should be given to prevent volume depletion.
- Growth factors (eg, granulocyte colony stimulating factor [G-CSF], granulocyte macrophage-colony stimulating factor [GM-CSF], recombinant erythropoietin) are permitted. Their use should follow published guidelines and/or institutional practice; however, alternative usage may be reviewed with the Janssen Clinical

or Medical Representative. Erythropoietin will be allowed in this study. Their use should follow published guidelines and/or institutional practice.

- Patients should be transfused with red cells and platelets as clinically indicated and according to institutional guidelines.

- Concomitant treatment with bisphosphonates will be permitted, as appropriate.

- Patients who experience worsening neuropathy from baseline may be observed for recovery and have dose reductions/delays as indicated in the protocol, and any supportive therapy or intervention may be initiated as appropriate at the discretion of the investigator.

- Supportive measures consistent with optimal patient care may be given throughout the study.

6.6 Precautions and Restrictions

- Fluid deficit should be corrected before initiation of treatment and during treatment.

- Nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided with impaired renal function given reported NSAID-induced renal failure in patients with decreased renal function.

Pregnancy

Pomalidomide can cause fetal harm when administered to a pregnant female. Pomalidomide is contraindicated in females who are pregnant. Pomalidomide is a thalidomide analogue and is teratogenic in both rats and rabbits when administered during the period of organogenesis. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential risk to a fetus.

Embryo-Fetal Toxicity
Pomalidomide is a thalidomide analogue and is contraindicated for use during pregnancy. Thalidomide is a known human teratogen that causes severe birth defects or embryo-fetal death. pomalidomide is only available through the pomalidomide REMS program.
Females of Reproductive Potential Females of reproductive potential must avoid pregnancy for at least 4 weeks before beginning pomalidomide therapy, during therapy, during dose interruptions and for at least 4 weeks after completing therapy.
Females must commit either to abstain continuously from heterosexual sexual intercourse or to use 2 methods of reliable birth control, beginning 4 weeks prior to initiating treatment with pomalidomide, during therapy, during dose interruptions, and continuing for 4 weeks following discontinuation of pomalidomide therapy. Two negative pregnancy tests must be obtained prior to initiating therapy. The first test should be performed within 10-14 days and

the second test within 24 hours prior to prescribing pomalidomide therapy and then weekly during the first month, then monthly thereafter in females with regular menstrual cycles, or every 2 weeks in females with irregular menstrual cycles.

Males
Pomalidomide is present in the semen of patients receiving the drug. Therefore, males must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking pomalidomide and for up to 4 weeks after discontinuing pomalidomide, even if they have undergone a successful vasectomy. Male patients taking pomalidomide must not donate sperm.

Pregnancy Testing
Pomalidomide can cause fetal harm when administered during pregnancy.
Verify the pregnancy status of females of reproductive potential prior to initiating pomalidomide therapy and during therapy. Advise females of reproductive potential that they must avoid pregnancy 4 weeks before therapy, while taking pomalidomide, during dose interruptions and for at least 4 weeks after completing therapy.
Females of reproductive potential must have 2 negative pregnancy tests before initiating pomalidomide. The first test should be performed within 10-14 days, and the second test within 24 hours prior to prescribing pomalidomide. Once treatment has started and during dose interruptions, pregnancy testing for females of reproductive potential should occur weekly during the first 4 weeks of use, then pregnancy testing should be repeated every 4 weeks in females with regular menstrual cycles. If menstrual cycles are irregular, the pregnancy testing should occur every 2 weeks. Pregnancy testing and counseling should be performed if a patient misses her period or if there is any abnormality in her menstrual bleeding. Pomalidomide treatment must be discontinued during this evaluation.

Contraception
Females
Females of reproductive potential must commit either to abstain continuously from heterosexual sexual intercourse or to use 2 methods of reliable birth control simultaneously: one highly effective form of contraception – tubal ligation, IUD, hormonal (birth control pills, injections, hormonal patches, vaginal rings, or implants), or partner's vasectomy, and 1 additional effective contraceptive method – male latex or synthetic condom, diaphragm, or cervical cap. Contraception must begin 4 weeks prior to initiating treatment on study, during therapy, during dose interruptions, and continuing for 4 weeks following discontinuation of pomalidomide and 12 weeks following discontinuation of daratumumab. Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy. Females of reproductive potential should be referred to a qualified provider of contraceptive methods, if needed.

6.7 Management of Clinical Events

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.

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.

Adverse drug reactions such as thrombocytopenia, diarrhea, fatigue, nausea, vomiting, and rash have been associated with pomalidomide treatment. Management guidelines regarding these events are outlined below. Further details of management of AEs are described in the pomalidomide IB.

Prophylaxis Against Risk of Reactivation of Herpes Infection

Patients may be at an increased risk of infection including reactivation of herpes zoster and herpes simplex viruses. Antiviral therapy such as acyclovir, valacyclovir, or other antivirals may be initiated as clinically indicated. Other antivirals are also acceptable.

Venous and Arterial Thromboembolism
Venous thromboembolic events (deep venous thrombosis and pulmonary embolism) and arterial thromboembolic events (myocardial infarction and stroke) have been observed in patients treated with pomalidomide. In Trial 2, where anticoagulant therapies were mandated, thromboembolic events occurred in 8.0% of patients treated with pomalidomide and low dose-dexamethasone (low-dose dex), and 3.3% of patients treated with high-dose dexamethasone. Venous thromboembolic events (VTE) occurred in 4.7% of patients treated with pomalidomide and Low-dose Dex, and 1.3% of patients treated with high-dose dexamethasone.
Arterial thromboembolic events include terms for arterial thromboembolic events, ischemic cerebrovascular conditions, and ischemic heart disease. Arterial thromboembolic events occurred in 3.0% of patients treated with pomalidomide and low-dose dex, and 1.3% of patients treated with high-dose dexamethasone.
Patients with known risk factors, including prior thrombosis, may be at greater risk, and actions should be taken to try to minimize all modifiable factors (e.g., hyperlipidemia, hypertension, smoking). Thromboprophylaxis is recommended, and the choice of regimen should be based on assessment of the patient's underlying risk factors.

Prophylaxis Against Risk of Peptic Ulcer Disease

Patients may be at an increased risk of peptic ulcer disease while on corticosteroids with dexamethasone. Pantoprazole or other oral proton-pump inhibitor to prevent peptic disease for the duration of treatment with dexamethasone

Nausea and/or Vomiting

Standard anti-emetics including 5-hydroxytryptamine 3 serotonin receptor antagonists are recommended for emesis if it occurs once treatment is initiated; prophylactic anti-emetics may also be considered at the physician’s discretion. Dexamethasone should not be administered as an anti-emetic. Fluid deficit should be corrected before initiation of study drug and during treatment.

Diarrhea

Prophylactic antidiarrheals will not be used in this protocol. However, diarrhea should be managed according to clinical practice, including the administration of antidiarrheals once infectious causes are excluded. Fluid intake should be maintained to avoid dehydration. Fluid deficit should be corrected before initiation of treatment and during treatment.

Hepatotoxicity
Hepatic failure, including fatal cases, has occurred in patients treated with pomalidomide. Elevated levels of alanine aminotransferase and bilirubin have also been observed in patients treated with pomalidomide. Monitor liver function tests monthly. Stop pomalidomide upon elevation of liver enzymes and evaluate. After return to baseline values, treatment at a lower dose may be considered.

Severe Cutaneous Reactions Including Hypersensitivity Reactions
Angioedema and severe cutaneous reactions including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported.
DRESS may present with a cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, fever, and/or lymphadenopathy with systemic complications such as hepatitis, nephritis, pneumonitis, myocarditis, and/or pericarditis. Discontinue POMALYST for angioedema, skin exfoliation, bullae, or any other severe cutaneous reactions such as SJS, TEN or DRESS, and do not resume therapy

Hematologic Toxicity
In trials 1 and 2 in patients who received pomalidomide + low-dose dex, neutropenia was the most frequently reported Grade 3/4 adverse reaction, followed by anemia and thrombocytopenia. Neutropenia of any grade was reported in 51% of patients in both trials. The rate of Grade 3/4 neutropenia was 46%. The rate of febrile neutropenia was 8%.
Monitor patients for hematologic toxicities, especially neutropenia. Monitor complete blood counts weekly for the first 8 weeks and monthly thereafter. Patients may require dose interruption and/or modification

Thrombocytopenia

Blood counts should be monitored regularly as outlined in the protocol with additional testing obtained according to standard clinical practice. Thrombocytopenia may be severe but has been manageable with platelet transfusions according to standard clinical practice. Pomalidomide administration should be modified as noted as per dose modification recommendations in the protocol when thrombocytopenia occurs (see Table 6-4). Therapy can be reinitiated at a reduced level upon recovery of platelet counts.

Neutropenia

Blood counts should be monitored regularly as outlined in the protocol with additional testing obtained according to standard clinical practice. Neutropenia may be severe but has been manageable. Growth factor support is not required but may be considered according to standard clinical practice. Pomalidomide administration should be modified as noted as per

dose modification recommendations in the protocol when neutropenia occurs (see Table 6-4). Therapy can be reinitiated at a reduced level upon recovery of ANCs.

Dizziness and Confusional State
In trials 1 and 2 in patients who received pomalidomide + low-dose dex, 14% of patients experienced dizziness and 7% of patients experienced a confusional state; 1% of patients experienced Grade 3 or 4 dizziness, and 3% of patients experienced Grade 3 or 4 confusional state. Instruct patients to avoid situations where dizziness or confusional state may be a problem and not to take other medications that may cause dizziness or confusional state without adequate medical advice.

Neuropathy
In trials 1 and 2 in patients who received pomalidomide + low-dose dex, 18% of patients experienced neuropathy, with approximately 12% of the patients experiencing peripheral neuropathy. Two percent of patients experienced Grade 3 neuropathy in trial 2. There were no cases of Grade 4 neuropathy adverse reactions reported in either trial.

Risk of Second Primary Malignancies
Cases of acute myelogenous leukemia have been reported in patients receiving pomalidomide as an investigational therapy outside of multiple myeloma.

Tumor Lysis Syndrome
Tumor lysis syndrome (TLS) may occur in patients treated with pomalidomide. Patients at risk for TLS are those with high tumor burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.

6.8 Preparation, Reconstitution, and Dispensing

Caution should be exercised when preparing daratumumab.

6.9 Packaging and Labeling

Daratumumab

The study drug daratumumab will be provided by Janssen Scientific Affairs, LLC. Packaging and labeling guidelines will be followed per manufacturer's instructions.

Pomalidomide

Commercial pomalidomide is planned for use.

Dexamethasone

The study drug dexamethasone will be commercially obtained and packaging and labeling guidelines will be followed per manufacturer's instructions.

6.10 Storage, Handling, and Accountability

Daratumumab

The final daratumumab SC product for oncology/hematology is daratumumab at a target concentration of 120 mg/mL co-formulated with rHuPH20 in a 25R vial at a nominal fill to deliver 15 mL. As a bridging strategy, administration of daratumumab by the SC route was after mixing the daratumumab IV drug product with rHuPH20 in polypropylene syringes.

Upon receipt at the investigative site, daratumumab vials should be stored in the original carton in a refrigerator at 2ºC to 8ºC and must not be utilized after the expiry date printed on the label. The product must be protected from light and must not be frozen. Since daratumumab does not contain preservatives, any unused portion remaining in the vial must be discarded.

Dexamethasone
Dexamethasone will be handled and stored as per manufacturers package insert.

6.11 Termination of Treatment and/or Study Participation

Patients will receive DPd at a dose defined by the treatment plan for up to 12 cycles, unless one of the following occurs:

- Hematologic disease progression.
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s) defined as:

  o Occurrence of an AE that is related to treatment with the study drug which, in the judgment of the investigator, compromises the patient's ability to continue study-specific procedures, or is considered to not be in the patient's best interest.

  o Persistent AE requiring a delay of therapy for more than 4 weeks (28 days).

- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Patient becomes pregnant
- Patient loses the ability to freely provide consent through imprisonment or involuntary incarceration for treatment of a psychiatric or physical illness
- Patient achieves complete remission (CR), and the patient and investigator feel that discontinuation of DPd is in the patient’s best interests, or
- Patient achieves a level of response that qualifies him or her for another therapy, such as high dose therapy with autologous stem cell transplantation, and the patient and investigator feel that discontinuation of DPd is in the patient’s best interests.

  Patients will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. At the time of withdrawal, all study procedures outlined for the End of Study visit should be completed. The

primary reason for patient's withdrawal from the study should be recorded in the source documents and CRF.

7. STUDY PROCEDURES

7.1 Screening

The screening (Pre-cycle) period occurs within 28 days prior to Cycle 1, Day 1 of therapy. Please see Schedule of Study Procedures for additional details.

7.2 Treatment Period

Clinical evaluations and laboratory assessments will be performed as per the Schedule of Study Procedures and as clinically indicated.

7.3 End of Treatment Visit

Unless a patient withdraws consent for study participation or is lost to follow-up, an End-of-Treatment Visit is to occur 90 days after the last dose of study treatment, or as soon as possible before the start of subsequent therapy. Every effort should be made to conduct the End-of-Treatment Visit before the patient starts subsequent treatment. After last administration of treatment, patients will be monitored for 90 days to identify any late toxicities that may occur as a result of immunotherapy.

7.4 Post-Treatment Observation Phase

For patients who complete all 32 cycles of treatment on study, if have not progressed or started new treatment, patients will be followed with disease evaluations every 90 days (+/- 30 days) until confirmed disease progression or for total duration of 24 months from last EOT visit, whichever comes first, and for OS for up to 10 years from date of enrollment or until death.

Patients who discontinue study treatment before disease progression has been observed, will undergo disease evaluations every 90 days (+/- 30 days) as specified in the Post-Treatment Observation Phase in the Study Calendar for a duration of 24 months or until confirmed hematologic disease progression, whichever comes first.

7.5 High-Dose Chemotherapy and Autologous Stem Cell Transplantation

Patients may undergo stem cell collection while on study. Mobilization agents can include granulocyte colony stimulating factor or plerixafor. Additional cyclophosphamide is permitted for chemotherapy-based mobilization. While undergoing stem cell collection, patients may hold their study treatment for a maximum of 4 weeks and should thereafter continue on treatment as per study protocol.

Patients who undergo high-dose chemotherapy and ASCT following 6 cycles of therapy after the secondary endpoint of overall hematologic response is assessed will be removed from study protocol. They will remain though in the Post-Treatment Observation phase for 24 months and undergo disease evaluations every evaluations every 90 days (+/- 30 days) as

specified in the Post-Treatment Observation Phase in the Study Calendar for a duration of 24 months or until confirmed hematologic disease progression, whichever comes first.

8. STATISTICAL AND QUANTITATIVE ANALYSES

8.1 Statistical Methods

The primary endpoint will be the ≥ VGPR response proportion as best response within the first 8 cycles of treatment. Based on historical data, the ≥ VGPR response proportion is approximately 9%; therefore, the target ≥ VGPR response proportion will be ≥ 25%.

This exact single-stage design yields a ≥ 0.80 probability of a positive result if the true ≥ VGPR response proportion is ≥ 25%. It yields a ≥ 0.95 probability of a negative result if the true ≥ VGPR response proportion is ≤ 9%. A 95% confidence interval constructed around the expected ≥ VGPR response proportion of 25% can be estimated to be within ± 17.9% of the observed ≥ VGPR response proportion.

Analysis Plan for Endpoints:

Primary Endpoint:
The primary endpoint is the ≥ VGPR response proportion as best response within the first 8 cycles of treatment; A 95% confidence interval will be estimated for the ≥ VGPR response proportion via binomial proportions.

Secondary endpoints:
Secondary endpoints include median PFS, OS, time to response and progression, DoR, TTNT, ORR, VGPR rate, CR or better rate, improvement in response rate during maintenance therapy and MRD negativity rate. Median PFS/OS, including survival curves, will be estimated using Kaplan-Meier methodology. Greenwood's formula will be used to calculate 95% confidence intervals for the Kaplan-Meier survival estimates.
All analyses will be performed in SAS Version 9.4 (SAS Institute, Inc., Cary, North Carolina) and Stata Version 15.0 (StataCorp, College Station, Texas).

8.1.1 Determination of Sample Size

The sample size computations were performed assuming a 5% level of significance and 80% power. The new regimen will be declared effective and worthy of further testing if 8 or more patients have ≥ VGPR among the 40 patients entered into the cohort.

Sample size recommendations for the current design are determined according to A'Hern's exact single-stage phase II design (A'Hern, RP, 2001). We project a ≥ VGPR response proportion of 9%, below which the regimen will be unacceptable, and a ≥ VGPR response proportion of 25%, above which the regimen will be considered worthy of further exploration. The null hypothesis that the ≥ VGPR response proportion is less than or equal to 9% will be tested against the alternative hypothesis that the ≥ VGPR response proportion is greater than or equal to 25%.

8.1.2 Randomization and Stratification

There is no randomization or stratification of this study.

8.1.3 Populations for Analysis

8.1.3.1 Enrolled Analysis Set

The enrolled analysis set will include all patients who signed an ICF and were enrolled.

8.1.3.2 Full Analysis Set

The full analysis set will include all patients enrolled on the study who received any amount of Daratumumab, Clarithromycin, Pomalidomide, and Dexamethasone and who had at least 1 post-baseline disease assessment.

8.1.4 Procedures for Handling Missing, Unused, and Spurious Data

Every effort must be made to avoid missing data. For all time-to-event endpoints, patients who do not have the event of interest will be censored at the date at which they were last known to be event-free. Missing data for quantitative endpoints will be replaced by the patient's last available value. Additional approaches for sensitivity analyses of the effects of missing data for secondary endpoints may be provided in the SAP.

8.1.5 Safety Analysis

Safety parameters will include SAEs, TEAEs, physical examination findings (including ECOG performance status), vital sign measurements, standard clinical laboratory parameters (serum chemistry, hematology, urinalysis), and ECG parameters. Adverse events will be graded according to the NCI-CTCAE v4. The incidence of DLTs will also be evaluated.

Safety analyses in general will be descriptive and will be presented in tabular format with the appropriate summary statistics.

A TEAE is defined as an adverse event that emerges during the treatment period (from first dose date till 30 (± 5) days after the last dosing date), having been absent at pre-treatment; or reemerges during treatment, having been present at baseline but stopped prior to treatment; or worsens in severity after starting treatment relative to the pre-treatment state, when the adverse event is continuous. The number and percentage of patients reporting TEAEs will be tabulated by the worst NCI- CTCAE grade, system organ class (SOC), and preferred term.

Similarly, the number and percentage of patients reporting treatment-emergent SAEs will be tabulated, as well as TEAEs/SAEs considered related to Daratumumab, Clarithromycin, Pomalidomide, and Dexamethasone.

A by-patient AE (including TEAE) data listing will be provided including, but not limited to, verbatim term, preferred term, SOC, NCI-CTCAE grade, and relationship to study drug.

Deaths, other SAEs, and other significant adverse events, including those leading to permanent discontinuation from Daratumumab, Pomalidomide, and Dexamethasone, will be listed.

8.1.6 Efficacy Analysis

Efficacy analysis will be performed for all patients enrolled on the study in the full analysis set.

Response

Parameters assessed will include stringent complete response (sCR), complete response (CR), very good partial response (VGPR), partial response (PR), and stable disease (SD) per standard IMWG response criteria. In addition, overall response rate (defined as greater than or equal to PR across all cycles of treatment), response duration, time-to-response (TTR), MRD negativity rate and improvement in response during maintenance therapy will be assessed.

Best overall response categories will be tabulated and overall for CR, VGPR, PR, SD, progressive disease, and relapse. A two-sided 95% exact binominal CI will be calculated for each category. The response rate (responses ≥ PR) will also be tabulated. Time-to-event analyses will be done using Kaplan- Meier analyses and will include time to response, duration of response, PFS, and OS, as data allow. If there is not enough data to apply the Kaplan-Meier test, the data will be summarized by descriptive statistics.

Time to response (for responders only) will be calculated as the time from the date of first study treatment dosing to the first date of documented response (PR or better) and will be summarized by descriptive statistics.

Duration of response (for responders only) is defined as the time from the earliest date of documented response (PR or better) to the earliest date when disease progression was confirmed. Patients who are non-responders will be excluded from this analysis. Detailed censoring rules for duration of response will be specified in the SAP.

PFS will be calculated as the time from the initial administration of Daratumumab, Clarithromycin, Pomalidomide, and Dexamethasone until documented disease progression, as determined using standard response criteria, or death from any cause, whichever occurs first. Kaplan-Meier methods will be used to estimate PFS over time and the median duration of PFS. Patients with no PFS event will be censored at the date of their last disease assessment.

Time to next therapy is defined as the time from the initial administration of Daratumumab, Clarithromycin, Pomalidomide, and Dexamethasone on trial to next treatment.

OS is defined as the time from the initial administration of Daratumumab, Clarithromycin Pomalidomide and Dexamethasone to death from any cause. Kaplan-Meier methods will be used to estimate the OS function. Patients who do not die will be censored at the date that the patient was last known to be alive.

8.1.7 Futility Analysis and Stopping Rules

If >4 deaths have been observed, regardless of how many patients have been enrolled at that point or by that time, the study will be stopped due to futility.

If Grade 3-4 infection rate >15% is seen, protocol enrollment will be put on hold and amendments for risk reduction will be implemented.

9. ADVERSE EVENTS

9.1 Overview

As the sponsor of the Study, 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 (co or 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

9.1.1 Adverse Event Definition

Adverse event (AE) means any untoward medical occurrence in a patient or patient administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug.

An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.

The investigator (or physician designee) is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for all adverse events for patients enrolled.

9.1.2 Serious Adverse Event Definition

Serious AE (SAE) means any untoward medical occurrence at any dose:

- Results in death.
- Is life-threatening (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalization or prolongation of an existing hospitalization (see clarification in the paragraph below on planned hospitalizations).

- Results in persistent or significant disability or incapacity. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a congenital anomaly/birth defect.
- Is a medically important event. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent 1 of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (eg, prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

  Clarification should be made between a serious AE (SAE) and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term severe is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as serious, which is based on patient/event outcome or action criteria described above and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm^3 to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

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

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.]
- Hospitalizations for close medical monitoring during a daratumumab infusion

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.

9.2 Procedures for Reporting Serious Adverse Events

9.2.1 Janssen SOP for Reporting Serious Adverse Events

As the sponsor of the study, the PI shall be solely responsible for complying, within the required timelines, any safety reporting obligation to competent Health Authorities, IRB/ECs and any participating (co or 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 PI 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.

9.2.1.1 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 and product quality complaints with or without an adverse event as described in this Exhibit will be reported from the time a patient has signed and dated an Informed Consent Form (ICF) until completion of the patient'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.

9.2.1.2 Definitions 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
- Tumor lysis syndrome
- HBV Reactivation
- Other malignancies
- Intravascular hemolysis – all grades

Any Adverse Event of Special Interest that is to be reported to 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**.

Individual Case Safety Report (ICSR)

An ICSR is applicable when submitting information regarding an SAE, AE of special interest, Product Quality Complaint (PQC), or a Special Reporting Situations. A valid ICSR must contain the four minimum criteria required to meet regulatory reporting requirements.

- an identifiable patient (but not disclosing personal information such as the patient'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
- patient details (patient 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

Product Quality Complaint (PQC)

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 patient. 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

9.2.1.3 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 daratumumab, the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure

9.2.1.4 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)
- 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)
- Suspected transmission of any infectious agent via administration of a medicinal product
- 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 by the PI/Research team.

9.2.1.5 Pregnancy

All initial reports of pregnancy must be reported to Janssen Scientific Affairs, LLC by PI/research team within 24 hours of becoming aware of the event using the Serious Adverse Event Form. Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomaly, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form.

Any patient who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study treatment.

Because the effect of the Janssen medicinal product on sperm is unknown, pregnancies in partners of male patients exposed to a Janssen medicinal product will be reported by PI/research team within 24 hours of their knowledge of the event using the Serious Adverse Event Form. Depending on local legislation this may require prior consent of the partner.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

9.2.1.6 Maintenance of Safety Information

All safety data should be maintained in a clinical database in a retrievable format. The PI/research team 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.

9.2.1.7 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 patient'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.

<u>SAEs and Special Reporting Situations</u>

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the patient'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 (patient or health care practitioner refusal to provide additional information, lost to follow- up after demonstration of due diligence with follow-up efforts)

  The PI/research team will transmit all SAEs and special situations following exposure to a Janssen product under study in a form provided by Janssen Scientific

Affairs, LLC in accordance with Section 9.2.1.9, Transmission Methods, in English within 24-hours of becoming aware of the event(s).

In the event the study is blinded, The PI/research team will submit an unblinded SAE or pregnancy exposure report to Janssen Scientific Affairs, LLC.

All follow-up information for serious adverse events that are not resolved at the end of the study or by the time of patient withdrawal must be reported directly by the PI/Research team, within 24 hours becoming aware, to Janssen Scientific Affairs, LLC using the Janssen Scientific Affairs, LLC Serious Adverse Event Report

All available clinical information relevant to the evaluation of a related SAE, serious ADR or special situation is required.

- The PI is responsible for ensuring that these cases are complete and if not are promptly followed-up. A safety report is not considered complete until all clinical details needed to interpret the case are received. Reporting of follow-up information should follow the same timeline as initial reports.
- Copies of any and all relevant correspondences with regulatory authorities and ethics committees regarding any and all serious adverse events, irrespective of association with the Janssen Product under study, are to be provided to Janssen Scientific Affairs, LLC by the PI/Research team, using a transmission method in Section 9.2.1.9 within 24 hours of such report or correspondence being sent to applicable health authorities.

Non-Serious AEs

All non-serious adverse events should be reported to Janssen Scientific Affairs, LLC, annually, according to the timeframe outlined in the Research Funding Agreement section entitled Reporting of Data.

PQC Reporting

A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of patients, investigators, and Janssen Scientific Affairs, LLC, and are mandated by regulatory agencies worldwide. Janssen Scientific Affairs, LLC has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information. Lot and/or Batch #s shall be collected or any reports failure of expected pharmacological action (i.e., lack of effect). The product should be quarantined immediately and if possible, take a picture.

All initial PQCs involving a Janssen medicinal product under study must be reported to Janssen Scientific Affairs, LLC by the PI/research team within 24 hours after being made aware of the event. The Janssen contact will provide additional information/form to be completed.

If the defect for a Janssen medicinal product under study is combined with either a serious adverse event or non-serious adverse event, the PI must report the PQC to Janssen Scientific Affairs, LLC according to the serious adverse event reporting timelines. A sample of the suspected product should be maintained for further investigation if requested by Janssen Scientific Affairs, LLC.

9.2.1.8 Reporting Procedures for Reporting Safety Data and Product Quality Complaints (PQCs) for Non-Janssen Medicinal Products

For SAEs, special reporting situations and PQCs following exposure to a non-Janssen medicinal product under study, The PI should notify the appropriate regulatory/competent authority or the manufacturer of that medicinal product (in the absence of appropriate local legislation) as soon as possible.

9.2.1.9 Transmission Methods

The following methods are acceptable for transmission of safety information to Janssen Scientific Affairs, LLC:

- Electronically via Janssen SECURE Email service (preferred): IIS-BIO-VIRO-GCO@its.jnj.com
- For business continuity purposes, if SECURE Email is non-functional:

  o Facsimile (fax), receipt of which is evidenced in a successful fax

  transmission report: 1-866-651-0219

  •Telephone (if fax is non-functional).

  Please use the contact information and process information provided by Janssen Scientific Affairs, LLC.

9.2.1.10 SAEs Listing

At a minimum, on a semi-annual basis and at the end of the Study, COMPANY will provide to the INSTITUTION and/or PRINCIPAL INVESTIGATOR, a listing of all SAEs reported to the COMPANY. PRINCIPAL INVESTIGATOR will review this listing and will resolve any discrepancies with the data provided by the COMPANY.

9.2.1.11 Dissemination of Safety Information from COMPANY to INSTITUTION/PRINCIPAL INVESTIGATORS

PRINCIPAL INVESTIGATOR will be responsible for submitting IND safety reports for the Study Product to INSTITUTION's IRB in accordance with Federal regulations 21 CFR 312.66. The PRINCIPAL INVESTIGATOR will provide a copy of each IND safety report to sub-investigators where the study design is either a multi-center or cooperative study.

COMPANY agrees to provide to the PRINCIPAL INVESTIGATOR IND safety reports for the Janssen Medicinal Product as they become available until all subjects in the Protocol have completed their last Study visit according to the Protocol (i.e. Last Subject Last Visit has occurred).

9.2.1.12 Contacting COMPANY Regarding Safety

The names (and corresponding contact information) of the individuals who should be contacted regarding safety issues will be provided separately by the COMPANY.

9.2.1.13 Final Study Report

The INSTITUTION/PRINCIPAL INVESTIGATOR will prepare a final report including a complete and full summary of all adverse events, special situations and pregnancy reports according to the timeframe outlined in the Research Funding Agreement.

9.2.2 Report of Adverse Events to the Institutional Review Board

The principal Investigator is required to notify his/her Institutional Review Board (IRB) by within 7 calendar days of observing or learning of a serious adverse event as per the IRB Immediate Reporting policy.

10. Data Safety and Monitoring Committee (DSMC)

The Data Safety Monitoring Committee (DSMC) at Weill Cornell Medical (WCM) will be composed of medical and statistical independent reviewers and will meet to review the efficacy and safety data and determine a risk/benefit analysis in this subject population.

The study (including AEs and SAEs) will be reviewed by the WCM DSMC twice per year. The first DSMC meeting will occur within 6 months of the first subject enrollment at WCM and every 6 months thereafter. The purpose of the DSMC is to advise on serious safety considerations, lack of efficacy and any other considerations within the charge to the Committee. The DSMC may request additional meetings or safety reports as deemed necessary. The DSMC can recommend to the sponsor that the trial be stopped if it is not effective, is harming participants, or is unlikely to serve its scientific purpose. The PI will be the safety contact for all DSMC related analysis outcomes. Decisions are communicated by the DSMC to the PI and the research team.

11. REFERENCES

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12. APPENDICES

12.1 Eastern Cooperative Oncology Group (ECOG) Scale for Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all predisease performance without restriction
1	Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work)
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5 (6):649-55.

12.2 Cockcroft-Gault Equation

For males:

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

For females:

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

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

12.3 List of common QT prolonging drugs

Zofran
Erythromycin
Quinolones
Azoles
Sotalol
Amiodarone
Amitryptyline
Fluoxetine
Sertraline
Venlafaxine
Quetiapine
Methadone
Sumatriptan

12.4 CYP3A4 Inducers

(Referenced from http://medicine.iupui.edu/clinpharm/ddis/main-table)

efavirenz
nevirapine
barbiturates
carbamazepineee
Enzalutamide
glucocorticoids
modafinil
oxcarbazepine
phenobarbital2
phenytoin2
pioglitazone
rifabutin
rifampin1
St. John's