Janssen Research & Development *

Clinical Protocol

A Randomized, Open-label, Multicenter, Multiphase Study of JNJ-63723283, an Anti-PD-1 Monoclonal Antibody, Administered in Combination with Daratumumab, Compared with Daratumumab Alone in Subjects with Relapsed or Refractory Multiple Myeloma

Protocol 54767414MMY2036
Phase 2 and 3
AMENDMENT 2

JNJ-63723283; JNJ-54767414 (DARZALEX®, daratumumab)

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JNJ-63723283 is being investigated in a Phase 1 study.
Daratumumab is being investigated in Phase 2 and 3 clinical studies.
Daratumumab is approved for marketing in 4 indications.

This study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).

EudraCT NUMBER: 2017-002611-34

Status: Approved
Date: 20 June 2018
Prepared by: Janssen Research & Development, LLC
EDMS number: EDMS-ERI-141773787, 4.0

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

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PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	05 July 2017
Amendment 1	23 Aug 2017
Amendment 2	20 June 2018

Amendments below are listed beginning with the most recent amendment.

Amendment 2 (20 June 2018)

The overall reason for the amendment:

As of 25 May 2018, the Sponsor terminated further enrollment into this study, 54767414MMY2036 (TUCANA), based on safety and efficacy findings in the 54767414LUC2001 (CALLISTO) study, which combined daratumumab with atezolizumab in non-small cell lung cancer. At the third planned Data Monitoring Committee (DMC) review on 23 May 2018, the DMC reviewed the subject data (n=88, 44 per arm) for the CALLISTO Study. The DMC determined that there was no observed benefit within the combination treatment arm, daratumumab plus atezolizumab, over atezolizumab alone, and recommended stopping enrollment of the study. In addition, the DMC recommended discontinuation of daratumumab treatment to all active subjects receiving combination therapy (subjects randomized to the combination Arm B, as well as subjects randomized to Arm A who have crossed over into Arm B). Although no unexpected imbalances in on-treatment toxicities were observed, the DMC noted a clear early difference in the number of deaths between the atezolizumab monotherapy (n=13) and combination arm (n=18). The discrepancy was observed within the first 3 months from dosing, where the number of deaths are 4 for the atezolizumab arm and 10 for the combination arm, giving rise to 3-month survival rates of 90.7% for the atezolizumab arm and 76.2% for the combination arm.

Since the benefit/risk ratio has changed for combination therapy in CALLISTO, the Sponsor has decided to suspend enrollment into other studies which combine daratumumab and a programmed death-1 (PD-1) or programmed death-ligand 1 (PD-L1) monoclonal antibody regardless of indication. In addition to discontinuing enrollment into this study, treatment with the combination of daratumumab and JNJ-63723283 will be discontinued and ongoing subjects will be given the option to continue on daratumumab monotherapy until subject meets one or more of the treatment discontinuation criteria in Section 10.1.1.

Applicable Section(s)	Description of Change(s)
Rationale: The benefit/risk ratio has changed for combination therapy in CALLISTO which has led to the discontinuing enrollment and treatment of combination therapy in this study.	
1.4 Overall Study Rationale and Anticipated Benefits and Risks of Combination Therapy; New Attachment 11: Daratumumab Monotherapy Period for Subjects No Longer Receiving JNJ-63723283 in Combination with Daratumumab; 4 Subject Population; 5 Treatment Allocation and Blinding	The rationale for stopping enrollment is discussed and it is clarified that subjects in Screening as of 25 May 2018 were deemed screen failures and were not randomized into the study.
Rationale: Ongoing subjects will be given the option to continue on daratumumab monotherapy. Assessments and data collection for the new Daratumumab Monotherapy Period are defined.	

Applicable Section(s)	Description of Change(s)
3.1 Overview of Study Design; 6.4 Dosage and Administration for Daratumumab Monotherapy Period; 9.1.1.1 Daratumumab Monotherapy period; 9.1.4 Follow-Up Phase; 9.2.1.1 Disease Assessments in Daratumumab Monotherapy Period; 9.3 Pharmacokinetics and Immunogenicity; 9.4 Biomarker Assessments 9.7 Safety Evaluations; 10.1.1 Discontinuation of Study Treatment in Daratumumab Monotherapy Period; 11.12 Statistical Methods Effective Protocol Amendment 2; 12.3.1.1 Daratumumab Monotherapy Period; 17.5 Case Report Form Completion; 17.8 Monitoring; 17.9.1.1 Study Completion for the Daratumumab Monotherapy Period; Attachment 11 Daratumumab Monotherapy Period For Subjects No Longer Receiving JNJ-63723283 In Combination With Daratumumab (Table 24)	A new Attachment and a new Time and Events Schedule are included for the Daratumumab Monotherapy Period. A new section for daratumumab monotherapy administration is included. Data collection will be limited (eg, no further pharmacokinetics or biomarker evaluations) and is described throughout the protocol. Data will no longer be recorded in the electronic case report form (eCRF) once Protocol Amendment 2 is implemented. Data collection after the final database lock will be limited to serious adverse event (SAE) reporting into the Sponsor's global safety database. Statistical analyses and reporting will also be limited for the Daratumumab Monotherapy Period.
Rationale: Added a window for the End-of-Treatment Visit.	
9.1.3 Open-Label Treatment Phase, End-of-Treatment Visit subheading	Unless a subject withdraws consent for study participation or is lost to follow up, an End-of-Treatment Visit is to occur 4 weeks **(±7 days)** after the last dose of study treatment.

Amendment 1 (23 August 2017)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: The overall reason for the amendment is to make changes based on the FDA IND review of the protocol, including revisions to the DLT criteria.
The rationale for and description of the changes are listed below, and representative revisions are sometimes provided; when revisions are provided verbatim, bold font denotes new text, and strikethrough denotes deleted text.

Applicable Section(s)	Description of Change(s)
Rationale: Revisions to DLT criteria	
3.2 Safety Evaluation (Table 4)	AST or ALT: Grade ≥3 persisting ≥~~14~~ **7** days after treatment with corticosteroids, Grade 4, or any case meeting Hy's Law criteria[b] Thrombocytopenia: **Grade ≥3 thrombocytopenia with clinically significant bleeding and** Grade 4 thrombocytopenia lasting more than 7 days despite BSC[c] **DLT criteria for both Non-hematologic and Hematologic Toxicity[a]:** **Any Grade 5 non-hematologic or hematologic event**

Applicable Section(s)	Description of Change(s)
Rationale: The eligibility criterion for recovery from toxicity from previous immunotherapy treatment is revised.	
4.2 Exclusion Criteria	11. Unresolved Grade ~~3~~ **2** or higher toxicity effects from previous treatment with immunotherapy **not recovered to Grade ≤1 or baseline**
Rationale: A criterion for dose delay because of non-immune-related AEs (irAEs) is added to the bulleted list.	
6.2.2 Dose Delay	**Grade ≥3 non-irAEs (except for hematologic toxicities not attributed to JNJ-63723283)**
Rationale: The split first dose of daratumumab is being replaced with the full daratumumab 16 mg/kg regimen (starting on Cycle 1 Day 1) to allow for additional safety monitoring after the first administration of JNJ-63723283.	
Synopsis (Dosage and Administration); Time and Events Schedule (Table 1); Pharmacokinetics and Immunogenicity Sample Collection (Table 2);	Removed text regarding the split dose of daratumumab on Cycle 1 Day 1 and Cycle 1 Day 2 throughout the protocol. Vital signs – removed reference to C1D2 for daratumumab monitoring. Study drug administration – removed row for the Run-in and Arm B because daratumumab will not be administered on C1D2 (same regimen is being used in all parts of the study). For C1D2, the predose and end of infusion daratumumab PK samples were removed.
3.1 Overview of Study Design; 3.3 Study Design Rationale; 6.1.1 Daratumumab Treatment Schedule and Administration; 6.1.3 Postinfusion Medication; 6.1.4 Monitoring During and After **Daratumumab and JNJ-63723283** Administration	Removed rationale related to the daratumumab split dose. Table 5 was simplified, consistent with the approved labelling for daratumumab administration. Text regarding corticosteroid administration after the second 8 mg/kg administration of daratumumab was removed. A table was added to clarify infusion durations and monitoring after infusion of daratumumab and JNJ-63723283.
Rationale: To clarify that communication with health authorities will occur before proceeding to Part 3.	
3.1 Overview of Study Design (Initiation of Part 3 (Phase 3)	After all 80 randomized subjects in Part 2 (Phase 2) have been followed for approximately 4 months or discontinued earlier, the Sponsor will determine whether the Part 2 primary efficacy endpoint was met and if the combination of the 2 drugs is safe. In addition, the secondary endpoint results, as well as all other available data, will be examined and taken into consideration. Based on the totality of the data, the Sponsor will decide whether Part 3 (Phase 3) will be initiated. **This decision will be made in consultation with health authorities and** the final decision will be communicated in writing to sites and independent ethics committees (IECs)/institutional review boards (IRBs), as appropriate.
Rationale: To add a new section regarding study termination for safety considerations.	
10.2 Study Termination for Safety Considerations	Added a new section regarding reasons for study termination because of safety issues. The final decision to terminate the study will be based on the totality of the benefit/risk assessment.
Rationale: To correct an error in criteria for subjects who may be replaced in Part 1.	
3.2 Safety Evaluation	A subject who received ≤**7**5% ~~25%~~ of a planned dose without experiencing a DLT may be replaced.

ABBREVIATIONS

ADA	anti-drug antibody
ADCC	antibody dependent cell-mediated cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
AE	adverse event
ALC	absolute lymphocyte count
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
Breg	regulatory B cell
BSC	best supportive care
CBC	complete blood count
CDC	complement-dependent cytotoxicity
CI	confidence interval
CMV	cytomegalovirus
COPD	chronic obstructive pulmonary disease
CR, sCR	complete response; stringent complete response
CRF	case report form
CT	computed tomography
DCF	data clarification form
DILI	drug-induced-liver-injury
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DoR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group Performance Status
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EOI	end of infusion
EOT	end of treatment
EQ-5D-5L	European Quality of Life 5-Dimensions Questionnaire
FEV-1	forced expiratory volume; maximal amount of air forcefully exhaled in 1 sec.
FLC	Free light chain
GCP	Good Clinical Practice
GHS	global health status
GLP	Good Laboratory Practice
HBc	hepatitis B core antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IAT	indirect antiglobulin test
ICF	informed consent form
ICH	International Council on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	independent ethics committee
IF	immunofluorescence
IFE	Immunofixation electrophoresis
Ig	immunoglobulin
IHC	immunohistochemistry
IMiD	immunomodulatory agent
IMWG	International Myeloma Working Group
INR	International Normalized Ratio
IPPI	Investigational Product Preparation Instructions
irAE	immune-related adverse event
IRB	institutional review board

IRR	infusion-related reaction
ISS	International Staging System
ITT	intent-to-treat
IWRS	interactive web response system
LDH	lactate dehydrogenase
LFT	liver function test
LLN	lower limit of normal
M-protein	monoclonal paraprotein
mAb	monoclonal antibody
MDSC	myeloid-derived suppressor cell
MedDRA	Medical Dictionary for Regulatory Activities
MLR	mixed lymphocyte reaction
MM	multiple myeloma
MR	minimal response
MRD	minimal residual disease
MRI	magnetic resonance imaging
MRU	medical resource utilization
MTD	maximum tolerated dose
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NFAT	nuclear factor of activated T cells
NGS	next-generation sequencing
NK	natural killer
NOAEL	no-observed-adverse-effect level
NSAIDs	nonsteroidal anti-inflammatory drugs
NSCLC	non-small cell lung cancer
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PC	plasma cell
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed death-1
PD-L1	programmed death-ligand 1
PET	positron emission tomography
PFS	progression-free survival
PI	proteasome inhibitor
PK	pharmacokinetic(s)
PO	oral administration
PQC	product quality complaint
PR	partial response
PRO	patient-reported outcome
PT	prothrombin time
PTT	partial thromboplastin time
QIg	quantitative immunoglobulin
RO	receptor occupancy
RP2D	recommended Phase 2 dose
RRMM	relapsed or refractory multiple myeloma
SAE	serious adverse event
SCT	stem cell transplant
SD	stable disease
SET	safety evaluation team
SIPPM	Site Investigational Product Procedures Manual
SPEP	serum M-Protein quantification by electrophoresis
SPM	second primary malignancy
SUSAR	suspected unexpected serious adverse reaction
SVR	sustained virologic response
TDAR	T cell-dependent antibody responses
Treg	regulatory T cell

TSH	thyroid stimulating hormone
ULN	upper limit of normal
UPEP	urine M-protein quantitation by electrophoresis
VAS	visual analog scale
VGPR	very good partial response
β-hCG	β-human chorionic gonadotropin

Definition of Terms
AUC = area under the plasma drug concentration-time curve
C_{max} = maximum observed concentration
C_{min} = minimum observed concentration

SYNOPSIS

A Randomized, Open-label, Multicenter, Multiphase Study of JNJ-63723283, an Anti-PD-1 Monoclonal Antibody, Administered in Combination with Daratumumab, Compared with Daratumumab Alone in Subjects with Relapsed or Refractory Multiple Myeloma

RATIONALE

JNJ-63723283 is a human immunoglobulin (Ig) G4 kappa monoclonal antibody that binds to the cell surface signaling molecule programmed cell death receptor 1 (PD-1) with high affinity and specificity. JNJ-63723283 blocks binding to both PD-1 ligands (PD-L1 and PD-L2), enhances pro-inflammatory cytokine production from ex vivo stimulated T cells, and reduces tumor volume in human PD-1 knock-in mice bearing MC38 murine colon carcinoma tumors. Daratumumab is a human IgG1κ monoclonal antibody (mAb) that binds with high affinity to a unique epitope on CD38, a transmembrane glycoprotein normally expressed on the surface of many immune cells, including CD4+, CD8+, B lymphocytes and natural killer (NK) cells, as well as on many tumor cells. Daratumumab is designed to attack tumor cells that overexpress CD38, such as in multiple myeloma.

Increased expression of PD-L1 in malignant plasma cells as well as upregulation of PD-1 on effector T cells and NK cells of multiple myeloma patients generates an immunosuppressive microenvironment that is associated with disease progression in multiple myeloma (Benson 2010; Rosenblatt 2017; Yousef 2015). Daratumumab leads to the rapid and sustained elimination of highly immunosuppressive subsets of CD38+ regulatory T cells (Tregs), CD38+ myeloid derived suppressor cells (MDSCs), and CD38+ regulatory B cells (Bregs) (Krejcik 2016). The elimination of these immunosuppressive cells and modulation of CD38 enzymatic activity leads to the increased clonal expansion of CD8+ and CD4+ T cells. Therefore, modulation of multiple myeloma-host immune responses by targeting both PD-1 and CD38 with JNJ-63723283 in combination with daratumumab may be an effective therapeutic approach in treating relapsed or refractory multiple myeloma.

OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

PRIMARY OBJECTIVES	PRIMARY ENDPOINTS
Part 1 (Safety Run-in)	
• To assess the safety of the combination of JNJ-63723283 and daratumumab	• Incidence of adverse events, including dose-limiting toxicities (DLTs)
Part 2 (Phase 2)	
• To compare the overall response rate (ORR) in subjects treated with JNJ-63723283 in combination with daratumumab versus daratumumab alone	• ORR, defined as the proportion of subjects with a best response of PR or better, as defined by IMWG response criteria
Part 3 (Phase 3)	
• To compare progression-free survival (PFS) in subjects treated with JNJ-63723283 in combination with daratumumab versus daratumumab alone	• PFS, defined as the time from the date of randomization to the date of disease progression or death due to any cause, whichever occurs first

See Section 2 for the secondary and exploratory endpoints.

Hypotheses

Part 2: The primary hypothesis is that JNJ-63723283 in combination with daratumumab will significantly improve ORR compared to daratumumab alone in subjects with relapsed or refractory multiple myeloma.

Part 3: The primary hypothesis is that JNJ-63723283 in combination with daratumumab will significantly improve PFS compared to daratumumab alone in subjects with relapsed or refractory multiple myeloma.

OVERVIEW OF STUDY DESIGN

This is a randomized, multicenter, multiphase study assessing the anti-tumor activity and safety of JNJ-63723283 administered in combination with daratumumab, compared with daratumumab alone in subjects with relapsed or refractory multiple myeloma. Subjects 18 years and older with multiple myeloma who have received at least 3 prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory inhibitor (IMiD) or whose disease is double refractory to both a PI and an IMiD are eligible. Approximately 6 subjects will be enrolled in Part 1 (a safety run-in cohort) followed by 80 subjects randomly assigned in a 1:1 ratio to the 2 treatment arms in Part 2 (Phase 2). After all subjects in Part 2 are followed-up for approximately 4 months or discontinue earlier, the Sponsor will review all available data and decide whether to initiate Part 3 (Phase 3) of this study, where an additional 300 subjects will be randomly assigned in a 1:1 ratio to the 2 treatment arms.

DOSAGE AND ADMINISTRATION

Treatment cycles will be 28 days in duration. Treatment groups include a Safety Run-in (JNJ-63723283+daratumumab); and Arm A (daratumumab alone), and Arm B (JNJ-63723283+ daratumumab) in Parts 2 and 3. Starting on Cycle 1 Day 1, daratumumab 16 mg/kg IV will be administered once every week (Weeks 1 to 8); then once every other week for 16 weeks (Weeks 9 to 24); thereafter once every 4 weeks (Week 25 onwards). JNJ-63723283 (Safety Run-in and Arm B) will be administered IV on Week 1 at a dose of 240 mg on Cycle 1 Day 2, Cycle 1 Day 15, and then every 2 weeks thereafter. When both drugs are administered on the same day, daratumumab will be administered before JNJ-63723283. All subjects will continue to receive study treatment until confirmed disease progression, unacceptable toxicity, or any other treatment discontinuation criteria are met.

EFFICACY EVALUATIONS

Assessment of tumor response and disease progression will be performed in accordance with the IMWG response criteria. For subjects who discontinue study treatments before disease progression, disease assessments should continue to be performed as scheduled until disease progression is confirmed or until the start of subsequent anti-myeloma therapy. Survival status and subsequent anticancer treatment data will be collected.

SAFETY EVALUATIONS

Safety evaluations will include adverse event monitoring, clinical laboratory parameters (hematology and chemistry), ECGs, vital sign measurements, physical examination findings, and assessment of ECOG performance status score.

STATISTICAL METHODS

Efficacy data will be analyzed separately for each Part of this study; safety data from each Part may be combined as deemed appropriate.

Part 2: Assuming the ORR for daratumumab monotherapy is approximately 30% and the addition of JNJ-63723283 would improve ORR by 20%, approximately 80 subjects will be randomized in a 1:1 ratio to achieve at least 70% power with a 2-sided alpha of 0.20 to reject the null hypothesis that there is no difference in ORR between the 2 treatment arms.

Part 3: Assuming a median PFS of 4 months for the daratumumab monotherapy group and a 33% reduction in risk of disease progression or death for the combination group (hazard ratio=0.67; median PFS=6 months), 230 PFS events are needed to achieve a power of 85% using a log-rank test with a 2-sided alpha of 0.05. With a 12-month accrual period and an additional 6-month follow-up, the sample size needed for the study is approximately 300 (150/treatment group) subjects.

Table 1: Time and Events Schedule – Parts 1, 2, and 3

Assessments	Screening Phase	Treatment Phase (28-day Cycles)													Follow-up Phase	
		Cycle 1					Cycle 2				Cycle 3-6		Cycle 7+		EOT	FUP	Survival
Study Day	**-28 to -1**	**1**	**2**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**15**	**1**	**15**	**Post Treat-ment Wk 4 (±7 d)**	**Post Treat-ment Wk 8**	**Every 12 Wks**
Procedures: Study procedures may occur within 3 days prior to Day 1																	
Informed consent	Subjects must sign the informed consent form before any study-specific procedures are performed.																
Eligibility criteria	X																
Spirometry test - subjects with known or suspected COPD	X																
Demography/height/medical history	X																
Physical examination	X	Only a symptom-directed physical examination is required															
Weight - only on Day 1 of each daratumumab cycle	X	X					X				X		X		X		
Vital signs (pulse, blood pressure, and temperature) Daratumumab: C1D1 - immediately before start of infusion; 0.5, 1, 1.5, 2, and 3.5 hr after start of infusion; end of infusion; and 0.5, and 1 hr after end of infusion. For all other daratumumab and JNJ-63723283 infusions: immediately before start of infusion and at the end of infusion.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
ECOG performance status	X	X					X				X		X		X		
Electrocardiogram 12-lead After ~5 minutes of rest, prior to any blood draw	X	As clinically indicated													X		
Laboratory Assessments - local laboratory analysis	**-14 to -1**	Up to 3 days prior to dosing. Laboratory test results must be reviewed by the investigator or qualified designee and found to be acceptable prior to administration of each dose of study drug.															
Biochemistry	X	X			X		X		X		X		X		X		
Hematology	X	X		X	X	X	X	X	X	X	X	X	X		X		
Blood group, type, and indirect antiglobulin (IAT). A study identification wallet card, including subject blood group, type and IAT [ABO, Rh, IAT] will be provided	X																

Table 1: Time and Events Schedule – Parts 1, 2, and 3

Assessments		Screening Phase	Treatment Phase (28-day Cycles)														Follow-up Phase	
			Cycle 1					Cycle 2				Cycle 3-6		Cycle 7+		EOT	FUP	Survival
Study Day		**-28 to -1**	**1**	**2**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**15**	**1**	**15**	**Post Treatment Wk 4 (±7 d)**	**Post Treatment Wk 8**	**Every 12 Wks**
Urine or serum pregnancy test - women of childbearing potential only		-14 to C1D1 dosing	As clinically indicated															
Coagulation; HBV/HCV Serology		X																
Thyroid function		X	X					X				Every 3rd cycle, D1						
Study Drug Administration See Section 6 and the IPPI for drug administration details, and Section 8 for preinfusion and postinfusion medications for daratumumab.																		
Daratumumab	Run-in, Arm A, Arm B		X		X	X	X	X	X	X	X	X	X	X				
JNJ-63723283	Run-in (Part 1) and Arm B (Parts 2 and 3)			X		X		X		X		X	X	X	X			
For Pharmacokinetics and Immunogenicity Samples: See Table 2.																		
Biomarkers and Pharmacodynamics All samples must be taken prior to dosing unless otherwise specified. If a dose delay occurs, then biomarker samples should be taken on the actual day of drug administration, not on the originally scheduled administration day.																		
Bone marrow aspirate, biopsy		See Disease Evaluations (Other)																
Diagnostic archival tissue		X																
Whole blood for immunophenotyping			X		X	X		X		X		C4 D1				At progression		
Whole blood for PBMC (peripheral blood mononuclear cell), serum, and plasma biomarker assessments			X		X	X		X		X		C4 D1				At progression		
Cytokines			X	Unscheduled A blood sample should be drawn within 6 hr of suspected cytokine-release syndrome, and the prepared serum sample should be sent to the central laboratory.														

Table 1: Time and Events Schedule – Parts 1, 2, and 3

Assessments	Screening Phase	Treatment Phase (28-day Cycles)													Follow-up Phase	
		Cycle 1					Cycle 2				Cycle 3-6		Cycle 7+		EOT	FUP	Survival
Study Day	**-28 to -1**	**1**	**2**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**15**	**1**	**15**	**Post Treat-ment Wk 4 (±7 d)**	**Post Treat-ment Wk 8**	**Every 12 Wks**
Disease Evaluations (Blood/Urine; central laboratory analysis) If collected within 14 days before Cycle 1 Day 1, not mandatory to collect again at the Cycle 1 Day 1 visit unless central lab results are not available for screening for any reason. If the 24-h urine collection (UPEP) began before informed consent was obtained as part of routine patient care, the sample may be used in this study as long as it is sent to the central lab for analysis after the informed consent is obtained. Unless otherwise stated, all blood and urine samples must be obtained before administration of study drug, within 3 days prior to the scheduled assessment day. All responses (including PD based on biochemical investigations) require 2 consecutive assessments by central lab for confirmation.																
Serum β_2-microglobulin	X																
QIgs (IgG, IgA, IgM, IgD, IgE)	X	Every 3 months (±1 month) during treatment. Testing for IgD and IgE will only be performed for subjects with IgD and IgE-type myeloma															
SPEP	X	X					X				X		X		X	X	
UPEP (24-hr urine sample)	X	X					X				X		X		X	X	
Serum calcium corrected for albumin	X	X					X				X		X		X	X	
Serum FLC & serum/urine immunofixation	X	All subjects: performed when CR is suspected or maintained. For light chain only disease, serum FLC performed on Day 1 of every cycle (±3 days), at EOT, and at follow-up until PD															
Disease Evaluations (Other)	-28 to -1; if per SOC: -42 to -1																
Bone marrow aspirate/biopsy Performed locally at Screening (morphology, cytogenetics [by conventional karyotype and/or fluorescence in-situ hybridization], and at least 1 of the following to determine clonality of plasma cells: immunohistochemistry, immunofluorescence, or flow cytometry). MRD and molecular subtyping: a portion of bone marrow aspirates collected at Screening will be sent to a central laboratory. For Screening, fresh aspirate is preferred. If not performed because a sample is available within 42 days before first study drug administration or randomization, non-decalcified aspirate slides (smears or clots) should be provided.	X if fresh, send portion to central lab for biomarker assessments	To confirm CR, sCR, and if feasible, at the time of disease progression. A portion of bone marrow aspirates will be sent to a central laboratory for evaluation of MRD and biomarker assessments (sampling for MRD at suspected CR or CR and sCR and every 6 months for those with maintained CR and sCR)														

Table 1: Time and Events Schedule – Parts 1, 2, and 3

Assessments	Screening Phase	Treatment Phase (28-day Cycles)													EOT	Follow-up Phase	
		Cycle 1					Cycle 2				Cycle 3-6		Cycle 7+				
Study Day	**-28 to -1**	**1**	**2**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**15**	**1**	**15**	**Post Treat-ment Wk 4 (±7 d)**	**FUP Post Treat-ment Wk 8**	**Survival Every 12 Wks**
Imaging for lytic bone disease Low-dose whole body CT is preferred. Skeletal survey, including the cranium at Screening. Additional imaging (X-ray or MRI): perform as clinically indicated (eg, to document response or progression)	X	As clinically indicated for imaging (X-ray, CT, or MRI). Same methodology used at Screening should be used throughout the study for comparison purposes.															
Imaging for extramedullary plasmacytomas At screening, by clinical exam or radiologic imaging (PET-CT or MRI). Use consistent methodology throughout study.	X	For subjects with a history of plasmacytomas or as clinically indicated for others. Measurable sites every 4 weeks ±3 days (if applicable) by physical examination and every 12 weeks ±14 days by imaging. Irradiated or excised lesions will not be considered measurable, and will be monitored for PD only. To confirm MR, PR, VGPR, CR, or sCR; at suspected PD; and as clinically indicated.														X	
Patient-reported outcomes (Part 3) EORTC-QLQ-C30, EQ-5D-5L. Both questionnaires must be administered and completed prior to any other study procedures/assessments for that study visit.	X Part 3 only	Part 3 only D1 of every 3rd cycle (eg, Cycles 3, 6, 9, 12) until PD													X	X	
Medical resource utilization (Part 3) (see Section 9.6)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Ongoing Subject Review																	
Adverse event monitoring	Continuous from ICF until 30 days after last study treatment dose, regardless of when EOT assessment occurs. For subjects that have received subsequent treatment for multiple myeloma, only adverse events that are considered to be possibly, probably, or definitely related to JNJ-63723283 or daratumumab need to be reported.															Drug-related SAEs, only	
Prior and Concomitant medication recording	Continuous from ICF until 30 days after last study treatment dose																
Subsequent anti-cancer therapy and Survival		Continuous from first dose of study drug until end of study															X

Abbreviations: C=Cycle; COPD=chronic obstructive pulmonary disease; CR=complete response; CT=computed tomography; D=Day; ECOG=Eastern Cooperative Oncology Group; EOT=End-of-Treatment; FLC=free light chain; FUP=Follow-up Phase; HBV=hepatitis B virus; HCV=hepatitis C virus; IAT= indirect antiglobulin; ICF=informed consent form; IPPI=Investigational Product Preparation Instructions; MR=minimal response; MRD=minimal residual disease; MRI=magnetic resonance imaging; PBMC (peripheral blood mononuclear cell); PET=positron emission tomography; PD=progressive disease; PR=partial response; QIgs= quantitative immunoglobulins; SAE=serious adverse event; sCR=stringent CR; SOC=standard of care; SPEP=Serum M-protein quantitation by electrophoresis; UPEP=urine M-protein quantitation by electrophoresis; VGPR=very good partial response

Table 2: Pharmacokinetics and Immunogenicity Sample Collection (Part 1, Part 2, and Part 3)

Visit/Timepoint		Daratumumab (Safety Run-in, Arm A, Arm B)		JNJ-63723283 (Safety Run-in, Arm B)	
		PK Sample[a]	Immunogenicity (taken from PK sample)[a]	PK Sample[a]	Immunogenicity (taken from PK sample)[a]
Cycle 1 Day 1	predose[a]	X	X	X	X
	dara EOI	X			
Cycle 1 Day 2	283 EOI			X	
Cycle 2 Day 1 Cycle 3 Day 1	predose	X	X	X	X
	dara EOI	X			
	283 EOI			X	
Cycle 5 Day 1	predose	X		X	
	dara EOI	X			
	283 EOI			X	
Cycle 7 Day 1 Cycle 12 Day 1	predose	X	X	X	X
	dara EOI	X			
	283 EOI			X	
Cycle 16 Day 1	predose			X	
	dara EOI				
	283 EOI			X	
Cycle 24 Day 1; every 12 cycles thereafter (C36D1, C48D1, etc) until EOT	predose	X	X	X	X
	dara EOI	X			
	283 EOI			X	
EOT (Week 4 ±1 week)		X	X	X	X
Follow-up (Week 8 ±1 week)		X	X	X	X

C=cycle; D=day; dara=daratumumab; EOI=end of infusion; EOT=end of treatment; PK=pharmacokinetics; 283=JNJ-63723283

a. Separate samples are taken for daratumumab and JNJ-63723283. JNJ-63723283 should be administered after daratumumab. In subjects receiving both agents on the same day, predose PK and immunogenicity samples for daratumumab and JNJ-63723283 should be obtained up to 2 hours before the start of the daratumumab infusion. End of infusion samples are to be taken within 2 hours after the end of the infusion of the respective drug. If a dose delay occurs, then samples should be taken on the actual day of drug administration, not on the originally scheduled administration day.

1. INTRODUCTION

JNJ-63723283 is a human immunoglobulin (Ig) G4 kappa (IgG4k) monoclonal antibody (mAb) containing the hinge-stabilizing S228P mutation. JNJ-63723283 binds to programmed death-1 (PD-1) receptor with high affinity and specificity, blocks binding to the programmed death ligands 1 and 2 (PD-L1 and PD-L2), enhances pro-inflammatory cytokine production from ex vivo stimulated T cells, and reduces tumor volume in human PD-1 knock-in (hPD-1KI) mice bearing MC38 murine colon carcinoma tumors. Several anti-PD-l and PD-L1 therapeutic antibodies (eg, nivolumab, pembrolizumab, atezolizumab) have been approved to treat various cancers.

Daratumumab is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody (mAb) that binds CD38-expressing cells with high affinity. CD38 is a transmembrane glycoprotein normally expressed on the surface of many immune cells, including CD4+, CD8+, B lymphocytes, and natural killer cells. Daratumumab is designed to attack tumor cells that overexpress CD38, such as in multiple myeloma (see Section 1.3 for information on the clinical experience with daratumumab in the patient population for this study).

For the most comprehensive nonclinical and clinical information regarding JNJ-63723283 and daratumumab, refer to the latest versions of the respective Investigator's Brochures. The term "Sponsor" used throughout this document refers to the entities listed in the Contact Information page, which will be provided as a separate document.

1.1. Background

Treatment options for multiple myeloma and vary depending on the aggressiveness of the disease, underlying prognostic factors, physical condition of the patient, and existing co-morbidities. Currently approved treatments for patients with relapsed/refractory multiple myeloma include PIs (eg, bortezomib, carfilzomib, ixazomib), IMiDs (thalidomide, lenalidomide, or pomalidomide), histone deacetylase inhibitors, and monoclonal antibodies (daratumumab, elotuzumab). Although recent advances in the development of targeted therapeutics and stem cell transplantation have improved overall and event-free survival, the great majority of patients with myeloma will relapse and experience disease progression, and there continues to be a significant unmet clinical need in this patient population. This study is designed to evaluate if JNJ-63723283 in combination with daratumumab will improve clinical responses in relapsed or refractory multiple myeloma by enhancing the anti-tumor and immunomodulatory effects of daratumumab through PD-1 blockade.

1.2. JNJ-63723283

1.2.1. Summary of Nonclinical Data

In vitro assays with JNJ-63723283 showed enhanced T cell function and reversed PD-1 mediated suppression of T cell receptor signaling by promoting nuclear factor of activated T cells (NFAT)-reporter transcriptional activity. These findings with JNJ-63723283 were comparable to the observed activities for 2 anti-PD-1 mAb analogues for nivolumab and pembrolizumab. In vivo, JNJ-63723283 inhibited tumor growth in human PD-1 knock-in mice

bearing MC38 murine colon carcinoma tumors and showed comparable antitumor efficacy to a nivolumab analogue.

Toxicology studies in cynomolgus monkeys indicate JNJ-63723283 was well tolerated and the pivotal Good Laboratory Practice (GLP) 5-week study demonstrated T-dependent antigen responses (TDAR). No JNJ-63723283-related effects were noted in the cardiovascular, respiratory, or central nervous system during the 5-week study. Primary JNJ-63723283-related findings noted in 4- and 5-week monkey studies at ≥10 mg/kg/wk included slight increases in blood monocyte counts and prothrombin times, and minor/transient decreases in absolute counts for blood CD3+ T, CD3+/CD4+ T-helper, and CD3+/CD8+ T-cytotoxic lymphocytes, increases in the IgM and IgG secondary TDAR response to keyhole limpet hemocyanin (KLH) antigen challenge, and minimally reduced thymic cellularity (decreased lymphocytes) that were considered not to be toxicologically significant. None of these findings were considered adverse and are anticipated to present low to no clinical risk in humans (eg, reduced thymic cellularity that was minimal in nature and was not associated with a correlative decrease in thymus weight or in thymus-to-body and thymus-to-brain ratios). In the 5-week study, the no-observed-adverse-effect level (NOAEL) was 100 mg/kg/wk (mean C_{max} 3,055.75 µg/mL and $AUC_{Day29-36}$ 12,658.15 µg day/mL following the dose on Day 29). Additionally, JNJ-63723283 did not induce hemolysis in whole human blood and was compatible with human serum at in vitro concentrations between 0.010 to 10 mg/mL, and the JNJ-63723283 cytokine response in vitro in human blood was similar to other immune-modulatory compounds that have a low risk of cytokine release syndrome.

1.2.2. Summary of Clinical Data

JNJ-63723283 is being evaluated as a monotherapy in an ongoing Phase 1/2, first-in-human study (63723283LUC1001). As of 18 May 2017, preliminary data are available for 17 subjects with solid tumors who have been treated with JNJ-63723283 at 3 dose levels (80 mg, 240 mg, and 460 mg) with a once every 2-week dosing schedule. Eight of the 17 subjects have been treated with 240 mg every 2 weeks and 2 of these subjects had a partial response (PR) at the first disease assessment. This study continues to enroll and 240 mg every 2 weeks is being explored as the recommended Phase 2 dose (RP2D) regimen. Refer to the JNJ-63723283 Investigator's Brochure for the most current information.

To date, the safety profile of JNJ-63723283 is similar to the safety profile of other anti-PD-1 mAbs with expected immune-related adverse events (irAEs) observed including rash and pneumonitis. The most common treatment-emergent AEs (in 3 or more subjects) reported in 63723283LUC1001 were dyspnea, hyponatremia, sinus tachycardia (5 subjects each); hypertension and nausea (4 subjects each); and anemia, alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, C-reactive protein increased, decreased appetite, headache, hypocalcemia, pleural effusion, vomiting (3 subjects each). Ten serious adverse events (SAEs) were reported in 7 subjects across the 3 dose levels: abdominal distension, abdominal pain, AST increased, bile duct obstruction, dysesthesia, dyspnea, pyrexia, pleural effusion, and pneumonitis. Each of the SAEs occurred in 1 subject each, except for pyrexia in 2 subjects, and all SAEs were Grade 3 except for dysesthesia (Grade 2) and 1 SAE of

pyrexia (Grade 1). One DLT was reported to date in this study: pleural effusion (Grade 3) in a subject with non-small cell lung cancer (NSCLC) who presented with Grade 1 pleural effusion at study entry. This subject continued study treatment and had stable disease at the first disease assessment.

Preliminary serum pharmacokinetics (PK) of JNJ-63723283 and PD-1 receptor occupancy (RO) were evaluated in 16 subjects in Study 63723283LUC1001 following every 2 week IV administration (n=4 at 80 mg, n=8 at 240 mg, n=4 at 460 mg; as of May 2017). JNJ-63723283 serum concentration data following the first dose showed that JNJ-63723283 exhibited approximately linear PK. Following the first dose, C_{max}, C_{min1}, and AUC_{tau} all increased in an approximately dose- proportional manner. Interpatient variability was generally consistent with monoclonal antibody therapeutics (see the Investigator's Brochure for further details). Evaluation of preliminary PD-1 RO on circulating CD3+ T cells indicated saturation at Dose 2 predose for all dose levels tested. The presence of anti-drug antibodies (ADAs) to JNJ-63723283 is currently under evaluation in Study 63723283LUC1001.

1.3. Daratumumab

Regulatory Approvals and Relevant Clinical Studies

In November 2015, daratumumab (DARZALEX®) was approved by the US FDA for the treatment of patients with MM who have received at least 3 prior lines of therapy, including a PI and an IMiD, or who are double-refractory to a PI and an IMiD agent. In May 2016, the European Commission granted approval of daratumumab as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy. Daratumumab in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least 1 prior therapy has also been approved in the US (Nov 2016) and EU (Apr 2017). In June 2017, the FDA approved daratumumab in combination with pomalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least 2 prior therapies including lenalidomide and a proteasome inhibitor. Refer to the daratumumab Investigator's Brochure for details on the clinical experience in patients treated with daratumumab.

Study MMY2002 (SIRIUS) enrolled patients with relapsed or refractory multiple myeloma (RRMM) who received at least 3 prior lines of therapy or were double refractory, the same target population as proposed in this study. Note that 95% of subjects in the study were double refractory to a PI and IMiD and subjects had received a median of 5 prior lines of therapy. Treatment with single-agent daratumumab resulted in an overall response rate (ORR) of 29.2% (95% confidence interval [CI]: 20.8, 38.9). Median duration of response was 7.4 months (95% CI: 5.5, not estimable [NE]). Stringent complete response (sCR) was reported in 2.8% of subjects, very good partial response (VGPR) in 9.4% of subjects, and partial response (PR) in 17 % of subjects. The most common AEs, which occurred in more than 20% percent of subjects, were fatigue, anemia, nausea, thrombocytopenia, back pain, neutropenia, and cough

(Lonial 2016).[22] While 4.7% of subjects discontinued treatment due to adverse events (AEs), none of which were considered drug-related, no subjects discontinued treatment due to infusion-related reactions (IRRs).

These results were supported by the Phase 1/2 GEN501 study, which enrolled a similar patient population and confirmed that daratumumab is an effective single-agent treatment option for patients with relapsed and refractory myeloma, especially for those who are resistant to other treatments or with unacceptable side effects from other treatments. In GEN501, daratumumab demonstrated a 36% ORR in subjects treated with a 16 mg/kg dose, with responses improving (or "deepening") over time (Lokhorst 2015).[2121] The safety profile was acceptable in this study.

1.4. Overall Study Rationale and Anticipated Benefits and Risks of Combination Therapy

Significant progress has been made in the management of multiple myeloma with the development of targeted immunotherapies and stem cell transplantation. However, it remains an incurable malignancy with significant unmet clinical need, particularly in the relapsed or refractory patient population. Novel approaches, particularly combination therapies, are required to improve treatment options for these patients.

Daratumumab is a human IgG kappa mAb that binds with high affinity to CD38, a transmembrane glycoprotein expressed by tumor cells, and induces tumor cell death through multiple mechanisms of action. These MoAs include several immune-mediated activities, including complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC), and antibody-dependent cellular phagocytosis (ADCP), and direct cytotoxicity by induction of apoptosis by Fc gamma receptor mediated crosslinking of tumor-bound monoclonal antibodies (de Weers 2011; Overdijk 2015; Phipps 2015; Jansen 2012).[9,28,31,15] In addition to its direct anti-tumor mechanisms, daratumumab leads to the rapid and sustained elimination of highly immunosuppressive subsets of CD38+ regulatory T cells (Tregs), CD38+ myeloid derived suppressor cells (MDSCs), and CD38+ regulatory B cells (Bregs) (Krejcik 2016).[17] It has also been shown that daratumumab may modulate the enzymatic activity of CD38 and may lead to a reduction in immunosuppressive adenosine levels (Horenstein 2013).[13] The elimination of these immunosuppressive cells and modulation of CD38 enzymatic activity leads to the increased clonal expansion of CD8+ and CD4+ T cells.

There is a compelling rationale for targeting PD-1 signaling in multiple myeloma. Increased expression of PD-L1 in malignant plasma cells as well as upregulation of PD-1 on effector T and natural killer (NK) cells of multiple myeloma patients generates an immunosuppressive microenvironment that is associated with disease progression (Benson 2010; Rosenblatt 2017; Yousef 2015).[4,35,41] Blockade of the PD-1/PD-L1 signaling was also associated with increased CD8+ cytotoxic T-lymphocyte activity and NK-mediated cell lysis in multiple myeloma preclinical models (Ray 2015).[34] Additionally, expression of PD-1 has been shown to correlate with resistance to myeloma therapies (Tamura 2013).[37]

However, PD-1 blockade alone may not be an optimal therapeutic approach in multiple myeloma, as indicated in a Phase 1 study of single-agent nivolumab, which failed to demonstrate objective responses (Lesokhin 2016).[19] Combination studies with anti-PD-1 agents in multiple myeloma have shown more favorable results (Jung 2017).[16] A Phase 2 single-arm study of pembrolizumab, pomalidomide, and dexamethasone in relapsed/refractory multiple myeloma showed an ORR of 60% with 6% sCR, 2% CR 9% VGPR, and 33% PR (Badros 2015).[2] Additionally, a study of pembrolizumab, lenalidomide, and dexamethasone showed an ORR of 76% (24% VGPR and 53% PR) (San Miguel 2015).[36]

Therefore, JNJ-63723283 in combination of with daratumumab may lead to significant improvement in clinical responses through multiple mechanisms of action in treating relapsed or refractory multiple myeloma. By targeting CD38, daratumumab exhibits not only conventional anti-tumor effects of CDC, ADCC, ADCP and apoptosis, but also immunomodulatory effects. By targeting PD-1, treatment with JNJ-63723283 should reactivate antitumor immune responses. By jointly targeting different epitopes on multiple myeloma cells, effector T and NK cells, as well as the bone marrow microenvironment through discrete and complementary mechanisms of action, this combination may be an effective therapeutic approach in treating relapsed or refractory multiple myeloma. This shift away from an immunosuppressive environment may lead to the generation of protective immune responses, which may be further potentiated by PD-1 blockade with JNJ-63723283, potentially leading to improved clinical responses.

Overlapping toxicities of JNJ-63723283 and daratumumab are not expected based on nonclinical and clinical data generated to date with each compound. While infusion-related reactions (IRRs) are observed in approximately half of patients treated with daratumumab, IRRs occur in only approximately 3/17 (18%) subjects treated with JNJ-63723283. Given the mechanism of action of JNJ-63723283, events associated with immune-mediated adverse events will also be considered as anticipated events. Because this is the first study of JNJ-63723283 in combination with daratumumab, other unforeseen toxicities or adverse events cannot be anticipated. The potential risks of this drug combination will be mitigated by comprehensive and careful medical monitoring and pre- and postinfusion medications to reduce mAb-associated IRRs during the conduct of the study. The protocol is designed with a safety run-in phase and the safety will be closely monitored by an SET. In addition, the protocol and the Investigator's Brochures also provide appropriate preventative measures and guidelines for managing potential toxicities.

Immune-related risks have been identified with other anti-PD-1 antibodies, including gastrointestinal AEs such as colitis and diarrhea, pneumonitis, renal AEs such as nephritis and acute renal failure, hepatic AEs such as hepatitis and liver enzyme elevations, endocrinopathies such as hypothyroidism and adrenal insufficiency, and rash. A series of precautions has been put into place to manage the potential risks that could rise in response to JNJ-63723283 administration. In addition, safety of all participating subjects will be closely monitored via collaboration between the investigator and the Sponsor. Symptom monitoring and management guidelines are provided in the protocol.

The potential effect of coadministration of JNJ-63723283 and daratumumab on the incidence of anti-drug antibodies to either drug is unknown. Serum drug concentrations, anti-drug antibodies,

and safety will be monitored throughout the study. Pharmacokinetic-based drug-drug interactions resulting in clinically significant changes to exposure are not anticipated based on the nature of metabolism for protein therapeutics.

In summary, the favorable benefit-risk profile of daratumumab in multiple myeloma, the available safety and efficacy data in JNJ-63723283, and the potential to improve clinical responses in multiple myeloma by further enhancing the anti-tumor and immunomodulatory effects of daratumumab through PD-1 blockade supports further investigation and evaluation of JNJ-63723283 and daratumumab in multiple myeloma.

As of 25 May 2018, the Sponsor terminated further enrollment into this study, 54767414MMY2036 (TUCANA), based on safety and efficacy findings in the 54767414LUC2001 (CALLISTO) study, which combined daratumumab with atezolizumab in non-small cell lung cancer.

At the third planned Data Monitoring Committee (DMC) review on 23 May 2018, the DMC reviewed the subject data (n=88, 44 per arm) for the CALLISTO Study. The DMC determined that there was no observed benefit within the combination treatment arm, daratumumab plus atezolizumab, over atezolizumab alone, and recommended stopping enrollment of the study. In addition, the DMC recommended discontinuation of daratumumab treatment to all active subjects receiving combination therapy (subjects randomized to the combination Arm B, as well as subjects randomized to Arm A who have crossed over into Arm B). Although no unexpected imbalances in on-treatment toxicities were observed, the DMC noted a clear early difference in the number of deaths between the atezolizumab monotherapy (n=13) and combination arm (n=18). The discrepancy was observed within the first 3 months from dosing, where the number of deaths are 4 for the atezolizumab arm and 10 for the combination arm, giving rise to 3-month survival rates of 90.7% for the atezolizumab arm and 76.2% for the combination arm.

Since the benefit/risk ratio has changed for combination therapy in CALLISTO, the Sponsor has decided to suspend enrollment into other studies which combine daratumumab and a PD-1 or PD-L1 monoclonal antibody regardless of indication. In addition to discontinuing enrollment into this study, treatment with the combination of daratumumab and JNJ-63723283 will be discontinued and ongoing subjects will be given the option to continue on daratumumab monotherapy until subject meets one or more of the treatment discontinuation criteria in Section 10.1.1 (see Attachment 11).

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

2.1. Objectives and Endpoints

OBJECTIVES	ENDPOINTS
Part 1 (Safety Run-in)	
Primary	
• To assess the safety of the combination of JNJ-63723283 and daratumumab	• Incidence of adverse events, including dose-limiting toxicities (DLTs)
Part 2 (Phase 2)	
Primary	
• To compare the overall response rate (ORR) in subjects treated with JNJ-63723283 in combination with daratumumab versus daratumumab alone	• ORR, defined as the proportion of subjects with a best response of PR or better, as defined by IMWG response criteria
Secondary	
• To assess the safety of the combination of JNJ-63723283 and daratumumab	• Incidence of adverse events, including immune-related AEs and infusion-related reactions
• To compare the complete response (CR) or better rate and very good partial response (VGPR) or better rate of JNJ-63723283 in combination with daratumumab versus daratumumab alone	• CR or better rate, VGPR or better rate, defined as the proportion of subjects with a best response of at least CR or at least VGPR, as defined by the IMWG response criteria
• To compare the duration of response and time to response of JNJ-63723283 in combination with daratumumab versus daratumumab alone	• Duration of response, defined as the time from onset of first response until date of disease progression or death
• To compare the progression-free survival (PFS) and overall survival (OS) of JNJ-63723283 in combination with daratumumab versus daratumumab alone	• Time to response, defined as the time between the date of randomization and the onset of first response
• To compare the minimal residual disease (MRD)-negative rate of JNJ-63723283 in combination with daratumumab versus daratumumab alone	• PFS, defined as the time from the date of randomization to the date of disease progression or death due to any cause, whichever occurs first
• To evaluate the pharmacokinetic and immunogenicity profile of JNJ-63723283 when given in combination with daratumumab	• Overall survival (OS), defined as the time from the date of randomization to the date of death
• To evaluate the pharmacokinetic and immunogenicity profile of daratumumab when given alone or in combination with JNJ-63723283	• MRD-negative rate, defined as the proportion of MRD- negative subjects
	• Serum JNJ-63723283 pharmacokinetic parameters including but not limited to C_{min} and C_{max}, and incidence of anti-JNJ-63723283 antibodies
	• Serum daratumumab pharmacokinetic parameters including but not limited to C_{min} and C_{max}, and incidence of anti-daratumumab antibodies
Part 3 (Phase 3)	
Primary	
• To compare progression-free survival (PFS) in subjects treated with JNJ-63723283 in combination with daratumumab versus daratumumab alone	• PFS, defined as the time from the date of randomization to the date of disease progression or death due to any cause, whichever occurs first
Secondary	
• To evaluate the overall response rate (ORR) and overall survival (OS)	• ORR, defined as the proportion of subjects with a best response of PR or better, as defined by the IMWG response criteria
• To compare the duration of response and time to response of JNJ-63723283 in combination with daratumumab versus daratumumab alone	• Overall survival (OS), defined as the time from the date of randomization to the date of death
• To compare the complete response (CR) or better rate	• Duration of response, defined as the time from

OBJECTIVES	ENDPOINTS
and very good partial response (VGPR) or better rate of JNJ-63723283 in combination with daratumumab versus daratumumab alone • To compare the MRD-negative rate of JNJ-63723283 in combination with daratumumab versus daratumumab alone • To assess the safety of the combination of JNJ-63723283 and daratumumab • To evaluate the pharmacokinetic and immunogenicity profile of JNJ-63723283 when given in combination with daratumumab • To evaluate the pharmacokinetic and immunogenicity profile of daratumumab when given alone or in combination with JNJ-63723283 • To compare the effect of JNJ-63723283 in combination with daratumumab versus daratumumab alone on disease-related symptoms, functioning, quality of life, and health status using the following patient reported outcomes (PROs) measures: - European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC-QLQ-C30) - European Quality of Life 5 Dimensions Questionnaire (EQ-5D-5L)	onset of first response until date of disease progression or death • Time to response, defined as the time between the date of randomization and the onset of first response • CR or better rate, VGPR or better rate, defined as the proportion of subjects with a best response of at least CR or at least VGPR, as per the IMWG response criteria • MRD-negative rate, defined as the proportion of MRD-negative subjects • Incidence of adverse events, including immune-related AEs and infusion-related reactions • Serum JNJ-63723283 concentration (C_{min}, C_{max}) and incidence of anti-JNJ-63723283 antibodies • Serum daratumumab concentration (C_{min}, C_{max}) and incidence of anti-daratumumab antibodies • Change from baseline in disease-related symptom scales, functioning scales, and Global Health Status (GHS) scale of the EORTC QLQ-C30, and the utility scale and visual analog scale (VAS) of the EQ-5D-5L.
Exploratory Objectives	
• To explore biomarkers predictive of response or resistance to therapy • To evaluate potential pharmacodynamic biomarkers in response to therapy • To explore the relationships between pharmacokinetics, pharmacodynamics, AE profiles, and clinical activity of JNJ-63723283 given in combination with daratumumab • To compare the health economic/resource utilization of JNJ-63723283 in combination with daratumumab versus daratumumab alone (Part 3 only)	

2.2. Hypothesis

Part 2: The primary hypothesis is that treatment with JNJ-63723283 in combination with daratumumab will improve ORR compared to daratumumab alone in subjects with relapsed or refractory multiple myeloma.

Part 3: The primary hypothesis is that treatment with JNJ-63723283 in combination with daratumumab will improve PFS compared to treatment with daratumumab alone in subjects with relapsed or refractory multiple myeloma.

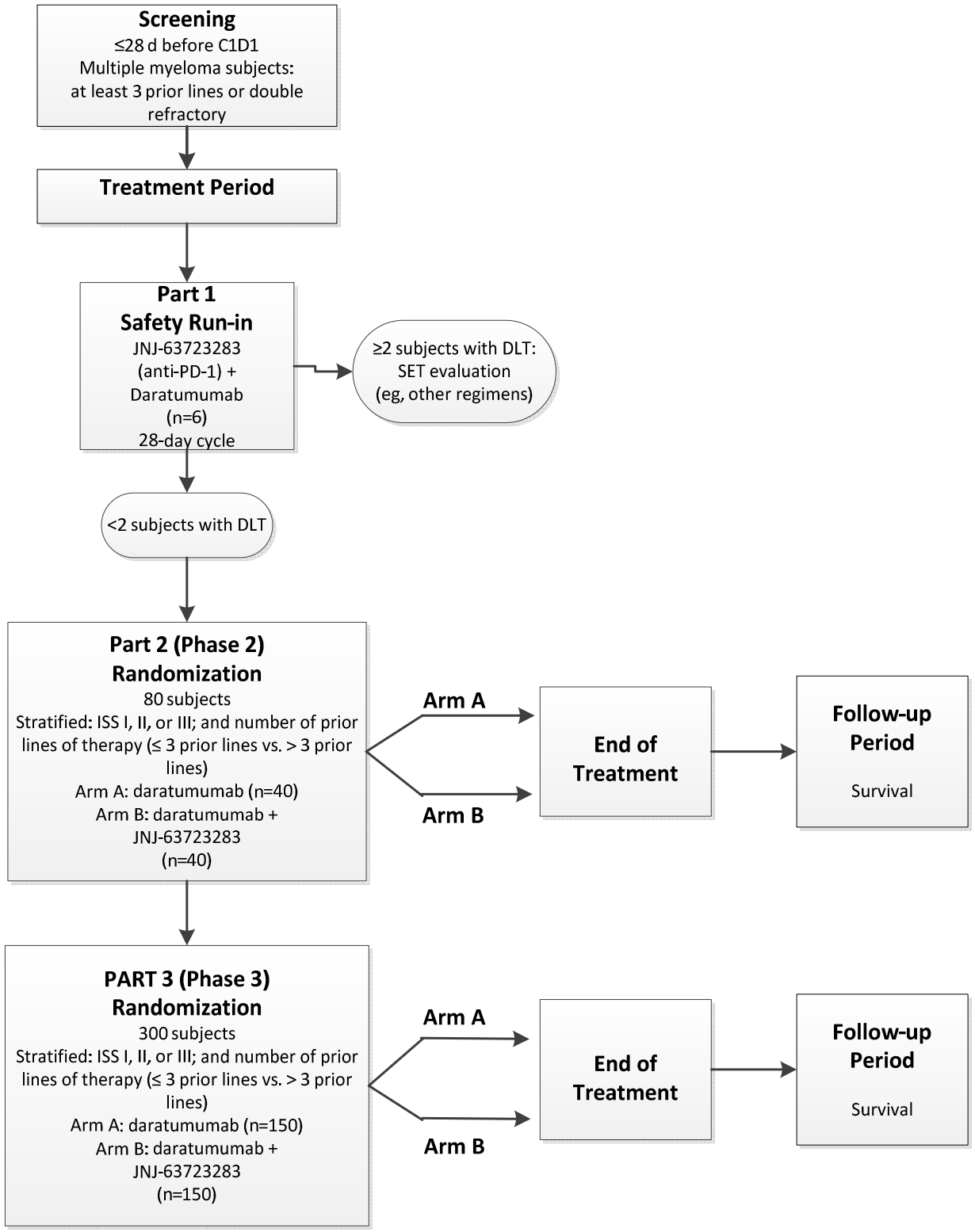
3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a randomized, open-label, multicenter, multiphase study assessing the efficacy and safety of JNJ-63723283 (an anti-PD-1 monoclonal antibody) in combination with daratumumab compared with daratumumab alone in subjects with multiple myeloma who have received at least 3 prior lines of therapy including a PI and an IMiD or whose disease is double refractory to both a PI and an IMiD.

A diagram of the study design is provided in Figure 1.

Figure 1: Study Scheme



Part 1: Safety Run-in Phase

A 6-subject Safety Run-in cohort will be evaluated by the Safety Evaluation Team (SET; see Section 3.2) to determine the safety and tolerability of JNJ-63723283 in combination with daratumumab before the start of the randomized phase of Part 2 of the study. The DLT evaluation period for the Safety Run-in cohort will be 1 cycle (28-days).

- Study drug administration:
  - Daratumumab: Daratumumab 16 mg/kg IV will be administered once every week (Weeks 1 to 8); then once every other week for 16 weeks (Weeks 9 to 24); then once every 4 weeks (Week 25 onwards).
  - JNJ-63723283: 240 mg IV (fixed dose) will be administered during Week 1 on Cycle 1 Day 2, Cycle 1 Day 15, then every 2 weeks thereafter.
  - Daratumumab will be administered prior to administration of JNJ-63723283. Subjects will continue to receive study treatment until confirmed disease progression, unacceptable toxicity, or any other treatment discontinuation criteria are met.
- If <2 of the first 6 DLT evaluable subjects experience a dose-limiting toxicity (DLT; see Section 3.2) during the first treatment cycle (ie, 28 days), the selected doses and dose regimens for JNJ-63723283+daratumumab combination therapy will be considered tolerable, and the study will proceed to the Part 2 randomized phase after the SET provides approval.
- If ≥2 subjects experience a DLT during the first treatment cycle (ie, 28 days), new subject enrollment into the Safety Run-in cohort will stop until after the SET convenes to review DLT data from those subjects and makes recommendations regarding the conduct of the study. The SET may consider the exploration of alternate doses and dose regimens, in an additional safety run-in cohort.
- Subjects in the Safety Run-in cohort may continue to receive additional cycles of JNJ-63723283+daratumumab while enrollment into the Safety Run-in cohort is ongoing and after the study has proceeded to the randomized phase until they meet protocol-specified discontinuation criteria. Subjects who experience unacceptable toxicity directly attributable to JNJ-63723283 may be eligible to receive daratumumab alone, after consultation with the Sponsor.

Part 2 (Phase 2) and Part 3 (Phase 3)

Subjects will be assigned randomly in a 1:1 ratio into 2 treatment arms as indicated in Table 3.

Table 3: Subject Randomization

	Planned Number of Subjects	
Study Arm	**Part 2**	**Part 3**
Arm A: daratumumab	40	150
Arm B: JNJ-63723283 + daratumumab	40	150

Treatment (Part 2 and Part 3)

Treatment cycles will be 28 days in duration.

- Daratumumab: Daratumumab 16 mg/kg will be administered IV once every week (Weeks 1 to 8); then once every other week for 16 weeks (Weeks 9 to 24); then once every 4 weeks (Week 25 onwards).
- JNJ-63723283: For Arm B, JNJ-63723283 240 mg IV (fixed dose) will be administered during Week 1 on Cycle 1 Day 2, Cycle 1 Day 15, then every 2 weeks thereafter. Daratumumab will be administered prior to administration of JNJ-63723283, when they are administered on the same dosing days.

Subjects will continue receiving the assigned study treatment (daratumumab or JNJ-63723283+daratumumab) until treatment discontinuation due to disease progression, unacceptable toxicity, or other protocol-defined treatment discontinuation criteria are met (see Section 10). Subjects in Arm B, who experience unacceptable toxicity directly attributable to JNJ-63723283 and who are experiencing clinical benefit (ie, stable disease or better) may stay on daratumumab until treatment discontinuation criteria are met, after discussion with the Sponsor. After disease progression is documented, survival status, subsequent anticancer treatment, and response to subsequent anticancer treatment will be recorded for all subjects until study end. The end of the study is defined in Section 17.9.1. Study evaluations (eg, disease assessments) are described in Section 9. The timing of study assessments is provided in the Time and Events Schedules (Table 1 and Table 2).

Initiation of Part 3 (Phase 3)

After all 80 randomized subjects in Part 2 (Phase 2) have been followed for approximately 4 months or discontinued earlier, the Sponsor will determine whether the Part 2 primary efficacy endpoint was met and if the combination of the 2 drugs is safe. In addition, the secondary endpoint results, as well as all other available data, will be examined and taken into consideration. Based on the totality of the data, the Sponsor will decide whether Part 3 (Phase 3) will be initiated. This decision will be made in consultation with health authorities and the final decision will be communicated in writing to sites and independent ethics committees (IECs)/institutional review boards (IRBs), as appropriate.

If Part 3 is initiated, after the primary efficacy analysis, subjects remaining in the study will continue to be followed up until 205 deaths have occurred in this part.

Overall Design for Daratumumab Monotherapy Period

As of 25 May 2018, the Sponsor terminated further enrollment into this study, 54767414MMY2036. In addition to discontinuing enrollment into this study, treatment with the combination of daratumumab and JNJ-63723283 will be discontinued and ongoing subjects will be given the option to continue on daratumumab monotherapy.

In the Daratumumab Monotherapy Period, each cycle is 28 days, and administration of daratumumab is to occur weekly for Cycles 1 and 2, every other week for Cycles 3 to 6, and

every 4 weeks for Cycles 7 and onwards until disease progression, pregnancy, unacceptable toxicity, loss of follow-up, withdrawal of consent, or death. Scheduled assessments to be performed during the daratumumab monotherapy period for subjects no longer receiving JNJ-63723283 in combination with daratumumab are outlined in the Time and Events Schedule in Attachment 11 / Table 24.

3.2. Safety Evaluation

Dose-Limiting Toxicity (DLT) Evaluation - Safety Run-in

Toxicities will be graded for severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03. During the 6-subject Safety Run-in phase, the DLT evaluation period is 28 days starting from the day of the first dose of study drug. Only toxicities that occur during the DLT evaluation period will be considered for DLT assessment. A subject who received ≤75% of a planned dose without experiencing a DLT may be replaced.

Dose-limiting toxicity is defined as any of the events listed in Table 4. Toxicities with a clear alternative explanation (eg, due to disease progression) or transient toxicities (≤72 hours) and abnormal laboratory values without associated clinically significant signs or symptoms based on investigator determination can be deemed a non-DLT.

Table 4: Criteria for Dose- limiting Toxicity

DLT criteria for Non-hematologic Toxicity[a]	
AST or ALT	Grade ≥3 persisting ≥7 days after treatment with corticosteroids, Grade 4, or any case meeting Hy's Law criteria[b]
Laboratory abnormality	Grade 3 persisting ≥7 days despite BSC[c] or Grade 4
Any other	Grade 3 persisting ≥7 days despite BSC[c] or Grade 4; except Grade ≥3 asymptomatic or mildly symptomatic rash that can be adequately managed with supportive care or resolves to become asymptomatic or Grade ≤2 within 7 days of supportive therapy.
Infusion-related reaction	Grade 4 infusion-related reaction that occurs during or within 24 hours after the infusion of JNJ-63723283 or daratumumab.
DLT criteria for Hematologic Toxicity[a]	
Neutropenia	Grade 4 neutropenia lasting more than 7 days despite BSC[c], or Grade 3 febrile neutropenia (ANC <1000 cells/mm^3 and a single temperature >38.3°C or a sustained temperature ≥38°C for >1 hour), or sepsis
Thrombocytopenia	Grade ≥3 thrombocytopenia with clinically significant bleeding and Grade 4 thrombocytopenia lasting more than 7 days despite BSC[c]
Anemia	Grade 4 for more than 7 days despite BSC[c]
DLT criteria for both Non-hematologic and Hematologic Toxicity[a]	
Any Grade 5 non-hematologic or hematologic event	

ALT=alanine aminotransferase, AST=aspartate aminotransferase, ALP=alkaline phosphatase; BSC=best supportive care

a. Toxicity graded according to the NCI-CTCAE, Version 4.03.

b. Hy's Law criteria, defined as ALT or AST value ≥3 x upper limit of normal (ULN), total bilirubin ≥2 x ULN, and ALP ≤2 x ULN; with no alternative etiology.

c. Best supportive care (BSC) if available, according to institutional standards.

Safety Evaluation Team (SET)

Ongoing safety evaluation during Part 1 and Part 2 will be overseen by the SET. The SET established by the Sponsor will monitor all available treatment-emergent adverse events on an ongoing basis. The SET will also be responsible for reviewing the safety data during the safety run-in phase and making a recommendation on whether the study will proceed to the 80-subject randomized phase (Part 2) based on the DLT rules set forth above.

The SET will be chaired by the Sponsor's Study Responsible Physician. Membership will include a Sponsor clinical scientist, safety physician, statistician, clinical pharmacologist, along with additional Sponsor staff, as appropriate. Additionally, the investigators who have enrolled the subjects in Part 1 and 2 will be members. The team will meet during the safety run-in phase and as necessary during the remainder of Part 1 and Part 2. Decisions with the potential to affect subject safety (eg, unfavorable change in benefit/risk assessment) will be promptly communicated to investigators and regulatory authorities as appropriate. Additional details will be specified in a separate SET charter.

Independent Data Monitoring Committee (IDMC) – Part 3 (Phase 3)

In Part 3, ongoing safety evaluation will be performed by the IDMC. In addition, a formal safety review will be performed after 50 subjects have been treated for at least 8 weeks or discontinued the study treatment. The purpose of this safety review is to have a comprehensive evaluation of safety for the new drug product for JNJ-63723283 (see Section 14.1) in combination with daratumumab.

The IDMC, consisting of 2 clinicians and 1 statistician, will be established by the Sponsor to review efficacy and safety results at the pre-planned analyses. After the interim reviews, they will make recommendations regarding the continuation of the study. The details will be provided in a separate IDMC charter.

3.3. Study Design Rationale

Rationale for Study Design

Adequate steps have been taken to ensure the validity of data in an open-label study design. This includes performing tumor assessments at the same frequency in both arms, adhering to protocol-defined schedules, and determining the strategy for the final analysis of the primary endpoint prior to study start, including predefined methods for handling missing data and censoring rules.

Randomization will be used to minimize bias in the assignment of subjects to treatment groups. To further minimize imbalance across treatment arms and to allow for balanced enrollment in important subgroup analyses, subjects will be stratified based on ISS staging and number of prior lines of therapy (≤3 prior lines vs. >3 prior lines).

Rationale for Daratumumab Dose Selection

The daratumumab dose regimen used in this study (16 mg/kg) is approved in many regions as monotherapy and in combination with other therapies for the treatment of subjects with relapsed and refractory multiple myeloma. This dose regimen was selected based on an acceptable safety profile, maximal clinical activity, and pharmacokinetics consistent with saturation of the target. This dose and similar schedules have been shown to be tolerable in several combination studies.

Rationale for JNJ-63723283 Monotherapy Dose Selection

As of May 2017, 17 subjects have been dosed with JNJ-63723283 monotherapy and completed DLT evaluation in the first-in-human study in patients with advanced solid tumors (Study 63723283LUC1001). This study continues to enroll subjects with various advanced solid tumor types and has expanded to Part 2, where subjects with selected tumor types are dosed at a recommended Phase 2 dose (RP2D) regimen of 240 mg every 2 weeks. The maximum dose regimen of JNJ-63723283 in the first-in-human study to date is 460 mg every 2 weeks; no maximum tolerated dose has been identified. To date, the safety profile of JNJ-63723283 is similar to the safety profile of other anti-PD-1 mAbs. Adverse events have been broadly consistent across tumor types following monotherapy and have not demonstrated a clear dose-response relationship (see Section 1.2.2 and the Investigator's Brochure for additional details).

The clinically efficacious dosing regimen for JNJ-63723283 is anticipated to be in the same range as similar anti-PD-1 mAbs. The approved dose regimens for these drugs include nivolumab 3 mg/kg or 240 mg every 2 weeks and pembrolizumab 2 mg/kg or 200 mg every 3 weeks (the body weights across nivolumab and pembrolizumab clinical studies have been reported as 79 kg [mean] and 77 kg [median], respectively, (Bajaj 2017; Freshwater 2017)[3,11].

The RP2D regimen for JNJ-63723283 is 240 mg every 2 weeks in all tumor types based on the following:

- JNJ-63723283 demonstrated similar in vitro binding affinity to human PD-1 as pembrolizumab and nivolumab analogues (within 3-fold), similar potency in ex vivo mixed lymphocyte reaction and cytomegalovirus (CMV) assays as pembrolizumab and nivolumab analogues, and similar tumor growth inhibition in a MC38 mouse syngeneic model as a nivolumab analogue (see the Investigator's Brochure for additional details).
- Pharmacokinetic simulations based on preliminary modeling of observed clinical PK data through May 2017 (n=14, median body weight 75 kg) showed that following 240 mg IV JNJ-63723283 every 2 weeks, the predicted steady-state trough concentration, or $C_{min,ss}$ of JNJ-63723283 (47 µg/mL) is expected to be similar to reported nivolumab $C_{min,ss}$ at 3 mg/kg every 2 weeks (57 µg/mL) (CDER 2014)[6] and approximately double the reported pembrolizumab $C_{min,ss}$ at 2 mg/kg every 3 weeks (23 µg/mL) (CDER 2014)[7].
- Preliminary PD-1 RO assessment on circulating CD3+ T cells following JNJ-63723283 dosing suggests dose-independent saturation from 80 to 460 mg, similar to the dose-independent clinical RO observed for nivolumab from 1 to 10 mg/kg (Topalian 2012)[38].
- A semi-mechanistic translational PK/pharmacodynamics (PD) model was developed using PK, RO, and tumor growth inhibition data from MC38 syngeneic mouse studies as well as PK and RO data from healthy cynomolgus monkey studies. This translational PK/PD model suggested that IV doses ≥240 mg every 2 weeks in humans (corresponding to a predicted serum $C_{min,ss}$ of 42 µg/mL) would lead to maximum tumor killing effect in patients with non-small cell lung cancer (NSCLC). This prediction is consistent with the established clinically efficacious doses for nivolumab and pembrolizumab.
- Preliminary PK modeling of observed JNJ-63723283 clinical PK data through May 2017 projected a serum $C_{min,ss}$ of 47 µg/mL following 240 mg every 2 week dosing, providing further evidence that the targeted JNJ-63723283 trough concentrations can be achieved at this dosing regimen.
- No clinically relevant impact of tumor type on drug exposure or clearance has been observed for nivolumab or pembrolizumab (Bajaj 2017; Ahamadi 2017)[3,1].

Rationale for JNJ-63723283 Dose Selection in Combination with Daratumumab

The JNJ-63723283 monotherapy RP2D regimen selection, was based on an acceptable safety profile, similarity to other anti-PD-1 mAbs, and preliminary evidence that target concentrations are achieved (see Rationale for JNJ-63723283 Monotherapy Dose Selection). JNJ-63723283 has not been clinically evaluated in combination with other agents. In patients with advanced hematologic malignancies including multiple myeloma, nivolumab has demonstrated a similar safety profile as in patients with solid tumors and Hodgkin lymphoma at a dose of 3 mg/kg every

2 weeks (Lesokhin 2016)[19]. JNJ-63723283 at 240 mg every 2 weeks (equivalent to 3 mg/kg based on a body weight of 80 kg) is expected to have a similar safety profile as nivolumab. In combination cohorts, JNJ-63723283 will be administered following completion of daratumumab infusions (on Cycle 1 Day 2 and on Day 1 for all other doses) in order to better manage daratumumab-associated IRRs.

Rationale for Pharmacokinetics and Immunogenicity Assessments

The coadministration of JNJ-63723283 and daratumumab in relapsed or refractory multiple myeloma is not expected to substantially alter the pharmacokinetics of either agent but may impact the incidence of immunogenicity. Minimum and maximum observed concentrations (C_{min} and C_{max}) will be assessed for all parts of the study and will contribute to the characterization of study drug pharmacokinetic profiles. The JNJ-63723283 concentration results after combination dosing may be compared with available data from other JNJ-63723283 clinical studies to assess if there is any alteration in JNJ-63723283 pharmacokinetics when co-administered with daratumumab in this study population and to correlate any clinical activity and safety events. The daratumumab concentration results after monotherapy and combination dosing will be evaluated (and may be compared with available data from other daratumumab clinical studies) to assess if there is any alteration in daratumumab pharmacokinetics when co-administered with JNJ-63723283 and to correlate any clinical activity and safety events. Data may also be used for a population pharmacokinetic analysis to estimate additional pharmacokinetic parameters and provide information about the determinants of inter-subject variability in this population. The presence of antibodies to JNJ-63723283 and daratumumab (immunogenicity) will be assessed to evaluate impact of anti-drug antibodies on pharmacokinetics.

Rationale for Biomarker Evaluations

Published results suggest that PD-1 is highly expressed on multiple myeloma malignant plasma cells (Yousef 2015).[41] Engagement of PD-1 on T-cells by PD-L1 expressed on malignant plasma cells and other immune cells may be one mechanism of tumor immune evasion. Another mechanism of tumor immune evasion includes accumulation of immunosuppressive cells such as MDSCs, Tregs, and Bregs. Previous studies have demonstrated that treatment with daratumumab leads to a reduction in CD38+ immunosuppressive MDSCs, Tregs, and Bregs in addition to an increase in the absolute T-cell count, T-cell clonality, and T-cell functionality (Krejcik 2016)[17]. Therefore, the combination of JNJ- 63723283 with daratumumab may enhance the magnitude and duration of response by targeting different mechanisms of immunosuppression allowing for a more robust anti-myeloma T-cell response. Based on data from single-agent studies, blood and bone marrow samples will be collected to explore biomarkers predictive of response or resistance and evaluate potential pharmacodynamic biomarkers in response to JNJ-63723283 given in combination with daratumumab.

Rationale for Patient-reported Outcomes Assessments

The EORTC QLQ-C30 and the EQ-5D-5L instruments will assess the effect of the study drugs on subject functional status, well-being, and symptoms to support market access and requests from payers (see Attachment 10). The EORTC QLQ-C30 has been widely used among cancer

patients and in prior multiple myeloma clinical trials. The EQ-5D-5L is a standardized preference instrument for use as a measure of health status and to calculate utility values.

4. SUBJECT POPULATION

Screening for eligible subjects will be performed within 28 days before enrollment in either the safety run-in or randomized phases. The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. Enrollment/randomization will occur after the Sponsor reviews and approves subject eligibility (inclusion and exclusion criteria). Waivers are not allowed.

As of 25 May 2018, this study is closed to further enrollment.

4.1. Inclusion Criteria

Each potential subject must satisfy all of the following criteria to be enrolled in the study.

1. At least 18 years of age.
2. Have received at least 3 prior lines of therapy (refer to Attachment 6) including a PI and an IMiD in any order during the course of treatment for multiple myeloma.

   or

   Have disease that is refractory to both a PI and an IMiD. (For subjects who have received more than 1 type of PI, their disease must be refractory to the most recent one. Similarly, for those who have received more than 1 type of IMiD, their disease must be refractory to the most recent one.)

3. Evidence of a response (PR or better based on investigator's determination of response by IMWG criteria) to at least 1 prior treatment regimen.
4. Documented measurable disease for multiple myeloma at screening as defined by the criteria below:
   - IgG multiple myeloma: Serum monoclonal paraprotein (M-protein) level ≥1.0 g/dL or urine M-protein level ≥200 mg/24 hours; or
   - IgA, IgM, IgD, or IgE multiple myeloma: serum M-protein level ≥0.5 g/dL or urine M-protein level ≥200 mg/24 hours; or
   - Light chain multiple myeloma without measurable disease in the serum or urine: Serum immunoglobulin free light chain ≥10 mg/dL and abnormal serum immunoglobulin kappa lambda free light chain ratio.
5. Have relapsed or refractory disease at time of enrollment as defined below:

- Relapsed disease is defined as an initial response to previous treatment, followed by PD by IMWG criteria >60 days after cessation of treatment.
- Refractory disease is defined as <25% reduction in M-protein or PD by IMWG criteria during previous treatment or ≤60 days after cessation of treatment.

6. ECOG performance status score of 0, 1, or 2 (refer to Attachment 5).

7. Laboratory criteria:

- Adequate bone marrow function:
  a) hemoglobin ≥7.5 g/dL (≥5 mmol/L; it is not permissible to transfuse a subject to reach this level)
  b) absolute neutrophil count (ANC) ≥1.0 x 109/L (granulocyte colony stimulating factor [GCSF] use is permitted);
  c) platelet count ≥75 × 109/L in subjects in whom <50% of bone marrow nucleated cells are plasma cells and platelet count ≥50 x 109/L in subjects in whom ≥50% of bone marrow nucleated cells are plasma cells (it is not permissible to transfuse a subject to reach this level)
- Adequate liver function:
  a) aspartate aminotransferase (AST) ≤2.5 x upper limit of normal (ULN);
  b) alanine aminotransferase (ALT) ≤2.5 x ULN;
  c) total bilirubin ≤2.0 x ULN, except in subjects with congenital bilirubinemia, such as Gilbert syndrome (direct bilirubin ≤2.0 x ULN)
- Adequate renal function:
  a) estimated creatinine clearance ≥30 mL/min (refer to Attachment 3)
- Corrected serum calcium ≤14 mg/dL (≤3.5 mmol/L); or free ionized calcium ≤6.5 mg/dL (≤1.6 mmol/L) (Attachment 4)

8. A woman of childbearing potential must have a negative serum or urine pregnancy test within 14 days prior to study drug administration.

9. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for subject participating in clinical studies.

   Before enrollment, a woman must be either:

   – Not of childbearing potential defined as:

   postmenopausal

   A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy, however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

   permanently sterile

   Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy.

- Of childbearing potential and practicing 2 methods of reliable birth control simultaneously: 1 highly effective method of contraception (failure rate of <1% per year when used consistently and correctly) and 1 additional effective method.

Examples of highly effective contraceptives include:

- user-independent methods:

  implantable progestogen-only hormone contraception associated with inhibition of ovulation; intrauterine device (IUD); intrauterine hormone-releasing system (IUS); vasectomized partner; sexual abstinence (s*exual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.*)

- user-dependent methods:

  combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, and transdermal; progestogen-only hormone contraception associated with inhibition of ovulation: oral and injectable

Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies. Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method.

Examples of additional effective contraceptive methods include:

- male latex or synthetic condom, diaphragm, or cervical cap

- agrees to remain on the 2 contraception methods (1 highly effective and 1 additional reliable method) throughout the study and for at least 3 months after last dose of daratumumab or 5 months after the last dose of JNJ-63723283. In addition, during the study and for 3 months after receiving the last dose of daratumumab or 5 months after the last dose of JNJ-63723283, a woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction.

Note: If the childbearing potential changes after start of the study or the risk of pregnancy changes (eg, a woman who is not heterosexually active becomes active) a woman must begin a highly effective method of contraception and 1 additional reliable method, as described throughout the inclusion criteria.

If reproductive status is questionable, additional evaluation should be considered.

10. During the study and for a minimum of approximately 3 months after the last dose of daratumumab or 5 months after the last dose of JNJ-63723283, in addition to the highly effective method of contraception, a man

- who is sexually active with a woman of childbearing potential must agree to use a barrier method of contraception (eg, condom with spermicidal foam/gel/film/cream/suppository)
- who is sexually active with a woman who is pregnant must use a condom
- must agree not to donate sperm.

11. Willing and able to adhere to the prohibitions and restrictions specified in this protocol.
12. Must sign an informed consent form (ICF) indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study.

4.2. Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the study:

1. Received any of the following prescribed medications or therapies in the past:
   - Anti-CD38 antibody, including daratumumab
   - Anti-PD-1 and anti-PD-L1 antibodies
2. Received any of the following prescribed medications or therapies within the specified period:
   - Antimyeloma treatment within 2 weeks or 5 pharmacokinetic half-lives of the treatment, whichever is longer, prior to first administration of study drug. The only exception is emergency use of a short course of corticosteroids (equivalent of dexamethasone 40 mg/day for a maximum of 4 days) for palliative treatment prior to first administration of study drug.
   - An allogenic stem cell transplant (SCT) at any time; or autologous SCT within 12 weeks prior to first administration of study drug.
   - Other investigational agent (including investigational vaccines), participation in another clinical study with therapeutic intent, or used an invasive investigational medical device within 28 days or 5 pharmacokinetic half-lives of the investigational agent (whichever is longer) prior to first administration of study drug.
   - Systemic radiotherapy within 14 days prior to first administration of study drug.
3. Plans to undergo a stem cell transplant prior to progression of disease on this study (these subjects should not be enrolled to reduce disease burden prior to transplant).
4. History of malignancy (other than multiple myeloma) within 2 years prior to first administration of study drug (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or malignancy that in the opinion of the investigator, with concurrence with the Sponsor's medical monitor, is considered cured with minimal risk of recurrence within 3 years).
5. Clinical signs of meningeal involvement of multiple myeloma.
6. Either of the following:

- Known chronic obstructive pulmonary disease (COPD) with a forced expiratory volume in 1 second (FEV1) <50% of predicted normal. Note that FEV1 testing is required for subjects suspected of having COPD and subjects must be excluded if FEV1 is <50% of predicted normal.
- Known moderate or severe persistent asthma within the past 2 years (see Attachment 8), or uncontrolled asthma of any classification. Note that subjects who currently have controlled intermittent asthma or controlled mild persistent asthma are allowed to participate in the study.

7. Any of the following:
   - Known to be seropositive for human immunodeficiency virus (HIV).
   - Known to be seropositive for hepatitis B (defined by a positive test for hepatitis B surface antigen [HBsAg]) or with known prior hepatitis B infection without evidence of immunity (ie patients who are positive for antibodies to hepatitis B core antigen (anti-HBc) but negative for antibodies to hepatitis B surface antigen (anti-Hbs)
   - Known to be 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).
8. Clinically significant cardiac disease, including:
   - Myocardial infarction within 6 months (except for those with normal cardiac function, eg, normal LVEF) before first administration of study drug, or unstable or uncontrolled disease/condition related to or affecting cardiac function (eg, unstable angina, congestive heart failure, New York Heart Association Class III-IV)
   - Cardiac arrhythmia (Common Terminology Criteria for Adverse Events [CTCAE] Grade 3 or higher) or clinically significant electrocardiogram (ECG) abnormalities.
   - Screening 12-lead ECG showing a baseline corrected QT interval (QTc) >470 msec.
9. Known allergies, hypersensitivity, or intolerance to mannitol or corticosteroids, monoclonal antibodies or human proteins, or their excipients (refer to Investigator's Brochures), or known sensitivity to mammalian-derived products.
10. Prior diagnoses of autoimmune disease including but not limited to uncontrolled autoimmune thyroid disease or Type 1 diabetes, systemic lupus erythematosus, Sjögren's syndrome, glomerulonephritis, multiple sclerosis, rheumatoid arthritis, vasculitis, idiopathic pulmonary fibrosis (IPF, including bronchiolitis obliterans organizing pneumonia), and inflammatory bowel disease, will be excluded from study participation, with the exception of subjects:
    - with autoimmune thyroid disease or type 1 diabetes that is well controlled on a stable medication regimen
    - with vitiligo, alopecia, or resolved childhood asthma/atopy
    - with psoriasis not requiring systemic therapy
    - with transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent (eg, acute Lyme arthritis)

11. Criterion modified per Amendment 1

    11.1 Unresolved Grade 2 or higher toxicity effects from previous treatment with immunotherapy not recovered to Grade ≤1 or baseline

12. Vaccination with live attenuated vaccines within 4 weeks prior to first study agent administration

13. Women who are pregnant, lactating, or intending to become pregnant during the study or within at least 3 months after last dose of daratumumab or 5 months after the last dose of JNJ-63723283; men who intend to father a child during the study or within at least 3 months after the last dose of daratumumab or 5 months after the last dose of JNJ-63723283.

14. Concurrent medical or psychiatric condition or disease (eg, active systemic infection, uncontrolled diabetes, acute diffuse infiltrative pulmonary disease) that is likely to interfere with the study procedures or results, or that in the opinion of the investigator, would constitute a hazard for participating in this study.

15. Major surgery within 2 weeks prior to first study drug administration, or will not have fully recovered from surgery, or has surgery planned during the time the subject is expected to participate in the study or within 2 weeks after the last dose of study treatment. Note: subjects with planned surgical procedures to be conducted under local anesthesia may participate. Kyphoplasty or vertebroplasty are not considered major surgery.

16. Plasmapheresis within 28 days prior to first study drug administration

17. Known or suspected of not being able to comply with the study protocol (eg, because of alcoholism, drug dependency, or psychological disorder). Subject has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments. Subject is taking any prohibited medications as per Section 8.3.

4.3. Prohibitions and Restrictions

Potential subjects must be willing and able to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation:

1. Refer to Section 8 Concomitant Therapy for details regarding prohibited and restricted therapy during the study.

2. Agree to follow the contraceptive requirements as noted in the inclusion criteria.

3. Typically, IV contrast is NOT used in computed tomography (CT) scanning of subjects with secretory multiple myeloma because of the risk to the kidney. If administration of IV contrast is necessary, then adequate precautions including hydration are indicated.

5. TREATMENT ALLOCATION AND BLINDING

Following the safety run-in, central randomization will be implemented in this open-label study. Randomization for Part 2 and Part 3 will be performed separately. Subjects enrolled in Part 2 will not be eligible for Part 3.

For each Part, subjects will be assigned randomly to 1 of the 2 treatment groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the Sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by International Staging System (ISS; I, II, or III) and number of prior lines of therapy (≤3 prior lines vs. >3 prior lines). The interactive web response system (IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study drug kit for the subject. The requestor must use his or her own user identification and personal identification number when contacting the IWRS, and will then give the relevant subject details to uniquely identify the subject.

As of 25 May 2018, subjects in Screening were deemed Screen Failures and were not randomized into the study.

6. DOSAGE AND ADMINISTRATION

6.1. Daratumumab

Daratumumab will be administered to subjects as described in the Time and Events Schedule Table 1. Daratumumab should always be administered prior to JNJ-63723283, when they are administered on the same dosing day. Subjects will continue to receive daratumumab until disease progression, unacceptable toxicity, or other reasons as listed in Section 10. Refer to the Investigational Product Preparation Instructions (IPPI) and the Site Investigational Product and Procedures Manual (SIPPM) for detailed descriptions for preparation and administration of daratumumab.

6.1.1. Daratumumab Treatment Schedule and Administration

Each cycle is 28 days. The daratumumab administration dose and schedule is summarized below:

- Daratumumab 16 mg/kg IV will be administered once every week (Weeks 1 to 8); then once every other week for 16 weeks (Weeks 9 to 24); thereafter once every 4 weeks (Week 25 onwards).

Each subject's dose will be calculated based on the subject's weight at Cycle 1 Day 1 rounded to the nearest kilogram. The dose of daratumumab does not need to be recalculated for weight changes <10% from baseline. Subjects will receive preinfusion medications and postinfusion medications as outlined in Sections 6.1.2 and 6.3.1.

The dilution volumes, initial infusion rates, and increment of infusion rates for the first, second, and subsequent doses in the absence of an infusion-related reaction >Grade 1 are provided in Table 5.

Table 5: Daratumumab Administration

	Dilution Volume	Initial Infusion Rate (first hour)	Incremental Increases in Infusion Rate[a]	Maximum Infusion Rate
Week 1 infusion (Cycle 1 Day 1)	1000 mL	50 mL/hour	50 mL/every hour	200 mL/hour
Week 2 infusion[b]	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Subsequent infusions[c]	500 mL	100 mL/hour	50 mL/hour every hour	200 mL/hour

a. Consider titration of the infusion rate only in the absence of infusion-related reactions.
b. Dilution volume of 500 mL should be used only if there were no Grade 1 (mild) or greater infusion-related reactions during the first 3 hours of the first infusion. Otherwise, continue to use a dilution volume of 1000 mL.
c. Use a modified initial rate for subsequent infusions (ie, third infusion onwards) only if there were no Grade 1 (mild) or greater infusion-related reactions during a final infusion rate of ≥100 mL/h in the first two infusions. Otherwise, continue to use instructions for the second infusion.

As noted in Table 1 (Time and Events Schedule), vital signs for subjects in the Safety Run-in and Arm B cohorts should be monitored frequently on Cycle 1 Day 1 before, during, and after the first infusion of daratumumab. For all subsequent infusions, vital signs should be measured before the start of infusion and at the end of the infusion. If a subject experiences any significant medical event, then the investigator should assess whether the subject should stay overnight for observation. If the subject has not experienced a significant medical event but is hospitalized overnight only for observation, then the hospitalization should not be reported as a serious adverse event.

6.1.2. Preinfusion Medication

Preinfusion medications for subjects receiving daratumumab will be administered on all daratumumab infusion days (see the Time and Events Schedule; Table 1). On daratumumab infusion days, subjects will receive the following medications approximately 1 hour prior to daratumumab infusion; premedication up to 3 hours before the dose of daratumumab is permitted:

- An antipyretic: paracetamol (acetaminophen) 650 to 1000 mg IV or orally (PO).
- An antihistamine: diphenhydramine 25 to 50 mg IV or PO, or equivalent). Avoid the use of IV promethazine (see Attachment 1 for a list of antihistamines that may be used).
- A corticosteroid: methylprednisolone 100 mg IV or PO or equivalent for the first 2 doses and 60 mg for all subsequent doses (in the absence of IRR adverse events in the first 2 doses). Substitutions for methylprednisolone are allowed (refer to Attachment 2).

In addition, a leukotriene inhibitor (optional; montelukast 10 mg PO) may be administered up to 24 hours before infusion as per investigator discretion.

If necessary, all PO preinfusion medications may be administered outside of the clinic on the day of the infusion, provided they are taken 1 to 3 hours before the infusion.

6.1.3. Postinfusion Medication

Postinfusion medication should be administered to reduce the risk of delayed infusion-related reactions in all subjects:

- Oral corticosteroid (20 mg methylprednisolone PO or equivalent) in accordance with local standards) on the 2 days following each daratumumab administration (beginning the day after study drug administration). In the absence of IRR adverse events after the first 3 doses, postinfusion corticosteroids should be administered per investigator discretion.

For subjects with a higher risk of respiratory complications (eg, subjects with COPD who have an FEV1 <80% or subjects with asthma), the following postinfusion medications should be considered:

- antihistamine (diphenhydramine or equivalent) on the first and second days after each infusion;
- short-acting β2 adrenergic receptor agonist such as salbutamol aerosol; and
- control medications for lung disease (eg, inhaled corticosteroids ± long-acting β2 adrenergic receptor agonists for subjects with asthma; long-acting bronchodilators such as tiotropium or salmeterol ± inhaled corticosteroids for subjects with COPD).

In addition, these at-risk subjects may be hospitalized for monitoring for up to 2 nights after study drug administration. If these at-risk subjects are hospitalized, then their FEV1 should be measured and managed per local standards before discharge. If these subjects are not hospitalized, then a follow-up telephone call should be made to monitor their condition within 48 hours after each study drug administration. If the subject has not experienced a significant medical event but is hospitalized overnight only for observation, then the hospitalization should not be reported as a serious adverse event. Investigators may prescribe bronchodilators, antihistamines, and corticosteroids that are deemed necessary to provide adequate supportive care in the event a bronchospasm occurs after subjects are released from the hospital/clinic. If an at-risk subject experiences no major IRRs, then these postdose medications may be waived after 4 doses at the investigator's discretion.

6.1.4. Monitoring During and After Daratumumab and JNJ-63723283 Administration

Subjects should be observed carefully during study agent infusions. Trained study staff at the clinic should be prepared to intervene in case of any IRRs occurring, and resources necessary for resuscitation (eg, agents such as epinephrine and aerosolized bronchodilator, also medical equipment such as oxygen tanks, tracheostomy equipment, and a defibrillator) must be available at the bedside. If an IRR develops, then the infusion should be paused. Guidelines outlined in Section 6.3 must be followed to manage IRRs.

Subjects should be monitored for at least 2 hours after the completion of the first infusion and may be discharged if considered clinically stable and all other study procedures have been completed (see Table 6 below). The investigator will determine the duration of safety monitoring

for subsequent administrations. In addition, subjects should be monitored for symptoms of tumor lysis syndrome, see Section 8.1.2.

Table 6: Infusion Duration and Monitoring After Infusion of Daratumumab and JNJ-63723283

Cycle 1 Day 1	**Daratumumab – First infusion** Daratumumab is administered over a 6 to 8 hour infusion period followed by a 2-hour observation period. The subject may be discharged if considered clinically stable and all other study procedures have been completed
Cycle 1 Day 2	**JNJ-63723283 – First Infusion** 1-hour infusion followed by a 4-hour observation period. The subject may be discharged if considered clinically stable and all other study procedures have been completed
Cycle 1 Day 8	**Daratumumab – Second infusion** If the first daratumumab infusion is well tolerated (defined as no Grade 1 or higher IRRs), then the second daratumumab infusion should administered over 3 to 4 hours, followed by a 2-hour observation period. However, if the first daratumumab infusion is not well tolerated, then the second daratumumab infusion will follow the C1D1 daratumumab infusion schedule, as described above and in Table 5.
Cycle 1 Day 15	**Daratumumab and JNJ-63723283** Daratumumab is administered over a 3 to 4 hour infusion period, followed by a 30-minute JNJ-63723283 infusion (approximately 30 min. if no IRRs with the initial 1-hour infusion of JNJ-63723283; see also Section 6.2.1). A 2-hour observation period will be conducted after the completion of the JNJ-63723283 infusion.
Cycle 1 Day 22	**Daratumumab** Daratumumab is administered over a 3 to 4 hour infusion period and then followed by a 2-hour observation period.
Cycle 2 Day 1 and subsequent infusions	**Daratumumab and JNJ-63723283** If all the infusions in Cycle 1 are well tolerated, then starting on C2D1, the observation period can be 1-hour after sequential combination dosing of daratumumab and JNJ-63723283. If not well tolerated (ie, Grade 1 or higher infusion-related reactions), then follow the C1D15 procedures.

6.1.5. Dose Delay

Dose modification of daratumumab is not permitted. Dose delay is the primary method for managing daratumumab-related toxicities.

On the first day of each new treatment cycle and before each daratumumab dose, the subject will be evaluated by the treating physician for possible toxicities that may have occurred after the previous dose(s). Toxicities are to be assessed according to NCI-CTCAE, Version 4.03. Dose delays will be made based on the toxicity experienced during the previous infusion or newly encountered on Day 1 of a new cycle.

The study treatment must be held if any of the following criteria below are met, to allow for recovery from toxicity, regardless of relationship to daratumumab.

The criteria for a dose delay are:

- Grade 4 hematologic toxicity, except for Grade 4 lymphopenia
- Grade 3 or higher thrombocytopenia with bleeding
- Febrile neutropenia

- Neutropenia with infection, of any grade
- For all other adverse events, daratumumab should be withheld for Grade 3 or higher toxicities with the following exceptions:
  - Grade 3 nausea that responds to antiemetic treatment within 7 days
  - Grade 3 vomiting that responds to antiemetic treatment within 7 days
  - Grade 3 diarrhea that responds to antidiarrheal treatment within 7 days
  - Grade 3 fatigue that was present at baseline or that lasts for <7 days after the last administration of daratumumab
  - Grade 3 asthenia that was present at baseline or that lasts for <7 days after the last administration of daratumumab

Administration of daratumumab may be restarted upon recovery from toxicity to Grade 1 or baseline, with the exception of Grade 2 laryngeal edema, Grade 2 bronchospasm or febrile neutropenia, which must be fully recovered. If daratumumab administration does not commence within the prespecified window (Table 7) of the scheduled administration date, then the dose will be considered a missed dose. Administration may resume at the next planned dosing date. A missed dose will not be made up. A delay in daratumumab dosing will result in a subsequent delay in JNJ-63723283 dosing. In the case of daratumumab missed dose(s), JNJ-63723283 should continue to be administered per schedule and not delayed or alternatively, dosing decisions should be discussed with the Sponsor.

Table 7: Daratumumab-related Toxicity Management

Cycles	Frequency	Dose Held	Dosing Restart
1 and 2	Weekly (q1wk)	>3 days	Next planned weekly dosing date
3 to 6	Biweekly (q2wks)	>7 days	Next planned biweekly dosing date
7+	Every 4 weeks (q4wks)	>14 days	Next planned every 4 weeks dosing date

If 2 consecutive planned doses of daratumumab are missed due to any adverse event, then consultation with the Sponsor is required before dosing may be continued.

For subjects whose dose is held for more than 28 days for any drug related adverse event or who miss 3 or more consecutive planned doses of daratumumab due to any adverse event, then the treatment should be permanently discontinued. Dose holds of more than 28 days for other reasons should be discussed with the Sponsor. If daratumumab is permanently discontinued, then JNJ-63723283 should be permanently discontinued.

If a dose delay occurs, then pharmacokinetic and biomarker assessments should be performed on the actual daratumumab administration day, not on the originally scheduled administration day.

6.2. JNJ-63723283

JNJ-63723283 will be administered to subjects as described in the Time and Events Schedule Table 1. JNJ-63723283 will be administered after daratumumab, when they are administered on

the same dosing day. Subjects will continue to receive JNJ-63723283 until disease progression, unacceptable toxicity, or other reasons as listed in Section 10. The IPPI and SIPPM provide detailed descriptions for preparation and administration of JNJ-63723283. The manufacturing processes for the drug substance and drug product for JNJ-63723283 will be changed during this study, see Section 14.1 for more information.

6.2.1. JNJ-63723283 Treatment Schedule and Administration

A summary of JNJ-63723283 administration details are provided in Table 8. Additional dose levels and schedules will be considered based on the emerging JNJ-63723283 safety, pharmacokinetics, pharmacodynamics, and any other available data.

Table 8: JNJ-63723283 Administration

Study Drug	JNJ-63723283
Dose/schedule	240 mg (fixed dose) every 2 weeks
Route/Regimen	Administered IV, initially over a 50-70 minute infusion. In the absence of infusion-related reactions, subsequent infusions may be administered IV over 25-40 minutes. Study drug is to be administered under the supervision of site staff.

See Section 6.1.4 for information on monitoring during and after infusion.

6.2.2. Dose Delay

Dose delay is the primary method for managing JNJ-63723283-related toxicities. In the event of a toxicity that meets the criteria below or is otherwise considered to be clinically significant by the treating physician, treatment will be held and supportive therapy administered as clinically indicated. If clinically significant drug-related toxicity is present, treatment should be delayed until the toxicity resolves (with or without supportive therapy) to baseline or Grade ≤1 except for alopecia, hyperthyroidism and rash for which resolution to ≤Grade 2 is required for subsequent treatment. If the toxicity does not resolve to ≤Grade 1 or baseline within 12 weeks of identification of the toxicity, withdrawal from the study is recommended unless otherwise agreed to by the Sponsor medical monitor and the investigator based on evidence of clinical benefit.

Dose delays will be required if:

- Grade 2 pneumonitis (recurrent Grade 2 pneumonitis, study drug must be permanently discontinued)
- Grade 2 or 3 diarrhea or colitis
- Grade 2 nephritis with creatinine >1.5 to 3.0 x upper limit of normal (ULN)
- Grade 2 or 3 creatinine elevation
- Grade 2 elevation in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) (3-5 x ULN) except for subjects with tumor involvement in the liver at baseline, or total bilirubin (1.5-3 x ULN) except in subjects with congenital bilirubinemia, such as Gilbert syndrome (direct bilirubin 3 x ULN)
- Symptomatic endocrinopathies (including hypothyroidism, hyperthyroidism, hypophysitis, adrenal insufficiency, and diabetes)

- Grade 3 rash
- Grade ≥3 non-irAEs (except for hematologic toxicities not attributed to JNJ-63723283)

The criteria for discontinuation of study treatment are described in Section 6.2.3 and Section 10.

6.2.3. Toxicities Leading to Discontinuation of Study Treatment

A subject must discontinue study treatment if:

- Grade 2 or 3 irAEs that persist despite treatment modifications or corticosteroid dosing cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks
- A treatment-related AE does not resolve to Grade ≤1 within 12 weeks of the last dose of study drug unless otherwise agreed to by the Sponsor medical monitor and the investigator based on evidence of clinical benefit
- Any non-hematologic treatment-related event occurs a second time at Grade ≥3 severity
- Grade ≥3 (or recurrent Grade 2) pneumonitis
- Grade ≥3 nephritis with creatinine ≥3xULN
- Grade ≥3 elevation of AST or ALT >5xULN or total bilirubin >3xULN
- Grade 4 infusion-related reactions (IRRs) due to JNJ-63723283
- Immune-mediated encephalitis

If a subject's study treatment is discontinued, this will not result in automatic withdrawal of the subject from the study. Following treatment discontinuation, the subject should complete the End-of-Treatment Visit as described in Table 1. Once a subject discontinues treatment with JNJ-63723283, the subject may not be retreated with the study drug. If JNJ-63723283 is permanently discontinued, then treatment with daratumumab may be continued with discussion with the Sponsor.

If a dose delay occurs, then pharmacokinetic and biomarker assessments should be performed on the actual daratumumab administration day, not on the originally scheduled administration day.

6.2.4. Guidelines for Management of Immune-Related Adverse Events and Adverse Events of Clinical Interest

Therapy with immuno-oncology agents such as JNJ-63723283 may lead to specific irAEs that differ in nature, severity and duration as compared to AEs caused by agents with a different mode of action. Early recognition and management of these irAEs may mitigate more severe/subsequent toxicity. However, differential diagnoses including non-inflammatory etiologies as well as the impact of the underlying malignant disease and/or concomitant medication should be evaluated according to standard medical practice.

Management algorithms have been developed to assist investigators in assessing and managing specific irAEs following administration of nivolumab (SmPC; PI)[25,26] and pembrolizumab (SmPC; PI).[29,30] These guidelines are presented below and should be followed for JNJ-63723283. In addition to the management algorithms provided in following sections, it is recommended that

irAEs are managed according to the general treatment guidelines outlined for ipilimumab (PI).[14] These guidelines recommend the following:

1. Subjects should be evaluated to identify any alternative etiology.
2. In the absence of a clear alternative etiology, all events of an inflammatory nature should be considered immune related.
3. Symptomatic and topical therapy should be considered for low-grade events.
4. Systemic corticosteroids should be considered for a persistent low-grade event or for a severe event.
5. More potent immunosuppressives should be considered for events not responding to systemic corticosteroids (eg, anti-TNF agents or mycophenolate).

If delaying the dose is necessary to ameliorate toxicity, follow the guidance in Section 6.2.2.

6.2.4.1. Gastrointestinal Adverse Events

Diarrhea and colitis have been observed in subjects receiving anti-PD-1 therapies. Early recognition and treatment of diarrhea and colitis are critical to their management (see Table 9). Subjects should be advised to seek immediate medical evaluation if they develop new-onset diarrhea, blood in stool, or severe abdominal pain or if they have worsening of baseline diarrhea. In subjects with pre-existing diverticulosis or diverticulitis receiving concomitant medication with corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), and opioid analgesics together with anti-PD-1 therapies, diverticular perforation has been observed.

Table 9: Management of Immune-Related Gastrointestinal Adverse Events

Guidelines for dose delay can be found in Section 6.2.2.	
Grade 1	Symptomatic treatment according to institutional standards Close monitoring; instruct subject to report worsening immediately and treat as Grade ≥2
Grade 2	≤5 days: Symptomatic treatment according to institutional standards >5 days or recurrence: 0.5–1.0 mg/kg/d methylprednisolone; consider prophylactic antibiotics; Persistence or worsening despite steroids >3 days: treat as Grade 3/4 Improvement to ≤Grade 1: taper steroids over at least 4 weeks, consider prophylactic antibiotics for opportunistic infections, resume study therapy per protocol
Grade 3-4	Immediately: 1.0–2.0 mg/kg/d methylprednisolone IV; consider prophylactic antibiotics and lower endoscopy Persistence >3 days or recurrence: add infliximab 5 mg/kg (if no contraindication such as perforation or sepsis) Improvement to ≤Grade 2 within ≤3 days: taper steroids over at least 4 weeks
General	The oral corticosteroid equivalent of the recommended IV dose may be considered for ambulatory patients; the lower bioavailability of oral corticosteroids needs to be considered. Clinical caution should be exercised, for subjects receiving concomitant medications of corticosteroids, NSAID, or opioid analgesics. In addition, monitor for signs and symptoms of potential perforation, especially in subjects with known diverticular disease. Narcotics should be used with caution as pain medicines may mask the signs of colonic perforation.

6.2.4.2. Hepatic Adverse Events

Hepatic AEs, including elevated liver function tests (LFTs) and, infrequently, drug-induced-liver-injuries (DILI) have been observed following treatment with anti-PD-1 therapies. Early recognition and treatment of elevated LFTs and DILI are critical to their

management (see Table 10). Subjects should be advised to seek medical evaluation if they notice jaundice (yellow appearance of skin or sclera) or if they develop bruising, bleeding, or right-sided abdominal pain. LFTs should be monitored prior to treatment.

Table 10: Management of Immune-Related Hepatic Adverse Events

Guidelines for dose delay can be found in Section 6.2.2.	
Grade 1	Monitor LFTs as outlined in the protocol; Worsening: treat as Grade ≥2
Grade 2	Monitor every 3 days; Returning to baseline: resume per protocol monitoring LFT elevation >5 days or worsening: 0.5-1.0 mg/kg/d methylprednisolone IV or oral equivalent; consider prophylactic antibiotics LFT return to ≤Grade 1 or baseline: taper steroids over at least 4 weeks; resume routine monitoring and resume study treatment per protocol
Grade 3-4	Monitor every ≤2 days; Immediately: 1.0-2.0 mg/kg/d methylprednisolone IV or IV equivalent; start prophylactic antibiotics; consult gastroenterologist Persistence >3 days or recurrence: add mycophenolate mofetil 1g bid; if no response within ≤5 days consider other immunosuppressants per local guidelines LFT return to Grade 2: stop immunosuppressants LFT return to ≤Grade 1: taper steroids over at least 4 weeks

6.2.4.3. Endocrinopathies

Endocrinopathies have been observed following treatment with anti-PD-1 therapies. The events have typically been identified through either routine periodic monitoring of specific laboratory tests (eg, TSH) or as part of a work-up for associated symptoms (eg, fatigue) (see Table 11). Events may occur within weeks of beginning treatment, but also have been noted to occur after many months (while still on treatment). More than 1 endocrine organ may be involved (eg, hypophysitis [pituitary inflammation] may need to be evaluated at the time adrenal insufficiency or thyroid disorder is suspected). Subjects should be advised to seek medical evaluation if they notice new-onset fatigue, lightheadedness, or difficulty with vision or if baseline fatigue worsens.

Table 11: Management of Immune-Related Endocrinopathies

Guidelines for dose delay can be found in Section 6.2.2.	
Asymptomatic TSH elevation	TSH <0.5xLLN or TSH >2xULN or TSH >ULN in 2 subsequent measurements: include free T4 assessment prior/after subsequent cycles of study treatment; consider endocrinology consultation
Symptomatic endocrinopathy	Assess endocrine function with appropriate laboratory testing; consider pituitary magnetic resonance imaging (MRI) scan. With abnormal lab and pituitary scan: 1.0–2.0 mg/kg/d methylprednisolone IV or oral equivalent; initiate appropriate hormone therapy; consider prophylactic antibiotics • In hyperthyroidism, non-selective beta-blockers (eg, propranolol) are suggested as initial therapy. • In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyronine, is indicated per standard of care. Clinical and laboratory improvement: taper steroids over at least 4 weeks; patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component Without abnormal lab and pituitary scan but symptoms persist: repeat laboratory assessments in ≤3 weeks and MRI in 4 weeks
Suspicion of adrenal crisis (eg, severe dehydration, hypotension, shock out of proportion to current illness)	Rule out sepsis Immediately: initiate/stress dose of IV steroids with mineralocorticoid activity; fluids IV; consult endocrinologist Adrenal crisis ruled out: treat as symptomatic endocrinopathy
Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)	For T1DM or Grade 3-4 hyperglycemia: Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria. Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.
General	Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. The lower bioavailability of oral corticosteroids need to be considered.

6.2.4.4. Rash

Rash and pruritus are the most common skin irAEs observed following treatment with anti-PD-1 therapies. Typically, it is a focal rash with a maculopapular appearance. It is usually distributed on the trunk, back, or extremities. Most cases have been of low or moderate grade. In some cases, rash and pruritus resolved without intervention. Subjects should be advised to seek medical evaluation if they notice new-onset rash (see Table 12 regarding action to be taken). A case of toxic epidermal necrolysis occurred in a subject receiving concomitant prophylaxis with trimethoprim/sulfamethoxazole, and it is possible that the initial rash was due to a sulfa-hypersensitivity reaction that was eventually augmented by anti-PD-1 therapy. This case highlights the potential importance of discontinuing other suspected drugs in the management of rash.

Table 12: Management of Rash

Guidelines for dose delay can be found in Section 6.2.2.	
Grade 1-2	Immediately: Symptomatic therapy (eg, antihistamines, topical steroids) Persistence ≤2 weeks or recurrence: consider skin biopsy; consider 0.5-1.0 mg/kg/d methylprednisolone IV or oral equivalent; consider prophylactic antibiotics Improvement to ≤Grade 1: taper steroids over at least 4 weeks Worsening to >Grade 2: treat as Grade 3-4
Grade 3-4	Immediately: consult dermatologist; consider skin biopsy; start 1.0-2.0 mg/kg/d methylprednisolone IV or IV equivalent; add prophylactic antibiotics Improvement to ≤Grade 1: taper steroids over at least 4 weeks
General	Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. The lower bioavailability of oral corticosteroids need to be considered

6.2.4.5. Renal Adverse Events

Elevated creatinine and biopsy-confirmed tubulointerstitial nephritis and allergic nephritis have been infrequently observed following treatment with anti-PD-1 therapies. Creatinine should be monitored regularly (see Table 13).

Table 13: Management of Renal Adverse Events

Guidelines for dose delay can be found in Section 6.2.2.	
Grade 1	Monitor creatinine weekly Creatinine returns to baseline: continue monitoring per protocol Creatinine increases: treat as Grade ≥2
Grade 2-3	Monitor creatinine every ≤3 days Immediately: start 0.5-1.0 mg/kg/d methylprednisolone IV or oral equivalent; consider prophylactic antibiotics; consider renal biopsy Improvement to ≤Grade 1: taper steroids over at least 4 weeks Persistence >7 days or worsening: treat as Grade 4
Grade 4	Monitor creatinine daily Immediately: consult nephrologist; consider renal biopsy; start 1.0-2.0 mg/kg/d methylprednisolone IV or IV equivalent; add prophylactic antibiotics Improvement to ≤Grade 1: taper steroids over at least 4 weeks
General	Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. The lower bioavailability of oral corticosteroids need to be considered

6.2.4.6. Neurological Adverse Events

Neurological AEs have been observed uncommonly following treatment with anti-PD-1 therapies. Neurological AEs may manifest as central abnormalities (eg, aseptic meningitis or encephalitis) or peripheral sensory/motor neuropathies (eg, Guillain-Barre Syndrome). The onset has been observed as early as after a single treatment. Early recognition and treatment of neurologic AEs is critical to their management (see Table 14). Subjects should be advised to seek medical evaluation if they notice impairment in motor function (eg, weakness), changes in sensation (eg, numbness), or symptoms suggestive of possible central nervous system abnormalities such as new headache or mental status changes.

Table 14: Management of Neurological Adverse Events

Guidelines for dose delay can be found in Section 6.2.2.	
Grade 1	Monitor per protocol Worsening: treat as ≥Grade 2
Grade 2	Immediately: treat symptoms according to institutional standards; consider 0.5-1.0 mg/kg/d methylprednisolone IV or oral equivalent Worsening: treat as Grade 3-4
Grade 3-4	Immediately: consult neurologist; treat symptoms according to institutional standards; start 1.0-2.0 mg/kg/d methylprednisolone IV or IV equivalent; prophylactic antibiotics Worsening or atypical presentation: consider immunoglobulins IV (IVIG) or other immunosuppressive therapies according to institutional standards Improvement to ≤Grade 2: taper steroids over at least 4 weeks
General	Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. The lower bioavailability of oral corticosteroids need to be considered

6.2.4.7. Pulmonary Adverse Events

Pulmonary AEs including radiographic changes (eg, focal ground glass opacities and patchy infiltrates) indicative of drug-related pneumonitis have been observed in subjects receiving anti-PD-1 therapies. These pulmonary AEs were either asymptomatic or associated with symptoms such as dyspnea, cough, or fever. The initial occurrence of pulmonary AEs may be as early as after a single dose of anti-PD-1 therapies or delayed after prolonged therapy. Early recognition and treatment of pneumonitis is critical to its management (see Table 15). Subjects should be advised to seek medical evaluation promptly if they develop new-onset dyspnea, cough, or fever or if they have worsening of these baseline symptoms.

Table 15: Management of Pulmonary Adverse Events

Guidelines for dose delay can be found in Section 6.2.2.	
Grade 1	Monitor for symptoms every 2-3 days; consider pulmonary and infectious-disease consult; re-image every 3 weeks Worsening: treat as ≥Grade 2
Grade 2	Monitor symptoms daily; re-image every 1-3 days; pulmonary and infectious-disease consultation; consider bronchoscopy and lung biopsy; consider hospitalization Immediately: start 1.0 mg/kg/d methylprednisolone IV or oral equivalent; prophylactic antibiotics Persistence for 2 weeks or worsening: treat as Grade 3-4 Improvement to ≤Grade 1 or baseline: taper steroids over at least 4 weeks
Grade 3-4	Hospitalize; pulmonary and infectious-disease consult; consider bronchoscopy and lung biopsy Immediately: 2-4 mg/kg/d methylprednisolone or IV equivalent; add prophylactic antibiotics; Persistence for 2 days or worsening: add immunosuppression (eg, infliximab, cyclophosphamide, IVIG, or mycophenolate mofetil) Improvement to ≤Grade 2: taper steroids over at least 6 weeks
General	Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. The lower bioavailability of oral corticosteroids need to be considered

6.2.4.8. Uveitis and Visual Complaints

Immune therapies have been uncommonly associated with visual complaints. Inflammation of components within the eye (eg, uveitis) is an uncommon, but clinically important, event. An ophthalmologist should evaluate visual complaints with examination of the conjunctiva, anterior and posterior chambers, and retina (see Table 16). If the subject has double vision, prompt medical evaluation should occur. In addition to ocular inflammatory events, a work-up should also consider pituitary inflammation as a cause.

Table 16: Management of Uveitis and Visual Complaints

Guidelines for dose delay can be found in Section 6.2.2.	
Grade 1	Thorough eye examination Topical corticosteroids should be considered Persisting despite topical steroids, treat as Grade 3-4
Grade 2	
Grade 3-4	Thorough eye examination Systemic corticosteroids

6.2.4.9. Lipase/Amylase Elevations

Asymptomatic elevations in lipase and amylase have been reported in anti-PD-1 therapy studies in which systemic monitoring was used. Very few subjects reported associated symptoms (eg, abdominal pain) or radiographic findings (eg, stranding) consistent with pancreatitis. Thus, there does not seem to be clinical significance to the elevated laboratory values. The recommended management of anti-PD-1 therapy-related elevated lipase/amylase values centers around close observation. Physicians should ensure that subjects have no associated symptoms consistent with pancreatitis, such as abdominal pain. Corticosteroids do not seem to alter the natural history of lipase/amylase elevations. Laboratory values tend to fluctuate on a day-to-day basis and eventually return to baseline or low-grade levels over the course of weeks, whether or not subjects receive corticosteroids. Asymptomatic elevations should be monitored approximately weekly.

6.2.5. Infection

Subjects with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice.

6.3. Treatment of Infusion-related Reactions (IRRs)

6.3.1. Guidelines for Management of Daratumumab IRRs

For infusion reactions of any grade/severity, immediately interrupt the daratumumab infusion and manage symptoms. Management of infusion reactions may require reduction in the rate of infusion, or discontinuation of daratumumab (see Table 17).

Table 17: Management Guidelines for Daratumumab Infusion-related Reactions

Guidelines for dose delay can be found in Section 6.1.5.	
Severity of IRR	**Management**
Grade 1-2 (mild to moderate)	Once IRR symptoms resolve and the subject's condition is stable, the infusion may be restarted at the investigator's discretion. Resume the infusion at no more than half the rate at which the IRR occurred. If the subject does not experience any further IRR symptoms, infusion rate escalation may resume at increments and intervals as clinically appropriate up to the maximum rate of 200 mL/hr (see Table 5).
Grade 2 or higher laryngeal edema, or bronchospasm	If the subject experiences a Grade 2 or higher event of laryngeal edema, or a Grade 2 or higher event of bronchospasm that does not respond to systemic therapy and does not resolve within 6 hours from onset, then the subject must permanently discontinue daratumumab treatment.
Grade 3 (severe)	Once reaction symptoms resolve, consider restarting the infusion at no more than half the rate at which the IRR occurred. If the subject does not experience additional symptoms, then resume infusion rate escalation at increments and intervals as outlined in Table 5. Repeat the procedure above in the event of recurrence of Grade 3 symptoms or discontinue the subject from treatment. At the subsequent infusion, permanently discontinue daratumumab if the subject experiences a Grade 3 IRR for a third time.
Grade 4 (life threatening)	Permanently discontinue daratumumab treatment.

IRR = infusion-related reaction.

6.3.2. Guidelines for Management of JNJ-63723283 IRRs

For infusion reactions of any grade/severity, immediately interrupt the JNJ-63723283 infusion and manage symptoms. Management of infusion reactions may require reduction in the rate of infusion, or discontinuation of JNJ-63723283 (see Table 18).

Table 18: Management of Infusion-Related Reactions for JNJ-63723283

Guidelines for dose delay can be found in Section 6.2.2.	
Severity of IRR	**Management**
Grade 1	No intervention indicated; remain at bedside and monitor subject until recovery from symptoms, Consider diphenhydramine 50 mg (or equivalent) and or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional study drug administration
Grade 2	Stop infusion; start IV saline infusion; give diphenhydramine 50 mg (or equivalent) IV and/or paracetamol 325 to 1000 mg (acetaminophen); consider corticosteroids and bronchodilator therapy; remain at bedside and monitor subject until recovery from symptoms Restart infusion at 50% of initial rate: if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate; monitor subject closely. Symptoms recur: stop and discontinue further treatment at that visit; administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the CRF.
Grade 3-4	Stop infusion; start IV saline infusion; recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Study drug will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritis within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids).
General	Prophylactic medications (after initial event): diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional study drug administrations; if necessary, corticosteroids (recommended dose: up to 80 mg of IV methylprednisolone or equivalent) may be used Appropriate resuscitation equipment should be available in the room and a physician readily available during the infusion of study drug.

6.4. Dosage and Administration for Daratumumab Monotherapy Period

The start of each cycle (i.e., Day 1) may occur within ±3 days of the scheduled day in order to accommodate the schedule of the site or subject. If the start of a cycle is delayed, Day 1 of the subsequent cycle should be adjusted accordingly to maintain the 28-day cycle duration. The weekly or bi-weekly study treatment administrations (i.e., Day 8, 15, and 22 dosing dates) may occur within ±1 day of the scheduled day to accommodate the schedule of the site or subject. Changes to within-cycle dosing should not impact Day 1 of the next cycle.

6.4.1. Daratumumab Monotherapy

Daratumumab will be administered to subjects as described in the Time and Events Schedule Table 24. Subjects will continue to receive daratumumab until disease progression, unacceptable toxicity, or other reasons as listed in Section 10. Refer to the Investigational Product Preparation Instructions (IPPI) and the Site Investigational Product and Procedures Manual (SIPPM) for detailed descriptions for preparation and administration of daratumumab.

6.4.1.1. Daratumumab Treatment Schedule and Administration

Each cycle is 28 days. The daratumumab administration dose and schedule is summarized below:

- Daratumumab 16 mg/kg IV will be administered once every week (Weeks 1 to 8); then once every other week for 16 weeks (Weeks 9 to 24); thereafter once every 4 weeks (Week 25 onwards).

Each subject's dose will be calculated based on the subject's weight at Cycle 1 Day 1 rounded to the nearest kilogram. The dose of daratumumab does not need to be recalculated for weight changes <10% from baseline. Subjects will receive preinfusion medications and postinfusion medications as outlined in Sections 6.4.1.2 and 6.4.1.3.

The dilution volumes, initial infusion rates, and increment of infusion rates for the first, second, and subsequent doses in the absence of an infusion-related reaction >Grade 1 are provided in Table 19.

Table 19: Daratumumab Administration

	Dilution Volume	Initial Infusion Rate (first hour)	Incremental Increases in Infusion Rate[a]	Maximum Infusion Rate
Week 1 infusion (Cycle 1 Day 1)	1000 mL	50 mL/hour	50 mL/every hour	200 mL/hour
Week 2 infusion[b]	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Subsequent infusions[c]	500 mL	100 mL/hour	50 mL/hour every hour	200 mL/hour

a. Consider titration of the infusion rate only in the absence of infusion-related reactions.
b. Dilution volume of 500 mL should be used only if there were no Grade 1 (mild) or greater infusion-related reactions during the first 3 hours of the first infusion. Otherwise, continue to use a dilution volume of 1000 mL.
c. Use a modified initial rate for subsequent infusions (ie, third infusion onwards) only if there were no Grade 1 (mild) or greater infusion-related reactions during a final infusion rate of ≥100 mL/h in the first two infusions. Otherwise, continue to use instructions for the second infusion.

Vital signs should be measured before the start of each daratumumab infusion and at the end of each daratumumab infusion. If a subject experiences any significant medical event, then the investigator should assess whether the subject should stay overnight for observation. If the subject has not experienced a significant medical event but is hospitalized overnight only for observation, then the hospitalization should not be reported as a serious adverse event.

6.4.1.2. Preinfusion Medication

In an effort to prevent infusion related reactions, all subjects will receive the following medications 1 to 3 hours prior to the start of each daratumumab infusion (see the Time and Events Schedule; Table 24):

- An antipyretic: paracetamol (acetaminophen) 650 to 1000 mg IV or orally (PO).
- An antihistamine: diphenhydramine 25 to 50 mg IV or PO, or equivalent). Avoid the use of IV promethazine (see Attachment 1 for a list of antihistamines that may be used).
- A corticosteroid: methylprednisolone 100 mg IV or PO or equivalent for the first 2 doses and 60 mg for all subsequent doses (after 2 consecutive daratumumab infusions are completed with no IRR adverse events). Substitutions for methylprednisolone are allowed (refer to Attachment 2).

In addition, a leukotriene inhibitor (optional; montelukast 10 mg PO) may be administered up to 24 hours before infusion as per investigator discretion.

If necessary, all PO preinfusion medications may be administered outside of the clinic on the day of the infusion, provided they are taken 1 to 3 hours before the infusion.

6.4.1.3. Postinfusion Medication

Postinfusion medication should be administered to reduce the risk of delayed infusion-related reactions in all subjects:

- Oral corticosteroid (20 mg methylprednisolone PO or equivalent in accordance with local standards) on the 2 days following each daratumumab administration (beginning the day after study drug administration). After 3 consecutive daratumumab infusions with no IRR adverse events, postinfusion corticosteroids should be administered per investigator discretion.

For subjects with a higher risk of respiratory complications (eg, subjects with COPD who have an FEV1 <80% or subjects with asthma), the following postinfusion medications should be considered:

- antihistamine (diphenhydramine or equivalent) on the first and second days after each infusion;
- short-acting β2 adrenergic receptor agonist such as salbutamol aerosol; and
- control medications for lung disease (eg, inhaled corticosteroids ± long-acting β2 adrenergic receptor agonists for subjects with asthma; long-acting bronchodilators such as tiotropium or salmeterol ± inhaled corticosteroids for subjects with COPD).

In addition, these at-risk subjects may be hospitalized for monitoring for up to 2 nights after study drug administration. If these at-risk subjects are hospitalized, then their FEV1 should be measured and managed per local standards before discharge. If these subjects are not hospitalized, then a follow-up telephone call should be made to monitor their condition within 48 hours after each daratumumab administration. If the subject has not experienced a significant medical event but is hospitalized overnight only for observation, then the hospitalization should not be reported as a serious adverse event. Investigators may prescribe bronchodilators, antihistamines, and corticosteroids that are deemed necessary to provide adequate supportive care in the event a bronchospasm occurs after subjects are released from the hospital/clinic. If an at-risk subject experiences no major IRRs, then these postdose medications may be waived after 4 doses at the investigator's discretion.

6.4.1.4. Monitoring During and After Daratumumab Administration

Subjects should be observed carefully during study agent infusions. Trained study staff at the clinic should be prepared to intervene in case of any IRRs occurring, and resources necessary for resuscitation (eg, agents such as epinephrine and aerosolized bronchodilator, also medical equipment such as oxygen tanks, tracheostomy equipment, and a defibrillator) must be available at the bedside. If an IRR develops, then the infusion should be paused. Guidelines outlined in Section 6.3 must be followed to manage IRRs.

Subjects should be monitored for at least 2 hours after the completion of the first infusion and may be discharged if considered clinically stable and all other study procedures have been completed (see Table 20 below). The investigator will determine the duration of safety monitoring for subsequent administrations. In addition, subjects should be monitored for symptoms of tumor lysis syndrome, see Section 8.1.2.

Table 20: Infusion Duration and Monitoring After Infusion of Daratumumab

Cycle 1 Day 1	**Daratumumab – First infusion** Daratumumab is administered over a 6 to 8 hour infusion period followed by a 2-hour observation period. The subject may be discharged if considered clinically stable and all other study procedures have been completed
Cycle 1 Day 8	**Daratumumab – Second infusion** If the first daratumumab infusion is well tolerated (defined as no Grade 1 or higher IRRs), then the second daratumumab infusion should administered over 3 to 4 hours, followed by a 2-hour observation period. However, if the first daratumumab infusion is not well tolerated, then the second daratumumab infusion will follow the C1D1 daratumumab infusion schedule, as described above and in Table 5.
Cycle 1 Day 15	**Daratumumab** Daratumumab is administered over a 3 to 4 hour infusion period, followed by a 2-hour observation period.
Cycle 1 Day 22	**Daratumumab** Daratumumab is administered over a 3 to 4 hour infusion period, followed by a 2-hour observation period.
Cycle 2 Day 1 and subsequent infusions	**Daratumumab** If all the infusions in Cycle 1 are well tolerated, then starting on C2D1, the observation period can be 1-hour after dosing of daratumumab. If not well tolerated (ie, Grade 1 or higher infusion-related reactions), then follow the C1D15 procedures.

6.4.1.5. Dose Delay

Dose modification of daratumumab is not permitted. Dose delay is the primary method for managing daratumumab-related toxicities.

On the first day of each new treatment cycle and before each daratumumab dose, the subject will be evaluated by the treating physician for possible toxicities that may have occurred after the previous dose(s). Toxicities are to be assessed according to NCI-CTCAE, Version 4.03. Dose delays will be made based on the toxicity experienced during the previous infusion or newly encountered on Day 1 of a new cycle.

The study treatment must be held if any of the following criteria below are met, to allow for recovery from toxicity, regardless of relationship to daratumumab.

The criteria for a dose delay are:

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

Administration of daratumumab may be restarted upon recovery from toxicity to Grade 2 or baseline, with the exception of Grade 2 laryngeal edema, Grade 2 bronchospasm or febrile neutropenia, which must be fully recovered. If daratumumab administration does not commence within the prespecified window (Table 21) of the scheduled administration date, then the dose will be considered a missed dose. Administration may resume at the next planned dosing date. A missed dose will not be made up. Alternatively, dosing delays can be discussed with the Sponsor.

Table 21: Daratumumab-related Toxicity Management

Cycles	Frequency	Dose Held	Dosing Restart
1 and 2	Weekly (q1wk)	>3 days	Next planned weekly dosing date
3 to 6	Biweekly (q2wks)	>7 days	Next planned biweekly dosing date
7+	Every 4 weeks (q4wks)	>14 days	Next planned every 4 weeks dosing date

The start (ie, Day 1) of a cycle may be delayed up to 4 weeks. Day 1 of a cycle should never be skipped. If the start of a cycle is delayed, Day 1 of subsequent cycles should be adjusted accordingly to maintain the 28-day cycle duration. However, if a within-cycle dose (i.e., Day 8, Day 15, or Day 22) is delayed, then the dates of the subsequent within-cycle doses should **not** be adjusted.

If 2 consecutive planned doses of daratumumab are missed due to any adverse event, then consultation with the Sponsor is required before dosing may be continued.

For subjects whose dose is held for more than 28 days for any drug related adverse event or who miss 3 or more consecutive planned doses of daratumumab due to any adverse event, then the

treatment should be permanently discontinued. Dose holds of more than 28 days for other reasons should be discussed with the Sponsor.

7. TREATMENT COMPLIANCE

Study drugs (JNJ-63723283 and daratumumab) will be administered by qualified site staff, and the details of each administration will be recorded in the case report form (CRF). Additional details are provided in the SIPPM. A patient diary card may be used to record drugs taken at home to prevent IRR (eg, pre-infusion medication).

8. PRESTUDY AND CONCOMITANT THERAPY

All prior treatments for malignancies, including those since diagnosis, must be recorded at Screening. Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 8.3. The Sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

Routine systemic use of the following concomitant medications will be collected in the CRF and recorded in the source documents beginning with signing of the ICF to PD or until the start of subsequent anticancer treatment, if earlier: growth factors, transfusions, anti-infectives (antibacterials, antivirals, and antimycotics), corticosteroids, anti-arrhythmics and other cardiac supportive therapy, anti-epileptics, centrally acting psychiatric medication, anti-histamines and other medications targeting postinfusion systemic reactions, bisphosphonates, and any anticancer therapy (including radiation).

The use of concomitant medications used to treat adverse events or any infusion-related reactions will be collected in the CRF and recorded in the source documents beginning with the signing of the ICF until PD.

Prestudy therapies administered up to 30 days before first dose of study drug must be recorded at Screening. Concomitant therapies described above must be recorded throughout the study beginning with start of the first dose of study drug until the end of treatment assessment. Concomitant therapies should be recorded beyond 30 days after the last dose of study drug only in conjunction with serious adverse events that meet the criteria outlined in Section 12.3.2, Serious Adverse Events.

8.1. Recommended Therapies

8.1.1. Bisphosphonate Therapy

Bisphosphonate therapy is strongly recommended for all subjects with evidence of lytic destruction of bone or with osteopenia. Bisphosphonate therapy is recommended to be continued per treatment guidelines (Moreau 2017; NCCN 2017).[23,24] Commercially available IV bisphosphonates (pamidronate and zoledronic acid) are preferred when available, and should be used according to the manufacturer's recommendations, as described in the prescribing information, for subjects with osteolytic or osteopenic myelomatous bone disease. Oral

bisphosphonates may be used as alternatives if IV bisphosphonates are not available at the study site. Investigators should use the same route of bisphosphonate therapy for all subjects at their sites. Subjects with evidence of lytic destruction of bone or with osteopenia who are not using a bisphosphonate prior to first study drug administration should start a bisphosphonate as soon as possible during Cycle 1 or 2 of treatment. Investigators should not start bisphosphonate therapy during the study, unless it has been agreed with the Sponsor that there is no sign of disease progression.

8.1.2. Therapy for Tumor Lysis Syndrome

Subjects should be monitored for symptoms of tumor lysis syndrome. Management of tumor lysis syndrome, including hydration for abnormal laboratory test results such as hyperkalemia, hyperuricemia, and hypocalcemia, is highly recommended. High-risk subjects (ie, those with a high tumor burden) should be treated prophylactically in accordance with local standards (eg, rehydration, diuretics, allopurinol 300 mg daily, and medication to increase urate excretion). Subjects are to be provided prophylactic therapy to manage IRRs as described in Section 6.1.2 for daratumumab.

8.1.3. Therapy for *Pneumocystis carinii/jirovecii*

Pneumocystis carinii/jirovecii pneumonia (PCP) prophylaxis should be considered, as per institutional guidelines.

8.1.4. Prophylaxis for Herpes Zoster Reactivation

Antiviral prophylaxis should be considered for the prevention of herpes zoster virus reactivation.

8.2. Permitted Therapies

Subjects are to receive full supportive care during the study. The following medications and supportive therapies are examples of support therapies that may be used during the study:

- Antivirals
- Granulocyte colony stimulating factors, erythropoietin, and transfusion of platelets and red cells is allowed, except as prophylaxis during Cycle 1
- Prevention of constipation (eg, adequate hydration, high-fiber diet, and stool softeners if needed)
- Prophylactic antiemetics, with the exception of corticosteroids
- Loperamide is recommended for the treatment of diarrhea, starting at the time of the first watery stool. The loperamide dose and regimen is according to institutional guidelines. Prophylactic loperamide is not recommended.
- Adequate hydration is recommended for prevention of myeloma-related kidney disease.

- Oral contraceptives
- Hormone-replacement therapy

Other symptoms may be managed according to institutional guidelines provided prohibited therapies are not administered (see Section 8.3).

In general, investigators should manage subject care with supportive therapies as clinically indicated per local standards.

8.3. Prohibited Therapies

Use of the treatments listed below is prohibited during the study:

- Other agents that target CD38, PD-1 or its ligand, PD-L1.
- Concomitant administration of any other antineoplastic therapy for the intention of treating multiple myeloma is prohibited, including medications used for other indications that have anti-myeloma properties (eg, interferon and clarithromycin). Continuation of study treatment (during or after emergency orthopedic surgery or radiotherapy because subject benefit) may only occur in the absence of disease progression and after consultation with and approval by the Sponsor.
- Emergency radiotherapy may consist of localized radiotherapy for pain control or for stabilization of an extensive bone lesion at high risk of pathologic fracture or damage to surrounding tissues in a subject in whom delay of systemic therapy is not appropriate. Such local radiotherapy is to occur within the first 2 cycles of treatment and the absence of evidence of disease progression is to be reviewed and approved by the Sponsor.
- Concomitant administration of approved or investigational agents with activity against or under investigation for multiple myeloma is prohibited (including but not limited to conventional chemotherapies, IMiDs, or proteasome inhibitors). Systemic corticosteroids (>10 mg prednisone per day or equivalent for over 5 days) other than those given for IRRs, as described in Section 6.2.2 should be avoided. Nonsteroidal anti-inflammatory agents should be avoided to prevent myeloma-related kidney disease.
- Typically, IV contrast is not used in CT scanning of subjects with secretory multiple myeloma because of the risk to the kidney. If administration of IV contrast is necessary, then adequate precautions including hydration are indicated.
- Any live, attenuated vaccine within 4 weeks prior to administration of study drug or during treatment or within 5 months following the last JNJ-63723283 dose.

The Sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedules (Table 1 and Table 2) summarizes the frequency and timing of efficacy, safety, biomarker, PK, and immunogenicity measurements applicable to this study. Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1.1.1. Daratumumab Monotherapy Period

Subjects continuing with daratumumab monotherapy will follow the procedures as outlined in Attachment 11, Table 24.

9.1.2. Screening Phase

The signed ICF must be obtained before any study-specific procedures are performed. The Screening Phase begins when the first protocol specified Screening Phase assessment is performed (typically signing of the ICF). During the Screening Phase, eligibility criteria will be reviewed and a complete clinical evaluation will be performed as specified in the Time and Events Schedule (Table 1). Subjects will be stratified by International Staging System (ISS; I, II, or III), and number of prior lines of therapy (≤3 prior lines vs. >3 prior lines). Screening procedures will be performed within 28 days before enrollment. Subjects may be retested for laboratory values that do not meet eligibility criteria within the 28-day Screening Phase.

If a subject does not meet all inclusion and exclusion criteria (is a screen failure) but at some point in the future is expected to meet the subject eligibility criteria, the subject may be rescreened on 1 occasion. Subjects who are rescreened will be assigned a new subject number, undergo the informed consent process, and then restart a new Screening Phase.

Screening procedures will be performed within 28 days before Cycle 1, Day 1, with the exceptions of disease evaluations, laboratory tests, and pregnancy tests. Serum and urine baseline disease evaluations are to be performed by the central laboratory within 14 days before Cycle 1, Day 1. It is not mandatory to collect these samples again at the Cycle 1, Day 1 visit. Results from skeletal survey and radiologic plasmacytoma assessments performed as routine follow up for subject's disease within 42 days before Cycle 1, Day 1 and bone marrow aspirate/biopsy within a maximum of 42 days before Cycle 1, Day 1 may be used without these tests being repeated. If the 24-hour collection of urine M-protein quantitation by electrophoresis (UPEP) began before informed consent was obtained as part of routine patient care, the sample can be used in this study as long as it was sent to the central lab for analysis after the informed consent was obtained. During Screening, a pregnancy test must be performed within 14 days prior to dosing.

Prior to enrollment/randomization, the Sponsor will review key eligibility criteria for all subjects. Eligibility information will be provided to the Sponsor for review prior to approval for enrollment/randomization being granted by the Sponsor. If the Sponsor agrees that the eligibility criteria have been met, then the investigator will receive confirmation that the subject may be enrolled/randomized into the study. If the Sponsor considers that the eligibility criteria have not been met, then the Sponsor will contact the investigator to discuss the subject.

All evaluations will be done in all parts of the study, unless otherwise noted.

9.1.3. Open-Label Treatment Phase

Details of the procedures performed during the Treatment Phase are outlined in the Time and Events Schedule. Subjects should start study treatment within 72 hours after assignment to treatment. Subjects will be closely monitored for adverse events, laboratory abnormalities, and clinical response. Clinical evaluations and laboratory studies may be repeated more frequently, if clinically indicated. If disease progression is confirmed, then the subject will discontinue study treatment, complete the End-of-Treatment Visit, and enter the Follow-up Phase.

End-of-Treatment Visit

Unless a subject withdraws consent for study participation or is lost to follow up, an End-of-Treatment Visit is to occur 4 weeks (±7 days) after the last dose of study treatment. Every effort should be made to conduct the End-of-Treatment Visit before the subject starts subsequent treatment. If a subject is unable to return to the site for the End-of-Treatment Visit, then the subject should be contacted to collect information on adverse events and concomitant medications used to treat adverse events as specified in Section 12.3.1. If the End-of-Treatment visit occurs before 30 days, then the subject should be contacted after 30 days so that all adverse events that occurred within the 30-day period are recorded. Additional information on reporting of adverse events is presented in Section 12.

9.1.4. Follow-Up Phase

Each subject is to have a follow-up visit 8 weeks after the last dose of study treatment. Beyond the Week 4 End-of-Treatment Visit, information on serious adverse events considered related to study treatment will continue to be collected. For a subject who discontinues study treatment before disease progression, disease evaluations should continue to be performed as specified in the Time and Events Schedule. After disease progression is documented, subsequent anticancer treatment, response to subsequent treatment, and date of progression will be recorded and survival status will be obtained. If the information is obtained via telephone contact, then written documentation of the communication must be available for review in the source documents. If the subject has died, then the date and cause of death will be collected and documented on the eCRF.

During the Daratumumab Monotherapy Period, SAEs (including SPMs) must be reported continuously from time of ICF until EOT Visit or until the subject withdraws consent for study participation or until the subject starts subsequent anticancer therapy whichever occurs first. Beyond the EOT Visit reporting period after the last dose of study medication, information on

SAEs, including SPMs, considered possibly, probably or definitely related to study drug will continue to be collected.

9.2. Efficacy Evaluations

9.2.1. Disease Assessments

Disease evaluations must be performed every 28 days (±3 days), regardless of any changes to the dosing regimen, until disease progression. Disease evaluations will be performed by a central laboratory (unless otherwise specified). This study will use the IMWG consensus recommendations for multiple myeloma treatment response criteria (Durie 2006; Kumar 2016; Rajkumar 2011)[10,18,32] presented in Table 22 For quantitative Ig (QIg), M-protein, and immunofixation measurements in serum and 24-hour urine, the investigator will use results provided by the central laboratory. For subjects with light chain multiple myeloma, only serum free light chain assay will be performed routinely. Otherwise, serum free light chain assay test results will be analyzed by the central laboratory only for the assessment of sCR. For subjects with suspected daratumumab interference on serum M-protein quantitation by electrophoresis (SPEP) and immunofixation, a reflex assay will be performed (Attachment 7). Subjects with confirmed daratumumab interference who meet all other clinical criteria for CR or sCR will be considered CR/sCR. An assessment of MRD may be conducted centrally on bone marrow samples (see Section 9.4.2).

Table 22: International Uniform Response Criteria Consensus Recommendations

Response	Response Criteria
Stringent complete Response (sCR)	1. CR as defined below, *plus* 2. Normal FLC ratio, *and* 3. Absence of clonal PCs by immunohistochemistry, immunofluorescence[a] or 2- to 4-color flow cytometry
Complete response (CR)*	• Negative immunofixation on the serum and urine, *and* • Disappearance of any soft tissue plasmacytomas, *and* • <5% PCs in bone marrow
Very good partial Response (VGPR)*	• Serum and urine M-component detectable by immunofixation but not on electrophoresis, *or* • ≥90% reduction in serum M-protein plus urine M-protein <100 mg/24 hours
Partial response (PR)	• ≥50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥90% or to <200 mg/24 hours • If the serum and urine M-protein are not measurable, a decrease of ≥50% in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria • If serum and urine M-protein are not measurable, and serum free light assay is also not measurable, ≥50% reduction in bone marrow PCs is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥30% • In addition to the above criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required.
Minimal response	• ≥25% but ≤49% reduction of serum M-protein, *and* • Reduction in 24-h urine M-protein by 50–89% • In addition to the above criteria, if present at baseline, a 25% to 49% reduction in the size of soft tissue plasmacytomas also is required
Stable disease (SD)	• Not meeting criteria for CR, VGPR, PR, MR, or progressive disease

Response	Response Criteria
Progressive disease (PD)†	• Increase of 25% from lowest response value in any one of the following: • Serum M-component (absolute increase must be ≥0.5 g/dL), • Urine M-component (absolute increase must be ≥200 mg/24 hours), • Only in subjects without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL) • Only in subjects without measurable serum and urine M-protein levels and without measurable disease by FLC levels, bone marrow PC percentage (absolute percentage must be ≥10%) • Bone marrow plasma cell percentage: the absolute percentage must be >10% • Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas • Development of hypercalcemia (corrected serum calcium >11.5 mg/dL) that can be attributed solely to the PC proliferative disorder

FLC=free light chain; PC=plasma cell
All response categories (CR, sCR, VGPR, PR, and PD) require 2 consecutive assessments made at any time before the institution of any new therapy; CR, sCR, VGPR, PR, and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable on serum, urine, both, or neither.
Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. For PD, serum M-component increases of more than or equal to 1 g/dL are sufficient to define relapse if starting M-component is ≥5 g/dL.
* Clarifications to IMWG criteria for coding CR and VGPR in subjects in whom the only measurable disease is by serum FLC levels: CR in such subjects indicates a normal FLC ratio of 0.26 to 1.65 in addition to CR criteria listed above. VGPR in such subjects requires a >90% decrease in the difference between involved and uninvolved FLC levels.
† Clarifications to IMWG criteria for coding PD: Bone marrow criteria for PD are to be used only in subjects without measurable disease by M protein and by FLC levels; "25% increase" refers to M protein, FLC, and bone marrow results, and does not refer to bone lesions, soft tissue plasmacytomas, or hypercalcemia and the "lowest response value" does not need to be a confirmed value.
[a] Presence/absence of clonal cells is based upon the kappa/lambda ratio. An abnormal kappa/lambda ratio by immunohistochemistry or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is kappa/lambda of >4:1 or <1:2.

Clinical Relapse
Clinical relapse is defined using the definition of clinical relapse in IMWG criteria (Durie 2006; Kumar 2016; Rajkumar 2011).[10,18,32] In IMWG criteria, clinical relapse is defined as requiring one or more of the following direct indicators of increasing disease or end-organ dysfunction that are considered related to the underlying plasma cell proliferative disorder:
1. Development of new soft tissue plasmacytomas or bone lesions on skeletal survey, magnetic resonance imaging, or other imaging
2. Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion
3. Hypercalcemia (>11.5 mg/dL; >2.875 mM/L)
4. Decrease in hemoglobin of more than 2 g/dL (1.25 mM) or to less than 10 g/dL
5. Rise in serum creatinine by more than or equal to 2 mg/dL (≥177 mM/L)
6. Hyperviscosity

In some subjects, bone pain may be the initial symptom of relapse in the absence of any of the above features. However, bone pain without imaging confirmation is not adequate to meet these criteria in studies.

M-protein levels need to meet the definition of disease progression (see Table 22) for subjects to have disease progression. Disease evaluations will continue beyond relapse from CR until disease progression is confirmed.

Disease progression must be consistently documented across clinical study sites using the criteria in Table 22. It is important that instances of disease progression be reported to the Sponsor as soon as possible. Diagnosis and documentation of disease progression will be reported to the Sponsor within 24 hours of suspected disease progression. The medical monitor will review the information to confirm that the IMWG criteria for disease progression have been met. If the medical monitor agrees that disease progression has occurred, then a confirmation will be returned to the investigator, and the subject will be withdrawn from study treatment. If the

medical monitor considers that the IMWG criteria for disease progression have not been met, then the medical monitor will contact the investigator to discuss the subject.

For continuation of treatment, the IMWG response will be determined on an ongoing basis by the investigator. For data analysis and reporting, however, the Sponsor will use a validated computer algorithm that has been shown to provide consistent review of the data necessary to determine disease progression and response according to IMWG criteria.

For subjects who discontinue study treatment before disease progression, disease evaluations should continue to be performed as described in the Time and Events Schedule, until confirmed disease progression, death, start of a new treatment for multiple myeloma, withdrawal of consent for study participation, or the end of the study, whichever occurs first. Blood and urine for disease evaluations scheduled for treatment days should be collected before study treatment is administered.

9.2.1.1. Disease Assessments In Daratumumab Monotherapy Period

During the Daratumumab Monotherapy Period, disease evaluations will be conducted at the local site, including laboratory tests. Assessment of response to treatment will be determined by the investigator using local laboratory data. Disease assessments SPEP, UPEP, and serum calcium corrected for albumin should be collected at an interval consistent with the investigator's standard of care. The Sponsor recommends, but does not require, disease assessments to be performed every cycle for the first 18 months of this daratumumab monotherapy period and every-other-month thereafter.

Daratumumab interference testing will not be performed in the Daratumumab Monotherapy Period.

9.2.2. Myeloma Protein Measurements in Serum and Urine

Blood and 24-hour urine samples will be collected as specified in the Time and Events Schedule until the development of confirmed disease progression. Samples for M-protein measurements will be sent to and analyzed by a central laboratory. Only 1 serum and one 24-hour urine sample per time point are required by the central laboratory to perform the following tests:

- Serum quantitative immunoglobulins (QIgs)
- All subjects will be evaluated for IgG, IgA, IgM, IgD, and IgE at Screening. Every 3 months during treatment and at the EOT visit, subjects with IgD or IgE disease will be evaluated for IgG, IgA, IgM, IgD, and IgE and subjects with IgG, IgA, or IgM disease will be evaluated for IgG, IgA, and IgM.
- Serum M-Protein quantification by electrophoresis (SPEP)
- Serum immunofixation at Screening and thereafter when a CR is suspected. If daratumumab interference is suspected based on SPEP and immunofixation electrophoresis (IFE) results, additional reflex IFE testing may be performed.
- Serum free light chain assay

- 24-hour UPEP
- Urine immunofixation at Screening and thereafter when a CR is suspected

Disease progression based on 1 of the laboratory tests alone must be confirmed by at least 1 repeat investigation. Disease evaluations will continue beyond relapse from CR until disease progression is confirmed.

Subjects with measurable disease by UPEP at Screening will provide UPEP on the same schedule as SPEP. Subjects can stop post-baseline UPEP measurement if they have no measurable disease by UPEP at Screening, or if they have measurable disease by UPEP at Screening and then no measurable disease by UPEP at 2 consecutive post-baseline measurements. A urine sample to measure UPEP should be obtained at suspected disease progression and to confirm PD.

Serum and urine immunofixation test and serum free light chain assay will be performed at Screening and thereafter when a CR is suspected (when serum or 24-hour urine M-protein electrophoresis [by SPEP or UPEP] are 0 or nonquantifiable). For subjects with suspected daratumumab interference on serum immunofixation, another reflex assay using the anti-idiotype monoclonal antibody will be used to confirm daratumumab migration on immunofixation. Subjects that meet all other IMWG criteria for CR, and whose positive immunofixation is confirmed to be daratumumab, will be considered complete responders. However, for subjects with light chain multiple myeloma, serum free light chain assay will be performed routinely. Serum immunofixation assay samples will be split into 2 aliquots, with 1 reserved for potential follow-on testing if daratumumab interference with immunofixation is suspected. As daratumumab is a monoclonal IgG antibody, additional serum samples may be utilized to monitor for potential daratumumab interference with immunofixation.

Note: All attempts should be made to determine eligibility of the subject based on the central laboratory results of screening blood and urine M-protein measurements. In exceptional circumstances, the local laboratory results of blood and urine M-protein measurements may be used to determine eligibility, but only if the results are clearly (eg, 25% or more) above the thresholds for measurability. In such cases, central laboratory results are still required to be obtained in order to establish baseline values and confirm the results from the local laboratory.

9.2.3. Serum Calcium Corrected for Albumin

Blood samples for calculating serum calcium corrected for albumin will be collected as specified in the Time and Events Schedule and analyzed centrally until the development of confirmed disease progression. Development of hypercalcemia (corrected serum calcium >11.5 mg/dL or 2.8 mmol/L) may indicate disease progression or relapse if it is not attributable to any other cause (see disease response criteria in Table 19). Calcium binds to albumin and only the unbound (free) calcium is biologically active; therefore, the serum calcium level must be adjusted for abnormal albumin levels (“corrected serum calcium”). The formula for adjustment is presented in Attachment 4. When blood is analyzed at a local laboratory, measurement of free ionized calcium is an acceptable alternative to corrected serum calcium to determine hypercalcemia. Free

ionized calcium levels greater than the ULN (local laboratory reference ranges) are considered to be hypercalcemic for this study.

9.2.4. β2-microglobulin and Albumin

Blood samples for β2 microglobulin and albumin are to be collected at Screening, and will be analyzed by the central laboratory and used for the assessment of International Staging System staging at study entry. The central laboratory will also measure albumin at any time during the study that a serum calcium sample is taken.

9.2.5. Bone Marrow Examination

Bone marrow assessments to be performed locally and centrally are summarized in Table 23.

Table 23: Bone Marrow Testing

	Local Testing	Central Testing
Screening **Bone marrow aspirate/biopsy**	Disease characterization (morphology and either immunohistochemistry, immunofluorescence, or flow cytometry). Cytogenetics by FISH.	MRD and molecular subtyping: a portion of bone marrow aspirates collected at Screening will be sent to a central laboratory for evaluation of immunophenotype by flow cytometry and baseline assessment of MRD. For Screening, fresh aspirate is preferred. If not performed because a sample is available within 42 days prior to first study drug administration or randomization, non-decalcified aspirate slides (smears or clots) should be provided.
CR, sCR **Bone marrow aspirate or biopsy (or both)**	For morphology examination and either flow cytometry, immunohistochemistry, or immunofluorescence to confirm CR or sCR. For sCR: 2- to 4-color flow cytometry, or immunohistochemistry, or immunofluorescence (requires to record kappa/lambda ratio from analysis of ≥100 cells)	A portion of bone marrow aspirate will be sent to a central laboratory for evaluation of immunophenotype by flow cytometry and to assess MRD (at suspected CR or sCR, or post-CR every 6 months for those who maintain CR).
Disease Progression **Bone marrow aspirate or biopsy (or both)**	Not applicable	If feasible, a bone marrow aspirate may be collected from subjects at disease progression to evaluate mechanisms of daratumumab resistance.

CR=complete response; FISH=fluorescence in situ hybridization; MRD=minimal residual disease; sCR=stringent complete response

9.2.6. Assessment of Lytic Bone Disease

A complete skeletal survey (including skull, entire vertebral column, pelvis, chest, humeri, femora, and any other bones for which the investigator suspects involvement by disease) is to be performed and evaluated by the local laboratory by roentgenography (low-dose CT is preferred) during the Screening Phase. The same methodology used at Screening should be used throughout the study for comparison purposes. During the Treatment Phase and before disease progression is confirmed, x-rays should be performed to document response or progression whenever clinically indicated based on symptoms. Magnetic resonance imaging (MRI) or low-dose CT are acceptable methods for evaluation of bone disease and may be included at the discretion of the investigator (see the disease response criteria in Table 19). If a radionuclide bone scan was used at Screening in addition to the complete skeletal survey, then both methods must be used to

document disease status. These tests must be performed at the same time. However, a radionuclide bone scan does not replace a complete skeletal survey.

Subjects present with disease progression manifested by symptoms of pain due to bone changes. In these cases, disease progression may be documented by skeletal survey or other radiographs, depending on the symptoms that the subject experiences. If the diagnosis of disease progression is obvious by radiographic investigations, then repeat confirmatory x-rays are not necessary. In instances where changes may be subtle, a repeat x-ray may be needed in 1 to 3 weeks and then disease progression is assessed per IMWG criteria.

9.2.7. Documentation of Extramedullary Plasmacytomas

Sites of known extramedullary plasmacytomas must be documented during the Screening Phase. Clinical examination or MRI may be used to document extramedullary sites of disease. Computed tomography (CT) scan and positron emission tomography (PET)-CT scan evaluations are an acceptable alternative if there is no contraindication to the use of intravenous contrast. PET scan alone or ultrasound tests are not acceptable to document the size of extramedullary plasmacytomas. The diameters of long axis and short axis must be documented for identified extramedullary plasmacytomas.

For subjects with a history of plasmacytomas, extramedullary plasmacytomas should be assessed at Screening by clinical examination or radiologic imaging. They should also be assessed to confirm response, disease progression, or as clinically indicated.

To qualify for PR or better, the sum of products of the perpendicular diameters of the existing extramedullary plasmacytomas must have decreased by at least 50%, and new plasmacytomas must not have developed (see the disease response criteria in Table 19). To qualify for CR or better, all extramedullary plasmacytomas must have resolved. To qualify for disease progression, either the sum of products of the perpendicular diameters of the existing extramedullary plasmacytomas must have increased by at least 50% or a new plasmacytoma must have developed. In the cases where not all existing extramedullary plasmacytomas are reported, but the sum of products of the perpendicular diameters of the reported plasmacytomas have increased by at least 50%, this will also qualify as disease progression.

9.3. Pharmacokinetics and Immunogenicity

See Table 2 for pharmacokinetics and immunogenicity sample collection.

During the Daratumumab Monotherapy Period, pharmacokinetic and immunogenicity evaluations will not be performed.

9.3.1. Evaluations

Samples will be collected for measurement of serum concentrations of JNJ-63723283 and daratumumab and the assessment of anti-JNJ-63723283 and anti-daratumumab antibodies (immunogenicity) according to the Time and Events Schedule for Pharmacokinetic and Immunogenicity Assessments (Table 2). Serum samples should be collected at the final visit

from subjects who are discontinued from treatment or withdrawn from the study. Subjects who discontinue treatment will also be asked to return for immunogenicity evaluation during the Follow-up Phase. These samples will be tested by the Sponsor or Sponsor's designee.

The exact dates and times of blood sampling must be recorded. Refer to the Laboratory Manual for sample collection requirements. Collected samples must be stored under the specified and controlled conditions for the temperatures indicated in the Laboratory Manual. Additional information about the collection, handling, and shipment of biological samples can be found in the Laboratory Manual.

9.3.2. Analytical Procedures

Serum samples will be analyzed to determine concentrations of daratumumab, concentrations of JNJ-63723283, and the generation of antibodies to JNJ-63723283 or daratumumab using validated immunoassay methods. All samples collected for detection of anti-JNJ-63723283 and daratumumab antibodies will also be evaluated for serum concentration to enable interpretation of the antibody data. In separate immunogenicity assessments, serum samples will be screened for antibodies binding to JNJ-63723283 or daratumumab and serum titer will also be determined from confirmed positive samples. Other immunogenicity analyses (eg, assessment of neutralizing capabilities) may be performed to further characterize the immune responses that are generated.

9.3.3. Pharmacokinetic Parameters

The PK parameters are defined as:

C_{max} = Maximum observed concentration

C_{min} = Minimum observed concentration

For both JNJ-63723283 and daratumumab, the PK evaluations include C_{min} and C_{max}. If sufficient data are available, other PK parameters may be calculated. The C_{min} and C_{max} will be summarized by descriptive statistical methods for the Safety Run-in, Arm A, and Arm B. If there are sufficient data, then a population PK analysis of serum concentration-time data of daratumumab and JNJ-63723283 may be performed and may include data from other clinical studies. If performed, details will be provided in a population-PK analysis plan and the results of the analysis will be presented in a separate report.

9.4. Biomarker Assessments

Bone marrow and blood samples will be taken from all study subjects as outlined in the Time and Events Schedule for Biomarkers (Table 1). Bone marrow aspirate samples may be used to evaluate immune status and plasma cell expression of PD-L1 and CD38 in addition to depth of response through evaluation of MRD.

During the Daratumumab Monotherapy Period, no bone marrow and blood samples will be collected for central testing.

9.4.1. Biomarker Assays in Blood Samples

Blood samples will be obtained for biomarker evaluation from all eligible subjects. Whole blood immune profiling will be performed to explore immune markers associated with response or resistance to JNJ-63723283 and daratumumab. Samples will be processed to obtain plasma and serum for the determination of changes in blood-based biomarkers. Whole blood samples may be processed to obtain their derivatives (eg, RNA and DNA) and evaluated for immune-related, tumor type–related, and other exploratory biomarkers (eg, alterations in gene expression or clonal T-cell expansion). Currently, cytokine release syndrome has not been recognized as a known risk for PD-1 inhibitors or daratumumab. However, an unscheduled serum sample will be analyzed for selected cytokines (including but not limited to IFN gamma, TNF alpha, and IL-6) in the event of a suspected cytokine release syndrome. Also, based on emerging scientific evidence, the Sponsor may request additional blood samples for biomarker evaluation. In this case, such analyses will be limited to research related to the study drug(s) or diseases being investigated.

9.4.2. Minimal Residual Disease (MRD) Evaluation

Bone marrow aspirates will be collected to monitor MRD in those subjects who attain a CR/sCR. Minimal residual disease negativity is being evaluated as a potential surrogate for PFS and OS. Minimal residual disease will be monitored in subjects who achieve a CR/sCR using next generation sequencing (NGS) on bone marrow aspirate DNA. If this methodology is unavailable, or determined to be scientifically inferior, then alternative methods for MRD assessment may be utilized. Baseline bone marrow aspirates will be used to define the myeloma clones, and post-treatment samples collected as specified in the Time and Events Schedule will evaluate the MRD negativity. In cases where daratumumab is suspected of interfering with IFE and preventing clinical CR response calls, subjects with VGPR may also be evaluated for MRD. In the event fresh bone marrow aspirate will not be collected at Screening, non-decalcified diagnostic tissue (aspirate slides – smear or clot) should be collected to use as a baseline MRD sample.

9.4.3. Biomarker Bone Marrow Aspirate Evaluations

A portion of the bone marrow aspirate samples collected as specified in the Time and Events Schedule will be used to examine multiple myeloma cell expression of specific proteins presumed to be associated with immune-mediated ADCC/CDC/ADCP or other mechanisms of action of or resistance to JNJ-63723283 and daratumumab. Additionally, DNA or RNA may be extracted to determine whether specific mutations or molecular subgroups are responsive to the combination of JNJ-63723283 and daratumumab.

9.4.4. Stopping Analysis

Biomarker analyses are dependent upon the availability of appropriate biomarker assays and clinical response rates. Biomarker analysis may be deferred or not performed, if during or at the end of the study, it becomes clear that the analysis will not have sufficient scientific value for biomarker evaluation, or if there are not enough samples or responders to allow for adequate biomarker evaluation. In the event the study is terminated early or shows poor clinical efficacy, completion of biomarker assessments is based on justification and intended utility of the data.

9.4.5. Additional Collections

Based on emerging scientific evidence, the Sponsor may request additional material from previously collected tumor samples during or after study completion for a retrospective analysis. In this case, such analyses would be specific to research related to the study drug(s) or diseases being investigated.

9.5. Patient-reported Outcomes (Part 3)

The EORTC QLQ-C30 has been widely used among cancer patients and in prior multiple myeloma clinical trials. The EORTC QLQ-C30 includes 30 items resulting in 5 functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), 1 Global Health Status scale, 3 symptom scales (fatigue, nausea and vomiting, and pain), and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Reliability, validity, and clinically meaningful change have been demonstrated in multiple myeloma patients (Wisloff 1996; Wisloff 1997).[39,40] The focus of the PRO assessment will be the global health scale which is designated as a secondary endpoint. The remaining domains are included as exploratory endpoints.

The EQ-5D-5L is a standardized instrument for use as a measure of health status and utility. For purposes of this study, the EQ-5D-5L will be used to generate utility scores for use in cost effectiveness analyses. The EQ-5D-5L is a 5-item questionnaire that assesses 5 domains including mobility, self-care, usual activities, pain/discomfort and anxiety/depression plus a visual analog scale rating "health today" (Herdman 2011).[12]

Both questionnaires will be completed at the timepoints outlined in the Time and Events Schedule, for Part 3 only (see Attachment 10). All visit-specific PRO assessments should be conducted before any tests, procedures, or other consultations for that visit to prevent influencing subject perceptions.

9.6. Medical Resource Utilization (Part 3)

Medical resource utilization data will be collected to determine the medical cost impact of the two treatment arms that may be used to support the value story and cost-effectiveness modeling for market access. Medical resource utilization data associated with medical encounters, primarily hospitalizations, outpatient visits, and emergency department visits, will be collected in the eCRF by the investigator and study-site personnel for all subjects throughout the study. Protocol-mandated procedures, tests, and encounters are excluded. The data collected in Part 3 will include:

- Duration of hospitalization (total length of stay, including duration by each hospital unit)
- Number and character of diagnostic and therapeutic tests and procedures
- Outpatient medical encounters (including physician, nurse practitioner or emergency department visits, tests and procedures)

9.7. Safety Evaluations

Safety will be assessed by the incidence and severity of adverse events, laboratory test results, ECGs, vital sign measurements, physical examination findings, ECOG performance status score, and other evaluations, as described in the Time and Events Schedule (Table 1). Toxicities will be graded according to the NCI-CTCAE Version 4.03. Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the CRF. Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached.

Based on the previous human experience with daratumumab, in vitro studies, and animal toxicological findings, infusion-related reactions/allergic reactions, hemolysis, and thrombocytopenia will be closely monitored. Immune-related risks have been identified with other anti-PD-1 antibodies and this will be closely monitored. As JNJ-63723283 and daratumumab are both biologic agents, immunogenicity also will be monitored. Any of the safety monitoring assessments may be performed more frequently, and adverse events should be evaluated by the investigator according to the standard practice, if clinically indicated.

Adverse Events

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) for the duration of the study. Adverse events will be followed by the investigator as specified in Section 12, Adverse Event Reporting.

Clinical Laboratory Tests

Blood samples for clinical laboratory evaluation will be collected. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the CRF. The laboratory reports must be filed with the source documents.

The following tests will be performed by the local laboratory, unless otherwise specified:

Hematology	
– Hemoglobin	– White blood cell (WBC) – Absolute neutrophil count (ANC) – Absolute lymphocyte count (ALC) – Platelet count
Coagulation	
– Prothrombin time/International Normalized Ratio	– Activated partial thromboplastin time
Chemistry	
– Sodium – Potassium – Creatinine – Aspartate aminotransferase (AST) – Alanine aminotransferase (ALT)	– Total bilirubin[b] – Alkaline phosphatase – Calcium – Amylase, lipase

Other Tests	
Thyroid panel[a] – Thyroid stimulating hormone (TSH) – Triiodothyronine (free T3; total) – Free thyroxine (free T4)	Serology (hepatitis B, hepatitis C) and HCV Viral Load: – Hepatitis B: HBsAg, anti-HBc – Hepatitis C: anti-HCV; HCV RNA PCR, if necessary
Pregnancy Test (for women of childbearing potential only) – serum (<5 IU/mL) β-hCG at Screening; serum or urine thereafter as clinically indicated	

a. At baseline. If normal, then only TSH thereafter.
b. Direct bilirubin if Gilbert's disease.

During the Daratumumab Monotherapy Period, limited laboratory tests will be required as per the Time & Events Schedule (Table 24), but reporting in the eCRF is not required.

The following clinical laboratory tests will be performed by the local laboratory during treatment in the Daratumumab Monotherapy Period:

Hematology	
– Hemoglobin	– White blood cell (WBC) – Absolute neutrophil count (ANC) – Absolute lymphocyte count (ALC) – Platelet count
Chemistry	
– Sodium – Potassium – Creatinine – Aspartate aminotransferase (AST)	– Total bilirubin[b] – Alkaline phosphatase – Calcium – Alanine aminotransferase (ALT)

Indirect Antiglobulin Test (IAT) results

Blood group, type, and indirect antiglobulin test (IAT) should be assessed before the first dose of daratumumab. Subject red blood cell (RBC) phenotyping (standard or extended) is an alternative option to the IAT test, if locally required. Either must be completed prior to first daratumumab infusion.

Daratumumab interferes with the IAT, which is a routine pre-transfusion test performed to identify a subject's antibodies to minor antigens so that suitable donor blood can be given for transfusion. Daratumumab does not interfere with ABO/RhD typing. CD38 is expressed at very low levels on erythrocytes. Daratumumab binds to the CD38 on erythrocytes, which results in a positive IAT (Indirect Coombs Test). This positive result masks the detection of antibodies to minor antigens and may prevent or delay blood banks from issuing donor blood for transfusion. This effect occurs during daratumumab treatment and for up to 6 months after treatment ends. Subjects will receive a patient identification wallet card for the study that includes the blood profile (ABO, Rh, and IAT or phenotyping) determined before the first infusion of daratumumab along with information on the IAT interference for healthcare providers/blood banks. Subjects are to carry this card throughout the treatment period and for at least 6 months after treatment

ends. Blood banks can eliminate the daratumumab interference with IAT by treating reagent RBCs with dithiothreitol (DTT) (Chapuy 2015).[8]

Possible methods for blood banks to provide safe RBCs for transfusion to subjects receiving daratumumab include:

a. Providing ABO/RhD compatible, phenotypically (standard or extended phenotyping) or genotypically matched units
b. Providing ABO/RhD compatible, K-negative units after ruling out or identifying alloantibodies using DTT-treated reagent RBCs

Uncrossmatched, ABO/RhD compatible RBC units should be administered if transfusion is needed emergently as per local blood bank practice.

Despite daratumumab binding to CD38 on erythrocytes, no indication of clinically significant hemolysis has been observed in daratumumab studies. For additional details, refer to the Daratumumab Investigator's Brochure.

Pulmonary Function Test

Subjects with known or suspected COPD must have a FEV1 test during Screening. Refer to Section 6.2.4.7 of the protocol for details on subjects with higher risk of respiratory complications.

Electrocardiogram:

A 12-lead ECG will be performed at Screening and at End-of-Treatment; and as clinically indicated. During the collection of ECGs, subjects should be in a quiet setting without distractions (eg, television, cell phones). Subjects should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. If blood sampling or vital sign measurement is scheduled for the same timepoint as ECG recording, the procedures should be performed in the following order: ECG(s), vital signs, blood draw. Clinically significant abnormalities will be recorded as adverse events in the appropriate CRF.

Vital Signs

Temperature, pulse, and blood pressure will be performed as specified in the Time and Events Schedule (Table 1). Clinically significant abnormalities will be recorded as adverse events in the appropriate CRF. Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

Physical Examination and ECOG performance status

A complete physical examination should be performed during the Screening Phase. Thereafter, only a symptom directed physical examination is required. Height will be measured at Screening only; weight will be measured at Screening and as specified in Time and Events schedule. Abnormalities will be recorded in the appropriate section of the CRF. ECOG performance status will be used to evaluate the effect of the disease status on the activities of daily living (Attachment 5). When scheduled, ECOG assessments should be obtained prior to any other study procedures planned for the same day.

9.8. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the CRF or laboratory requisition form. Refer to the Time and Events Schedules for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the Laboratory Manual. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the Laboratory Manual.

10. DISCONTINUATION OF STUDY TREATMENT/ WITHDRAWAL FROM THE STUDY

10.1. Discontinuation of Study Treatment/Withdrawal from the Study

Discontinuation of Study Treatment

A subject will not be automatically withdrawn from the study if he or she has to discontinue treatment. The End-of-Treatment Visit and Follow-up visit assessments should continue as specified in the Time and Events Schedules.

A subject's study treatment must be discontinued if:

- The investigator believes that for safety reasons or tolerability reasons (eg, adverse event) it is in the best interest of the subject to discontinue study treatment
- The subject becomes pregnant
- The subject withdraws consent for administration of study treatment
- The subject experiences unacceptable toxicity, including IRRs described in Section 6.3
- The subject missed more than 3 consecutive planned daratumumab doses with a delay up to 4 weeks at Cycles 1 to 6 and up to 6 weeks beyond Cycle 6, due to daratumumab-related AEs
- The subject missed more than 12 weeks of planned does of JNJ-63723283 due to JNJ-63723283-related AEs

- For subjects whose JNJ-63723283 treatment is discontinued, they may continue to receive daratumumab alone. For subjects whose daratumumab is discontinued, JNJ-63723283 treatment should also be discontinued.
- The subject experiences confirmed disease progression per IMWG. However, subjects in either Arm A or Arm B may continue treatment in the setting of clinical benefit with Sponsor approval.
- A subject who experiences a second primary malignancy that cannot be treated by surgery alone must be withdrawn from the study. However, a subject who develops a malignancy that may be cured surgically may continue to receive the assigned study treatment and should continue to be followed for subsequent progression of multiple myeloma.

The primary reason for discontinuation of study treatment is to be recorded in the CRF.

Withdrawal from the Study

A subject will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent to study participation
- Pregnancy
- Second primary malignancy (see Discontinuation of Study Treatment for additional details)
- Death
- The study investigator, for any reason, stops the subject's participation in the study
- Sponsor terminated the study

Before a subject is lost to follow-up, every reasonable effort must be made by the study-site personnel to contact the subject and determine the reason for discontinuation/withdrawal. The measures taken to follow up must be documented.

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the CRF and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw will not be replaced. If a subject discontinues from treatment, end-of-treatment assessments should be obtained.

10.1.1. Discontinuation of Study Treatment in Daratumumab Monotherapy Period

A subject's study treatment must be discontinued if:

- The investigator believes that for safety reasons or tolerability reasons (eg, adverse event) it is in the best interest of the subject to discontinue study treatment
- The subject becomes pregnant
- The subject withdraws consent for administration of study treatment
- The subject experiences unacceptable toxicity, including IRRs described in Section 6.3

- The subject missed more than 3 consecutive planned daratumumab doses with a delay up to 4 weeks at Cycles 1 to 6 and up to 6 weeks beyond Cycle 6, due to daratumumab-related AEs
- The subject experiences disease progression.
- A subject who experiences a second primary malignancy that cannot be treated by surgery alone must be withdrawn from the study. However, a subject who develops a malignancy that may be cured surgically may continue to receive the assigned study treatment and should continue to be followed for subsequent progression of multiple myeloma.

The End-of-Treatment Visit assessments should continue as specified in the Time and Events Schedule (Table 24).

End of Study

Subjects will discontinue the study upon completion of the End of Treatment Visit.

Withdrawal from the Study

Prior to the End of Treatment Visit, a subject will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent to study participation
- Pregnancy
- Second primary malignancy (see Discontinuation of Study Treatment for additional details)
- Death
- The study investigator, for any reason, stops the subject's participation in the study
- Sponsor terminated the study

Before a subject is lost to follow-up, every reasonable effort must be made by the study-site personnel to contact the subject and determine the reason for discontinuation/withdrawal. The measures taken to follow up must be documented.

10.2. Study Termination for Safety Considerations

As described in Section 17.9.2, the Sponsor reserves the right to terminate the study at any time. Reasons for terminating the study because of safety issues and not proceeding to Part 3, may include, but are not limited to the following:

- The incidence or severity of adverse events indicates a potential health hazard to subjects, including a higher incidence of Grade ≥3 irAEs and Grade 4 or 5 drug-related adverse events compared with marketed anti-PD-1 products as well as in the ongoing single-agent Phase 1 study (637232283LUC1001).

The final decision to terminate the study will be based on the totality of the benefit/risk assessment. Procedures for managing toxicities, including irAEs, are described in Section 6.

10.3. Withdrawal from the Use of Research Samples

A subject who withdraws from the study will have the following options regarding the optional research samples:

- The collected samples will be retained and used in accordance with the subject's original informed consent for optional research samples.
- The subject may withdraw consent for optional research samples, in which case the samples will be destroyed and no further testing will take place. To initiate the sample destruction process, the investigator must notify the Sponsor study site contact of withdrawal of consent for the optional research samples and to request sample destruction. The Sponsor study site contact will, in turn, contact the biomarker representative to execute sample destruction. If requested, the investigator will receive written confirmation from the Sponsor that the samples have been destroyed.

Withdrawal from the Use of Samples in Future Research

The subject may withdraw consent for use of samples for research (refer to Section 16.2.5, Long-Term Retention of Samples for Additional Future Research). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF and in the separate ICF for optional research samples.

11. STATISTICAL METHODS

Statistical analysis will be done by the Sponsor or under the authority of the Sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan.

11.1. Subject Information

Safety will be evaluated for all subjects who have received at least 1 dose of study drug (JNJ-63723283 or daratumumab) in any part of the study. The subjects in the Safety Run-in cohort may be included in the efficacy analyses and listed separately. The pharmacokinetic analyses will be performed on the population described in Section 11.4.

Part 2:

The primary analysis population for the efficacy endpoints will be the intent-to-treat (ITT) population, which will include all randomized subjects in Part 2.

Part 3:

The primary analysis population for the efficacy endpoints will be the ITT population, which will include all randomized subjects in Part 3.

11.2. Sample Size Determination

Part 2:

Assuming the ORR for daratumumab monotherapy is approximately 30% and the addition of JNJ-63723283 improves ORR by 20%, approximately 80 subjects will be randomized in a 1:1 ratio to achieve at least 70% power with a 2-sided alpha of 0.20 to reject the null hypothesis that there is no difference in ORR between the 2 treatment arms.

Part 3:

Assuming a median PFS of 4 months for the daratumumab monotherapy group (Lokhorst 2015; Lonial 2016)[21,22] and a 33% reduction in risk of disease progression or death for the combination group (hazard ratio=0.67; median PFS=6 months), 230 PFS events are needed to achieve a power of 85% using a log-rank test with a 2-sided alpha of 0.05. With a 12-month accrual period and an additional 6-month follow-up, the sample size needed for the study is approximately 300 (150/treatment group) subjects.

Long-term survival follow-up will continue until 205 deaths have been observed. Therefore, Part 3 of this study will achieve approximately 80% power to detect a 33% reduction in the risk of death (hazard ratio=0.67) with a log-rank test (2-sided alpha=0.05).

11.3. Efficacy Analyses

Response to study treatment and progressive disease will be evaluated by a validated computer algorithm. Efficacy analyses will be performed separately for Part 2 and Part 3 of this study.

Part 2:

The primary endpoint, ORR, will be tabulated, and its two-sided 95% exact confidence interval will also be presented. For the calculation of ORR, those subjects who are not evaluable for response will be considered as non-responders In addition, the number and percentage of subjects in each response category will also be tabulated.

For time-to-event endpoints (PFS, OS, and duration of response), Kaplan-Meier estimates of the survival functions will be presented. For PFS and OS, treatment comparison will be made via a log-rank test. Cox's regression will be performed to obtain the hazard ratio estimate and the corresponding 95% CI, which will be used as a measure for treatment effect. Additional Cox's regression may be performed to include appropriate baseline prognostic variables.

Part 3:

For the primary endpoint of PFS, the primary analysis will consist of a stratified log-rank test for the comparison of the PFS distribution between the 2 treatment groups. The Kaplan-Meier method will be used to estimate the distribution of overall PFS for each treatment. The treatment effect (hazard ratio) and its two-sided 95% confidence intervals are to be estimated using a stratified Cox regression model with treatment as the sole explanatory variable.

Duration of response will be provided descriptively using the Kaplan-Meier method without formal statistical comparison. Other time-to-event efficacy endpoints will be analyzed similarly.

Comparison between the 2 treatment groups for ORR and other binary endpoints will be conducted using the stratified Cochran-Mantel-Haenszel test. The Mantel-Haenszel odds ratio will be provided along with its two-sided 95% confidence interval.

A multiplicity adjustment strategy will be implemented to control the overall family wise type I error rate for the Phase 3 part of this study. Additional details will be provided in the Statistical Analysis Plan.

11.4. Pharmacokinetic Analyses

Pharmacokinetic analyses will be performed on the PK-evaluable population, defined as subjects who have received at least 1 dose of daratumumab or JNJ-63723283 and have at least 1 postinfusion sample.

All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration database. Concentrations below the lowest quantifiable concentration will be treated as zero in the summary statistics. The number of subjects and samples excluded from the analysis will be clearly documented in the Clinical Study Report.

Descriptive statistics will be used to summarize daratumumab and JNJ-63723283 serum concentrations at each sampling time point. C_{min} is defined as the minimal concentration observed immediately before infusion and C_{max} is defined as the maximum concentration observed at the end of infusion, as presented in the summary of serum concentration by sampling time point. Other PK parameters, if available, may also be summarized.

If sufficient data are available, population-PK analysis of serum concentration-time data of daratumumab or JNJ-63723283 may be performed and may be combined with data from other studies. If the population-PK analysis is conducted, details will be given in a population-PK analysis plan and the results of the analysis will be presented in a separate report.

11.5. Immunogenicity Analyses

The incidence of anti-JNJ-63723283 and anti-daratumumab antibodies will be summarized for all subjects who receive at least 1 dose of JNJ-63723283 and daratumumab and have appropriate serum samples for detection of antibodies to JNJ-63723283 and daratumumab (ie, subjects with at least 1 sample obtained after their first dose). In addition, subjects who are positive for antibodies to JNJ-63723283 or daratumumab will be listed.

Other immunogenicity analyses may be performed to further characterize the immune responses that are generated.

11.6. Biomarker Analyses

Biomarker analyses will be stratified by clinical covariates or molecular subgroups using the appropriate statistical methods (eg, parametric or non-parametric, univariate or multivariate,

analysis of variance, or survival analysis, depending on the endpoint). Correlation of baseline expression levels or changes in expression levels with response to time-to-event endpoints will identify responsive (or resistant) subgroups in addition to genes and pathways attenuated following treatment with daratumumab.

Any pharmacodynamic measures will be listed, tabulated, and where appropriate, plotted. Subjects may be grouped by cohort, dose schedule, or clinical response. Results of biomarker and pharmacodynamic analyses may be presented in a separate report. Planned analyses are based on the availability of clinically valid assays and may be deferred if emerging study data show no likelihood of providing useful scientific information.

11.7. Pharmacokinetic/Pharmacodynamic Analyses

If sufficient data are available, then other pharmacokinetic/pharmacodynamic modeling may be performed, including exploring the relationship between serum concentrations of daratumumab and/or JNJ-63723283 and endpoints of clinical efficacy and safety. If performed, details and results of the analysis will be presented in a separate report.

11.8. Patient-reported Outcomes Analyses (Part 3)

The EORTC-QLQ-C30 scale scores, EQ-5D-5L utility value, and EQ-5D-5L VAS will be summarized at each timepoint, by treatment arm. Within-group and between-group treatment effect on the PRO endpoints will be assessed by change from baseline using mixed models for repeated measures.

11.9. Medical Resource Utilization Analyses (Part 3)

Medical resource utilization will be descriptively summarized by treatment group. Additional analyses may be conducted; details and results of any additional analyses will be presented in a separate report.

11.10. Safety Analyses

Safety data from each part of this study may be combined as deemed appropriate.

Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events are adverse events with onset during the treatment phase or that are a consequence of a pre-existing condition that has worsened since baseline. All reported adverse events will be included in the analysis. For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group. In addition, comparisons between treatment groups will be provided if appropriate.

Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an adverse event, or who experience a severe or a serious adverse event.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the Statistical Analysis Plan) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled timepoint. Changes from baseline results will be presented in pre- versus posttreatment cross-tabulations (with classes for below, within, and above normal ranges). A listing of subjects with any laboratory results outside the reference ranges will be provided. A listing of subjects with any markedly abnormal laboratory results will also be provided.

Parameters with predefined NCI-CTCAE toxicity grades will be summarized. Change from baseline to the worst adverse event grade experienced by the subject during the study will be provided as shift tables.

Electrocardiogram

Electrocardiogram data will be summarized based on categories of normal, abnormal either clinically significant or not clinically significant and listed.

Vital Signs

Descriptive statistics of temperature, pulse/heart rate, and blood pressure (systolic and diastolic) values and changes from baseline will be summarized at each scheduled timepoint. The percentage of subjects with values beyond clinically important limits will be summarized.

11.11. Interim Analyses for Part 3

For PFS, one interim analysis is planned. The interim analysis will be performed when 138 PFS events, which is 60% of the total planned PFS events, have been accumulated. The purpose of this interim analysis is to evaluate interim efficacy data. The significance level at this interim analysis will be calculated based on the observed number of PFS events at the interim analysis, using the O'Brien-Fleming boundaries as implemented by the Lan-DeMets alpha spending method. Assuming 138 (60%) PFS events are observed, the alpha to be spent in this interim analysis will be 0.00762 2-sided). If the observed PFS hazard ratio is greater than 1, favoring the daratumumab group, the study may be terminated for futility.

For OS, 2 interim analyses are planned. The timing of these analyses corresponds to that of PFS interim and final analyses, respectively; the final OS analysis will occur after 205 deaths have been observed. At the first interim analysis, an alpha of 0.0001 will be spent. For the second interim analysis and final analysis, the alpha to be spent will be determined by a linear alpha spending function based on the observed number of deaths at that time, ie, the cumulative alpha to be spent will be the total alpha (0.05) multiplied by the proportion of the observed number of deaths out of the total planned number of deaths (205). It is noted that, even if the significance of PFS has already been established, testing of OS may continue as planned until a definitive conclusion on OS is reached.

11.12. Statistical Methods Effective Protocol Amendment 2

As of 25 May 2018, the Sponsor terminated further enrollment into this study and subjects continuing study will receive daratumumab monotherapy. Since the total number of subjects treated in this study is small, no formal statistical hypothesis testing will be performed. A descriptive data summary will be provided only for all subjects who received study medication. Subject information will be summarized or listed for all treated subjects. Subject narratives may be provided, as appropriate. Safety assessment data (AEs, Laboratory values, vital signs etc.) will be listed for each subject.

12. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the Sponsor, and are mandated by regulatory agencies worldwide. The Sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the Sponsor or its affiliates will be conducted in accordance with those procedures.

Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting adverse events or serious adverse events. Open-ended and nonleading verbal questioning of the subject is the preferred method to inquire about adverse event occurrence.

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

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

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

Note: The Sponsor collects adverse events starting with the signing of the ICF (refer to Section 12.3.1, All Adverse Events, for time of last adverse event recording).

Serious Adverse Event

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

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

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

If a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the study drug and the event (eg, death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

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 JNJ-63723283 and daratumumab, the expectedness of an adverse event will be determined by whether or not it is listed within the Reference Safety Information in the Investigator's Brochures.

Adverse Event Associated With the Use of the Drug

An adverse event is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed in Section 12.1.2, Attribution Definitions.

12.1.2. Attribution Definitions

Not Related

An adverse event that is not related to the use of the drug.

Doubtful

An adverse event for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An adverse event that might be due to the use of the drug. An alternative explanation, eg, concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An adverse event that might be due to the use of the drug. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).

Very Likely

An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

12.1.3. Severity Criteria

The severity assessment for an adverse event or serious adverse event should be completed using the NCI-CTCAE Version 4.03 Any adverse event or serious adverse event not listed in the NCI-CTCAE Version 4.03 will be graded according to investigator clinical judgment by using the standard grades as follows:

Grade 1 (Mild): Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities

Grade 2 (Moderate): Sufficient discomfort is present to cause interference with normal activity

Grade 3 (Severe): Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities

Grade 4: Life-threatening or disabling adverse event

Grade 5: Death related to the adverse event

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (eg, laboratory abnormalities).

12.2. Special Reporting Situations

Safety events of interest on a Sponsor study drug that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a Sponsor study drug
- Suspected abuse/misuse of a Sponsor study drug
- Accidental or occupational exposure to a Sponsor study drug
- Medication error involving a Sponsor product (with or without subject/patient exposure to the Sponsor study drug, eg, name confusion)
- Exposure to a Sponsor study drug from breastfeeding

Special reporting situations should be recorded in the CRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page of the CRF.

12.3. Procedures

12.3.1. All Adverse Events

All adverse events and special reporting situations will be reported from the time a signed and dated ICF is obtained until 30 days after the last dose of study drug, or until start of subsequent anticancer therapy or the subject withdraws consent for study participation, if earlier, which may include contact for follow-up of safety. For subjects who have received subsequent treatment with therapeutic intent for multiple myeloma during the adverse event reporting period, only adverse events that are considered to be possibly, probably, or definitely related to JNJ-63723283 or daratumumab need to be reported. Serious adverse events, including those spontaneously reported to the investigator, must be reported using the Serious Adverse Event Form. Serious adverse events considered by the investigator to be related to JNJ-63723283 or daratumumab should continue to be reported during the follow-up period. The Sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Disease progression should not be recorded as an adverse event or serious adverse event term; instead, clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the serious adverse event definition (refer to Section 12.1.1). Death should not be recorded as an adverse event or serious adverse event, but as the outcome of an adverse event. The adverse event that resulted in the death should be reported as a serious adverse event. All events that meet the definition of a serious adverse event will be reported as serious adverse events, regardless of whether they are protocol-specific assessments. Anticipated events will be recorded and reported as described in Attachment 9.

All adverse events, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to Sponsor instructions.

The Sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The Sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). For anticipated events reported as individual serious adverse events the Sponsor will make a determination of relatedness in addition to and independent of the investigator's assessment. The Sponsor will periodically evaluate the accumulating data and, when there is sufficient evidence and the Sponsor has determined there is a reasonable possibility that the drug caused a serious anticipated event, they will submit a safety report in narrative format to the investigators (and the head of the institute).

The investigator (or Sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

Subjects (or their designees, if appropriate) will be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the subject is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local Sponsor's name and 24-hour contact telephone number (for medical staff only)
- Site number
- Subject number
- Blood type and IAT (as described in Section 9.7)

12.3.1.1. Daratumumab Monotherapy Period

Non-serious adverse events will not be reported during the daratumumab monotherapy period. However, SAEs (including SPMs) must be reported continuously from time of ICF until EOT Visit or until the subject withdraws consent for study participation or until the subject starts subsequent anticancer therapy whichever occurs first. Beyond the EOT Visit reporting period after the last dose of study medication, information on SAEs, including SPMs, considered possibly, probably or definitely related to study drug will continue to be collected.

Serious Adverse Event reporting after the final database lock, established once Protocol Amendment 2 is implemented at all sites, will be limited to SAE reporting into the Sponsor's global safety database, using SAE Form (paper form) faxed to Sponsor's Local Operational Company/Local Safety Officer.

SAEs (see Section 12.3.2) should include information on study agent administration and concomitant medications associated with an SAE**.**

12.3.2. Serious Adverse Events

All serious adverse events occurring during the study must be reported to the appropriate Sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Information regarding serious adverse events will be transmitted to the Sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site, and transmitted to the Sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be made by facsimile (fax).

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

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as a serious adverse event. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a study must be reported as a serious adverse event, except hospitalizations for the following:

- If the subject has not experienced a significant medical event but is hospitalized overnight only for observation following infusion of JNJ-63723283 or daratumumab, then the hospitalization should not be reported as a serious adverse event. A standard procedure for protocol therapy administration will not be reported as a serious adverse event. In addition, hospitalization due to a longer than anticipated infusion time. Hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as a serious adverse event.
- Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the CRF). Note: Hospitalizations that were planned before the signing of the ICF, 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.
- The administration of blood or platelet transfusions. Hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable serious adverse event.

- A procedure for protocol-related investigations (eg, surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling, pharmacokinetic, or biomarker blood sampling). Hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable serious adverse event.

12.3.3. Pregnancy

All initial reports of pregnancy in female subjects or partners of male subjects must be reported to the Sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study treatment.

Pregnancies in partners of male subjects included in the study will be reported as noted above, because the effect of the study drugs on sperm is unknown.

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

12.4. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

13. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. 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 subjects, investigators, and the Sponsor, and are mandated by regulatory agencies worldwide. The Sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the Sponsor or its affiliates will be conducted in accordance with those procedures.

13.1. Procedures

All initial PQCs must be reported to the Sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with a serious adverse event, the study-site personnel must report the PQC to the Sponsor according to the serious adverse event reporting timelines (refer to Section 12.3.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the Sponsor.

13.2. Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed in the Contact Information page(s), which will be provided as a separate document.

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drug(s)

The daratumumab supplied for this study is a colorless to yellow liquid and sterile concentrate of 20 mg/mL in a vial for IV administration. It will be manufactured and provided under the responsibility of the Sponsor. JNJ-63723283 is a colorless to yellow frozen liquid and sterile concentrate of 10 mg/mL in a vial for IV administration. Refer to the respective Investigator's Brochures for a list of excipients.

Manufacturing changes to the JNJ-63723283 drug substance and drug product used in this study are being proposed to support ongoing clinical development. During this study the drug product (DP-1) will be changed from a frozen liquid in vial, to a lyophilized drug product (DP-2). Additionally, a new cell line for the drug substance for DP-2 was developed to remove an unprocessed signal peptide variant; however, the host cell line and the core amino acid sequence of the JNJ-63723283 monoclonal antibody remains unchanged. Comprehensive nonclinical comparability studies will be performed to assess the biochemical, biophysical, and biological characteristics of DP-2 to ensure that there is no impact on subject safety and product quality. The drug substance and drug product manufacturing changes along with the results of the comparability studies will be submitted to the Health Authorities prior to the introduction of DP-2 into the clinical program. Part 1 of this study will start with DP-1. Once the comparability amendment is approved by the Health Authorities, DP-2 will be incorporated into the study, which is anticipated to be prior to initiating Part 3.

14.2. Packaging

JNJ-63723283 is supplied in glass vials containing JNJ-63723283 at a concentration of 10 mg/mL. Daratumumab is supplied in glass vials containing daratumumab at a concentration of 20 mg/mL.

14.3. Labeling

Study drug labels will contain information to meet the applicable regulatory requirements. Each vial will contain a study-specific label with a unique identification number.

14.4. Preparation, Handling, and Storage

JNJ-63723283 must be stored frozen -40C and protected from light. Daratumumab must be stored in the original carton in a refrigerator at controlled temperatures ranging from 2°C to 8°C, protected from light and must not be frozen.

Study drug must not be utilized after the expiry date printed on the label. JNJ-63723283 and daratumumab do not contain preservatives; therefore, any unused portion remaining in the vial must be discarded.

Refer to the SIPPM and IPPI for additional guidance on study drug preparation, handling, and storage.

14.5. Drug Accountability

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The study drug administered to the subject must be documented on the drug accountability form. All study drug will be stored and disposed of according to the Sponsor's instructions. Study-site personnel must not combine contents of the study drug containers.

Study drug must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study drug must be available for verification by the Sponsor's study site monitor during on-site monitoring visits. The return to the Sponsor of unused study drug will be documented on the drug return form. When the study site is an authorized destruction unit and study drug supplies are destroyed on-site, this must also be documented on the drug return form.

Potentially hazardous materials such as used ampules, needles, syringes and vials containing hazardous liquids, should be disposed of immediately in a safe manner and therefore will not be retained for drug accountability purposes.

Study drug should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study drug will be administered only to subjects participating in the study. Returned study drug must not be dispensed again, even to the same subject. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the Sponsor.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Investigator’s Brochures for JNJ-63723283 and daratumumab
- Site Investigational Product Procedures Manual (SIPPM)
- Investigational Product Preparation Instructions (IPPI)
- Laboratory manual
- IWRS manual
- eCRF completion guidelines

- Sample ICF
- Subject identification wallet card, including space for blood group/type and IAT result
- Subject diaries may be used for recording predose and postdose medications administered at home for the prevention of IRRs
- PRO questionnaires
- Other manuals and guidance documents as needed

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

This is the first clinical evaluation of JNJ-63723283 in combination with daratumumab in multiple myeloma subjects; hence, the benefits and risks of the combination in this population are unknown. However, as described in Section 1, subjects in clinical studies of JNJ-63723283 and daratumumab, as single agents, have shown safety issues including irAEs and IRRs, which will be monitored and managed with rapid intervention. Subjects will be closely monitored throughout the study, as discussed throughout this protocol, for both safety and clinical benefit. Subjects in both arms will receive daratumumab, which is approved for this study population in many regions (see Section 1.3 for an overview of the efficacy and safety results). As discussed in Section 1.4, based on the known data and the mechanism of action of both study drugs, there is adequate justification, including significant unmet clinical need, for evaluating these drugs in combination for the treatment of multiple myeloma in subjects who are eligible for this study. Daratumumab leads to the elimination of highly immunosuppressive subsets of CD38+ Tregs, CD38+ MDSCs, and CD38+ Bregs and induces clonal T cell expansion (Krejcik 2016).[17] This shift away from an immunosuppressive environment may lead to the generation of protective immune responses, which may be further potentiated by PD-1 blockade with JNJ-63723283, potentially leading to improved clinical responses.

Additionally, all subjects will undergo periodic disease assessments to monitor the underlying disease. The frequency of evaluations is similar to standard practice for patients outside of clinical trials and the overall risk is low. Subjects will have pre- and posttreatment bone marrow aspirations. In general, these procedures are routinely performed during a subject's diagnostic workup and follow-up care. Although bone marrow aspirate collection is associated with risk, the complication rate for these procedures is low. The data obtained from this procedure will generate valuable scientific data on the pharmacodynamic effect of the combination of these study drugs in multiple myeloma subjects.

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. They will be informed that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled.

The blood volume collection for a subject is estimated at approximately 35 mL/month. This blood volume is not burdensome and falls within the normal range of a single blood donation.

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

16.2.2. Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or Sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the subjects)
- Investigator's Brochure (or equivalent information) and amendments/addenda
- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the Sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and subject compensation programs, and the Sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study the investigator (or Sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the Sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- New edition(s) of the Investigator's Brochures and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of adverse events that are serious, unlisted/unexpected, and associated with the study drug
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the investigator (or Sponsor where required) will notify the IEC/IRB about the study completion (if applicable, the notification will be submitted through the head of investigational institution).

16.2.3. Informed Consent

Each subject or a legally acceptable representative must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the Sponsor and by the reviewing IEC/IRB and be in a language that the subject can read and understand. The informed consent should be in accordance with principles that originated in

the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and Sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential subjects or their legally acceptable representatives the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of his or her disease. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized Sponsor personnel without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject or legally acceptable representative is authorizing such access, which includes permission to obtain information about his or her survival status. It also denotes that the subject agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, and subsequent disease-related treatments, if needed.

The subject or legally acceptable representative will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of either the subject's or his or her legally acceptable representative's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject.

If the subject or legally acceptable representative is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the subject or legally acceptable representative is obtained.

When prior consent of the subject is not possible and the subject's legally acceptable representative is not available, enrollment procedures should be described in the protocol with documented approval/favorable opinion by the IEC/IRB to protect the rights, safety, and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or legally acceptable representative must be informed about the study as soon as possible and give consent to continue.

16.2.4. Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized

disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

The informed consent obtained from the subject or his or her legally acceptable representative includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The subject has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Exploratory biomarker research is not conducted under standards appropriate for the return of data to subjects. In addition, the Sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to subjects or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

16.2.5. Long-Term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand daratumumab and JNJ-63723283, to understand multiple myeloma, to understand differential drug responders, and to develop tests/assays related daratumumab and JNJ-63723283, and multiple myeloma. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Subjects may withdraw their consent for their samples to be stored for research (refer to Section 10.2, Withdrawal from the Use of Samples in Future Research).

16.2.6. Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 16.1, Study-Specific Design Considerations.

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

Neither the investigator nor the Sponsor will modify this protocol without a formal amendment by the Sponsor. All protocol amendments must be issued by the Sponsor, and signed and dated

by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the Sponsor. When the change(s) involves only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate Sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the Sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

17.2.2. Required Prestudy Documentation

The following documents must be provided to the Sponsor before shipment of study drug to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable

- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the Sponsor before enrollment of the first subject:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

17.3. Subject Identification, Enrollment, and Screening Logs

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the Sponsor study-site contact for completeness.

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification and date of birth. In cases where the subject is not enrolled or randomized into the study, the date seen and date of birth will be used.

The investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

17.4. Source Documentation

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: subject identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; concomitant medication; drug receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The minimum source documentation requirements for Section 4.1, Inclusion Criteria and Section 4.2, Exclusion Criteria that specify a need for documented medical history are as follows:

- Referral letter from treating physician or
- Complete history of medical notes at the site
- Discharge summaries

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by subject interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

An electronic source system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the Sponsor. If the electronic source system is utilized, references made to the CRF in the protocol include the electronic source system but information collected through the electronic source system may not be limited to that found in the CRF. Data in this system may be considered source documentation.

17.5. Case Report Form Completion

Electronic Data Capture (eDC) will be used for this study. Case report forms (CRF) are provided for each subject in electronic format. Study site personnel must log in eDC via a secure manner - personal password. The individual password must keep confidential for personal use.

The study data will be transcribed by study-site personnel from the source documents onto an CRF according to CRF completion guideline provided by the Sponsor. Data must be entered into CRFs in English. The CRF must be completed as soon as possible after a subject visit and the forms should be available for review at the next scheduled monitoring visit. Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the subject's source documentation.

All subjective measurements (eg, pain scale information or other questionnaires) shall be completed by the same individual who made the initial baseline determinations whenever possible. The investigator must verify that all data entries in the CRFs are accurate and correct.

All CRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel. If necessary, queries will be generated in the eDC tool. The investigator or study-site personnel must address the queries and update the CRF if applicable.

If necessary, queries will be generated in the eDC tool. If corrections to a CRF are needed after the initial entry into the CRF, this can be done in either of the following ways:

- Investigator and study-site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or Sponsor delegate can generate a query for resolution by the investigator and study-site personnel.

Daratumumab Monotherapy Period:

Data collection will be limited to SAE reporting into the Sponsor's global safety database.

No data will be entered in eCRF once Protocol Amendment 2 is implemented at a site. Once Protocol Amendment 2 is implemented at all sites, clinical database can be locked.

17.6. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, and periodic monitoring visits by the Sponsor, and direct transmission of clinical laboratory data from a central laboratory into the Sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for CRF completion will be provided and reviewed with study-site personnel before the start of the study. The Sponsor will review CRF for accuracy and completeness during on-site monitoring visits and after transmission to the Sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

17.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRF and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the Sponsor.

If it becomes necessary for the Sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

17.8. Monitoring

The Sponsor will use a combination of monitoring techniques central, remote, or on-site monitoring to monitor this study.

The Sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the CRF with the source documents (eg, hospital/clinic/physician's office medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the Sponsor and study-site personnel and are accessible for verification by the Sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The Sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site. Central monitoring will take place for data identified by the Sponsor as requiring central review.

Daratumumab Monotherapy Period:

Monitoring will be limited to on-site monitoring visits and remote contacts for the verification and follow-up of SAEs reported to the Sponsor.

17.9. Study Completion/Termination

17.9.1. Study Completion/End of Study

The end of the study in Part 1 and Part 2 is anticipated to be approximately 6 to 12 months after the last patient has been enrolled (last patient in) and the study may be extended to allow for follow-up of subjects. The end of the study in Part 3 will occur when 205 deaths have been documented. The final data from the study site will be sent to the Sponsor (or designee) after completion of the final subject assessment at that study site, in the time frame specified in the Clinical Trial Agreement.

17.9.1.1. Study Completion for the Daratumumab Monotherapy Period

Study completion in Part 1 and Part 2 will occur when the last patient has discontinued from study treatment and completed the End of Treatment Visit. Part 3 is no longer applicable for this study. The final data from the study site will be sent to the Sponsor (or designee) after completion of the final subject assessment at that study site, in the time frame specified in the Clinical Trial Agreement.

17.9.2. Study Termination

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

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

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

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

17.10. On-Site Audits

Representatives of the Sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Subject privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the Sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the Sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

17.11. Use of Information and Publication

All information, including but not limited to information regarding JNJ-63723283 and daratumumab or the Sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the Sponsor to the investigator and not previously published, and any data, including exploratory biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the Sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the Sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the Sponsor in connection with the continued development of JNJ-63723283 and daratumumab, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the Sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the Sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator. Results of exploratory biomarker analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study subject identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the Sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the Sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the Sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the Sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the Sponsor will review these issues with the investigator. The Sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally

should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), or the Sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of Clinical Studies and Disclosure of Results

The Sponsor will register and disclose the existence of and the results of clinical studies as required by law.

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Attachment 1: PREINFUSION Antihistamine Medications (DARATUMUMAB)

The following antihistamines may be used predose, before daratumumab IV infusion (including, but not limited to):

- Diphenhydramine
- Cetirizine
- Fexofenadine
- Loratadine
- Clemastine
- Dexchlorpheniramine
- Promethazine*

* The IV use of promethazine should be avoided.

Attachment 2: Conversion Table for Glucocorticosteroid Dose

Glucocorticoid	Approximate Equivalent Dose (mg)	Half-life (Biologic) hours
Intermediate-Acting		
Methylprednisolone	4	18-36
Prednisolone	5	18-36
Prednisone	5	18-36
Triamcinolone	4	18-36
Long-Acting		
Betamethasone	0.6 – 0.75	36-54
Dexamethasone	0.75	36-54

Attachment 3: Modified Diet in Renal Disease Formula

NOTE:

- These formulas estimate GFR in mL/min/1.73 m^2. No additional correction for body surface area is necessary.
- The unit for age is years.
- Different formulas are listed depending on the unit of standardized serum creatinine used.

For standardized serum creatinine (S_{Cr}) in **mg/dL**, the estimated glomerular filtration rate (eGFR) is:

$$eGFR = 175 \times [\text{standardized } S_{Cr}\ (\text{mg/dL})]^{-1.154} \times \text{age}^{-0.203} \times 1.212_{\text{if black}} \times 0.742_{\text{if female}}$$

Creatinine levels in µmol/L can be converted to mg/dL by dividing them by 88.4.

$$\text{creatinine (mg/dL)} = \frac{\text{creatinine (µmol)/L}}{88.4}$$

Alternatively, for standardized serum creatinine (S_{Cr}) in **µmol/L**, the estimated glomerular filtration rate (eGFR) is:

$$eGFR = 30{,}849 \times [\text{standardized } S_{Cr}\ (\text{µmol})/\text{L})]^{-1.154}) \times \text{age}^{-0.203} \times 1.212_{\text{if black}} \times 0.742_{\text{if female}}$$

Source: Levey 2006[20]

Attachment 4: Serum Calcium Corrected for Albumin

If calcium is expressed in mg/dL and albumin is expressed in g/dL:

Corrected calcium (mg/dL) =

serum calcium (mg/dL) + 0.8 × (4 - serum albumin [g/dL])

If calcium is expressed in mmol/L and albumin is expressed in g/L:

Corrected calcium (mmol/L) =

serum calcium (mmol/L) + 0.02 × (40 - serum albumin [g/L])

Source: Burtis 1999[5]

Attachment 5: ECOG Performance Status Scale

Grade	ECOG Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Source: Oken 1982[27]

Attachment 6: Prior Lines of Therapy for Multiple Myeloma

A line of therapy is defined as one or more cycles of a planned treatment program. This may consist of one or more planned cycles of single-agent therapy or combination therapy, as well as a sequence of treatments administered in a planned manner. For example, a planned treatment approach of induction therapy followed by autologous stem cell transplantation, followed by maintenance is considered one line of therapy. A new line of therapy starts when a planned course of therapy is modified to include other treatment agents (alone or in combination) as a result of disease progression, relapse, or toxicity. A new line of therapy also starts when a planned period of observation off therapy is interrupted by a need for additional treatment for the disease.

Source: Rajkumar 2015[33]

Attachment 7: Interpretation of Daratumumab Interference Reflex Assay (DIRA)

Background: Clinical response assessment in myeloma relies on serum protein electrophoresis (SPEP) and immunofixation electrophoresis (IFE). As daratumumab is a monoclonal IgG kappa antibody, the SPEP and IFE can be positive for daratumumab at the serum levels anticipated during this protocol for subjects who are randomly assigned to the daratumumab, lenalidomide, and dexamethasone group.

Implementation: To mitigate this interference, the Sponsor has developed the Daratumumab Interference Reflex Assay (DIRA) to distinguish a positive SPEP/IFE due to the presence of daratumumab versus the presence of the underlying (endogenous) monoclonal protein.[a] The DIRA test will be sent automatically to the central laboratory if a subject with IgG kappa multiple myeloma has an SPEP at or below 0.2 g/dL on 2 or more consecutive cycles. In addition, the DIRA test will be sent automatically to the central laboratory if a subject has an SPEP of zero, but persistently positive IFE for IgG kappa on 2 or more occasions.

Interpretation of results:

The results will be available to the investigator via the central laboratory interface and will be reported as either "POSITIVE" or "NEGATIVE".

POSITIVE: indicates that the sample is still *positive* for underlying (endogenous) monoclonal myeloma protein. Therefore, this patient is not in a complete response (CR), because the CR response criteria require a negative SPEP and serum IFE.

NEGATIVE: indicates that the sample is *negative* for underlying (endogenous) monoclonal myeloma protein. This subject may be in a CR if the other criteria for CR (including negative bone marrow aspiration/biopsy) are achieved.

[a] McCudden C, Axel A, Slaets D, et al. Assessing clinical response in multiple myeloma (MM) patients treated with monoclonal antibodies (mAbs): Validation of a daratumumab IFE reflex assay (DIRA) to distinguish malignant M-protein from therapeutic antibody. J Clin Oncol. 2015 (suppl; abstr 8590).

Attachment 8: ASTHMA Guidelines

Components of Severity		Classification of Asthma Severity											
		Intermittent			Persistent								
					Mild			Moderate			Severe		
		0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs
Impairment	Symptoms	≤ 2 days/week			≥ 2 days/week but not daily			Daily			Throughout the day		
	Nighttime awakenings	0	≤ 2x/month		1-2x/ Month	3-4x/month		3-4x/ month	> 1x/week but not nightly		> 1x/ month	Often 7x/week	
	SABA use for symptom control (not prevention of EIB)	≤ 2 days/week			≤ 2 days/week but not daily		>2 days/ week but not daily, and not more than 1x	Daily			Several time per day		
	Interference with normal activity	None			Minor limitation			Some limitation			Extremely limited		
Normal FEV_1/FVC: 8-19 yr 85% 20-39 yr 80% 40-59 yr 75% 60-80 yr 70%	Lung function	N/A	Normal FEV_1 between exacerbations	Normal FEV_1 between exacerbations	N/A			N/A			N/A		
	FEV1		> 80%	> 80%		> 80%	> 80%		60-80%	60-80%		< 60%	< 60%
	FEV1/FVC		> 85%	Normal		> 80%	Normal		75-80%	Reduced 5%		< 75%	Reduced
Risk	Exacerbations requiring oral systemic corticosteroids	0-1/year			≥ 2 exacerbations in 6 months requiring oral steroids or >4 wheezing episodes/1 year lasting >1 day and risk factors for persistent asthma	≥ 2/year Relative annual risk may be related to FEV_1.	≥ 2/year Relative annual risk may be related to FEV_1.	≥ 2 exacerbations in 6 months requiring oral steroids or >4 wheezing episodes/1 year lasting >1 day and risk factors for persistent asthma	≥ 2/year Relative annual risk may be related to FEV_1.	≥ 2/year Relative annual risk may be related to FEV_1.	≥ 2 exacerbations in 6 months requiring oral steroids or >4 wheezing episodes/1 year lasting >1 day and risk factors for persistent asthma	≥ 2/year Relative annual risk may be related to FEV_1.	≥ 2/year Relative annual risk may be related to FEV_1.
		Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category.											

Recommended Step for Initiating Treatment	Step 1	Step 2	Step 3 and consider short course of oral steroids	Step 3: medium dose ICS and consider short course of oral steroids	Step 3 and consider short course of oral steroids	Step 3 and consider short course of oral steroids	Step 3: medium dose ICS OR Step 4 and consider short course of oral steroids	Step 4 or 5 and consider short course of oral steroids
	In 2-6 weeks, evaluate level of asthma control that is achieved. 0-4 years: If no clear benefit is observed in 4-6 weeks, stop treatment and consider alternate diagnosis or adjusting therapy. 5-11 and 12+ years: adjust therapy accordingly.							

Components of Control		Classification of Asthma Control								
		Well Controlled			Not Well Controlled			Very Poorly Controlled		
		0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs
	Symptoms	≤ 2 days/week but not more than once on each day		≤ 2 days/ week	> 2 days/week or multiple times on ≤2 days/week		> 2 days/ week	Throughout the day		
Impairment	Nighttime awakenings	≤ 1x/month		≤ 2x/month	> 1x/month	≥ 2x/month	1-3x/week	> 1x/week	≥ 2x/week	≥ 4x/week
	Interference with normal activity	None			Some limitation			Extremely limited		
	SABA use for symptom control (not prevention of EIB)	≤ 2 days/week			> 2 days/week			Several times per day		
	Lung function FEV_1 or peak flow FEV_1/FVC	N/A	> 80% > 80%	> 80%	N/A	60-80% 75-80%	60-80%	N/A	< 60% < 75%	< 60%
	Validated questionnaires ATAQ ACQ ACT			0 ≤ 0.75 ≥ 20			1-2 ≥ 1.5 16-19			3-4 N/A ≤ 15
Risk	Exacerbations requiring oral systemic corticosteroids	0-1/year			≥ 2/year					
		Consider severity and interval since last exacerbation								
	Reduction in lung growth/ Progressive loss of lung function	Evaluation requires long-term follow-up								

Recommended Action for Treatment	• Maintain current step • Regular follow-up every 1-6 months • Consider step down if well controlled for at least 3 months	Step up 1 step • **Before step up**: Review adherence to medication, inhaler technique, and environmental control. If alternative treatment was used, discontinue it and use preferred treatment for that step. • **Reevaluate the level of asthma control in 2-6 weeks to achieve control**. 0-4 years: If no clear benefit is observed in 4-6 weeks, consider alternative diagnoses or adjusting therapy. 5-11 years: Adjust therapy accordingly. • **For side effects**, consider alternative treatment options.	Step up at least 1 step • Consider short course of oral steroids • Step up 1-2 steps • **Before step up**: Review adherence to medication, inhaler technique, and environmental control. If alternative treatment was used, discontinue it and use preferred treatment for that step. • **Reevaluate the level of asthma control in 2-6 weeks to achieve control**. 0-4 years: If no clear benefit is observed in 4-6 weeks, consider alternative diagnoses or adjusting therapy. 5-11 years: Adjust therapy accordingly. • **For side effects**, consider alternative treatment options.	• Step up 1 step • Reevaluate in 2-6 weeks • For side effects, consider alternative treatment options	• Consider short course of oral steroids • Step up 1-2 steps • Reevaluate in 2 weeks • For side effects, consider alternative treatment options	• Consider short course of oral steroids • Step up 1-2 steps • Reevaluate in 2 weeks • For side effects, consider alternative treatment options

Attachment 9: Anticipated Events

Anticipated Event

An anticipated event is an adverse event (serious or non-serious) that commonly occurs as a consequence of the underlying disease or condition under investigation (disease related) or background regimen.

For the purposes of this study, the following events will be considered anticipated events:

- Anaemia
- Bleeding
- Bone diseases
- Hypercalcaemia
- Hyperuricemia
- Hyperviscosity syndrome
- Infection
- Neutropenia
- Renal failure or insufficiency
- Thrombocytopenia

Given the mechanism of action of JNJ-63723283, events associated with immune-mediated adverse events will also be considered as anticipated events, including:

- Pneumonitis
- Colitis
- Endocrinopathies (diabetes mellitus, pancreatitis, adrenal insufficiency, or hyperthyroidism)
- Hepatitis
- Transaminitis Grade ≥ 2 (AST or ALT > 3xULN and bilirubin > 2xULN, or AST/ALT > 10xULN)
- Systemic lupus erythematosus
- Neurologic: Guillain-Barré syndrome, myasthenia gravis/myasthenic syndrome, meningoencephalitis
- Nephritis
- Events suggestive of hypersensitivity, cytokine release, influenza-like illness, systemic inflammatory response syndrome, systemic immune activation, infusion-related reactions syndrome

Because this is the first study of the combination of JNJ-63723283 and daratumumab, other adverse events cannot be anticipated.

Reporting of Anticipated Events

All adverse events will be recorded in the CRF regardless of whether considered to be anticipated events and will be reported to the Sponsor as described in Section 12.3.1, All Adverse Events. Any anticipated event that meets serious adverse event criteria will be reported to the Sponsor as described in Section 12.3.2, Serious Adverse Events. These anticipated events are exempt from expedited reporting as

individual single cases to Health Authorities. However, if based on an aggregate review, it is determined that an anticipated event is possibly related to study drug, the Sponsor will report these events in an expedited manner.

Statistical Analysis

Details of statistical analysis of anticipated events, including the frequency of review and threshold to trigger an aggregate analysis of anticipated events will be provided in a separate Anticipated Events Safety Monitoring Plan (ASMP).

Attachment 10: Patient-Reported Outcomes Questionnaires

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC-QLQ-C30)

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ____
Your birthdate (Day, Month, Year): ____
Today's date (Day, Month, Year): 31 ____

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

European Quality of Life 5 Dimensions Questionnaire (EQ-5D-5L)

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

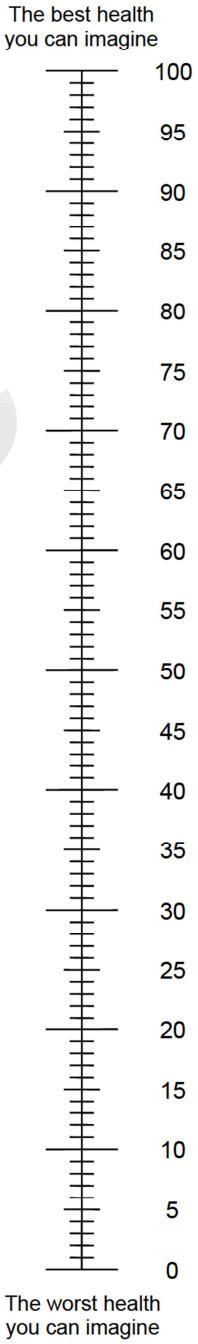
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



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Attachment 11: Daratumumab Monotherapy Period For Subjects No Longer Receiving JNJ-63723283 In Combination With Daratumumab

Overall Design for Daratumumab Monotherapy Period

Each cycle is 28 days, and administration of daratumumab is to occur weekly for Cycles 1 and 2, every other week for Cycles 3 to 6, and every 4 weeks for Cycles 7 and onwards until disease progression, pregnancy, unacceptable toxicity, loss of follow-up, withdrawal of consent, or death. Scheduled assessments to be performed during the Daratumumab Monotherapy Period for Subjects No Longer Receiving JNJ-63723283 in Combination with Daratumumab are outlined in the Time and Events Schedule in Table 24.

Table 24: Time and Events Schedule –Daratumumab Monotherapy Period for Subjects No Longer Receiving JNJ-63723283 in Combination with Daratumumab

	Treatment Phase (28 day cycles)							
	Cycles 1 and 2				Cycles 3 to 6		Cycles 7+	EOT [a]
Study Day	**1**	**8**	**15**	**22**	**1**	**15**	**1**	**Post-Treatment Week 4 (±7 days)**
Procedures/Assessments Study procedures may occur within 3 days of Day 1								
Informed consent	Subjects must sign the informed consent form before any study-specific procedures are performed.							
Physical Examination	Symptom-directed physical examination only							
Dosing								
Daratumumab 16 mg/kg dosing (IV)	X	X	X	X	X	X	X	
Preinfusion and postinfusion medications[b]	X	X	X	X	X	X	X	
Weight	X				X		X	X
Vital Signs (immediately before start and at end of each daratumumab infusion)	X	X	X	X	X	X	X	X
Laboratory Assessments[c]								
Urine or serum pregnancy test (women of childbearing potential only)	Only if clinically indicated.							
Biochemistry	X				X		X	X
Hematology	X	X	X	X	X	X	X	X
Investigator assessment of response[c]								
SPEP and 24-hour UPEP[d], Serum calcium corrected for albumin[d], Serum FLC & serum/urine immunofixation[d], Bone marrow aspirate/bone marrow biopsy	Local assessments of disease response as per standard of care until PD							
Skeletal survey/Assessment of lytic bone disease	As clinically indicated and per the local standard of care for imaging (X-ray, CT, or MRI may be used).							
Assess extramedullary plasmacytomas	As per local standard of care							
Ongoing Subject Review								
SAEs, including SPMs	Continuous from time of ICF until EOT Visit or until the subject withdraws consent for study participation or until the subject starts subsequent anticancer therapy[e] whichever occurs first. Beyond the EOT Visit reporting period after the last dose of study medication, information on SAEs, including SPMs, considered possibly, probably or definitely related to study drug will continue to be collected.							

Abbreviations: EOT=End-of-Treatment; FLC=free light chain; ICF=informed consent form; MRI=magnetic resonance imaging; SAE=serious adverse event; SPEP=Serum M-protein quantitation by electrophoresis; UPEP=urine M-protein quantitation by electrophoresis;

[a] To occur 4 weeks (±7 days) after the last dose of study drug or as soon as possible before the start of subsequent therapy.
[b] Refer to Section 6.4.1.2 and Section 6.4.1.3 for additional information.
[c] Evaluations will be conducted at the local laboratory and responses will be interpreted by the investigator.
[d] Disease assessments SPEP, UPEP, and serum calcium corrected for albumin should be collected at an interval consistent with the investigator's standard of care. For guidance, the Sponsor recommends (but does not require) local laboratory assessments to be conducted every cycle for the first 18 months after initiating daratumumab monotherapy, and every other month thereafter.
[e] For subjects who have received additional treatment with therapeutic intent for multiple myeloma during the SAE reporting period, only SAEs that are considered to be possibly, probably, or definitely related to daratumumab must be reported (unless the subject has been withdrawn from the study).

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Jordan Schecter, MD

Institution: Janssen Research & Development

Signature: [redacted] Date: 20 June 2018

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

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Approved, Date: 20 June 2018