Janssen Research & Development *

Clinical Protocol

A Phase 3 Study Comparing Daratumumab, Lenalidomide, and Dexamethasone (DRd) vs Lenalidomide and Dexamethasone (Rd) in Subjects with Previously Untreated Multiple Myeloma who are Ineligible for High Dose Therapy

Protocol 54767414MMY3008; Phase 3
AMENDMENT 9

JNJ-54767414 (daratumumab)

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

TABLE OF CONTENTS

LIST OF ATTACHMENTS

LIST OF IN-TEXT TABLES AND FIGURES

TABLES

FIGURES

PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	14 July 2014
Amendment INT-1	29 October 2014
Amendment INT-2	26 August 2015
Amendment INT-3	2 November 2016
Amendment INT-4	22 May 2017
Amendment 5	15 January 2019
Amendment 6	12 June 2019
Amendment 7	17 January 2020
Amendment 8	3 April 2020
Amendment 9	20 July 2021

Amendments below are listed beginning with the most recent amendment.

Amendment 9 (20 July 2021)

The overall reason for the amendment: To define the clinical cut-off for the final CSR analysis. This cut-off will mark the start of the long-term survival follow-up during which subjects will continue to receive study treatment and will be followed for overall survival (OS). Additionally, this amendment revises the end of study definition and defines the timing of the final overall survival (OS) analysis cut-off. This amendment also provides clarification that subjects who are benefiting from study treatment will be able to continue to receive study treatment from the final OS analysis until the end of study when alternative access to daratumumab is not available.

Applicable Section(s)	Description of Change(s)
Rationale: To define the timing of the following: the final CSR, the transition to long-term survival follow-up, and the final OS analysis.	
Synopsis Overview of Study Design; 3.1 Overview of Study Design; 10.1 Completion; 11.2 Sample Size Determination; 11.3 Efficacy Analysis; 17.9.1 Final OS Analysis/End of study	Text was revised to add the final CSR analysis, which will provide updates to the primary CSR analysis for both efficacy and safety. Text was added to include the final OS analysis. It was specified that the clinical cut-off of the final OS analysis will occur when approximately 390 deaths have occurred.
3.1 Overview of Study Design	Text was added to specify that following the positive second interim OS analysis, the study will have the final CSR analysis and then will transition to long-term survival follow-up.
Throughout the protocol	Reference to Section 9.1.8 was added to define the longterm survival follow-up. Reference to Section 9.1.9 was added to define the final OS analysis cut-off. Reference to Section 17.9.1 was added to define end of study.
Rationale: To clarify procedures after the final CSR analysis until final OS analysis	
Time and Events Schedule Overview; Time and Events Schedule, Dose Administration; 3.1 Overview of Study Design; 9.1.3 Treatment Phase; 9.1.4 Follow-up Phase; 9.2.1.1 Response Categories; 9.8 Safety Evaluations; 9.9 Sample Collection and Handling; 12.3.1 All Adverse Events; 12.3.2 Serious Adverse Events; 17.5 Case Report Form Completion; 17.9.1 Final OS Analysis/End of Study	Reference to Attachment 11 was added (description of study procedures for all subjects during the long-term survival follow-up).

Applicable Section(s)	Description of Change(s)
8 Concomitant Medications	Text was updated to clarify the timeframe of collection of concomitant medications.
Synopsis; 3.1 Overview of Study Design; 8.4 Subsequent Therapies; 9.1.3 Treatment Phase	Text was updated to clarify that PD confirmation by sponsor will not be required after the cut off date for the final CSR analysis.
8.4 Subsequent Therapies	Text was added to clarify procedures during long-term survival follow-up.
9.1.1 Overview	Text was added to specify that during the long-term survival follow-up, no blood will be collected, only local routine testing will be performed per local institutional practice
9.1.3 Treatment Phase	Text was added to clarify that for subjects continuing to receive study treatment after the final CSR analysis, routine safety monitoring should comply with local institution practice. Text was added to specify that after the final CSR analysis, end of treatment visits are no longer required.
9.1.4 Follow-up Phase	Text was added to clarify that Follow-up Phase procedures will be performed until the start of the long-term survival follow-up and reference is made to Attachment 11 for the Follow-up procedures after final CSR analysis.
9.1.7 Assessments Following the Interim OS Analysis;	Text was revised to specify that subject monitoring will continue as summarized until the cut-off for the final CSR analysis.
9.1.8 Final CSR Analysis and Long-term Survival Follow-up (new)	A new section was added to describe assessments and data collection following the final CSR analysis until the final OS analysis.
9.2.1.1 Response Categories	Text was added to clarify efficacy evaluation requirements for subjects who continue to receive study treatment after the final CSR analysis.
9.8 Safety Evaluations	Text was added to clarify hepatitis B virus DNA testing requirements for subjects who continue to receive study drug after the final CSR analysis.
9.8 Safety Evaluations; 12.3.1 All Adverse Events; 12.3.2 Serious Adverse Events	Text was added to specify that serious adverse event reporting will continue for those subjects receiving study treatment after the final CSR analysis.
9.9 Sample Collection and Handling	Text was added to clarify the sample collection and handling requirements after the final CSR analysis.
12.3.4 Pregnancy	Text was added to specify that pregnancy reporting will continue after the final CSR analysis.
12.3.1 All adverse events	Clarification was added that Anticipated events will be no longer be reported after the final CSR analysis.
Attachment 11 (new)	Attachment 11 (new) was added to clarify the study procedures and data collection all subjects during the long-term survival follow-up.

Rationale: The final OS analysis is distinct from the end of study, as such, the end of study definition was amended for clarity and text was updated to align with these definitions.	
Synopsis, Overview of Study Design; 17.9.1 Final OS Analysis/End of Study	Text was added to define the end of study (defined as when all subjects who are still receiving daratumumab after the final OS analysis have access to daratumumab through another source such as commercial availability, continued access through a dedicated long-term extension study, or a patient access program, or when all subjects have discontinued daratumumab treatment, or by 31 January 2026 , whichever occurs first).
3.1 Overview of Study Design; 9.1.8 Final CSR Analysis and Long-term Survival Follow Up; 10.1 Completion	Text was updated from "end of the study" to "until the final OS analysis".
9.1.9 Final OS analysis Until End of Study	A new section was added to describe assessments and data collection following the final OS analysis till end of study.
Rationale: To clarify access to daratumumab after the final OS analysis until the end of study for those subjects who are benefiting from study treatment.	
Synopsis; 3.1 Overview of Study Design; 17.9.1 Final OS analysis/End of Study	Text was updated to clarify that subjects benefiting from treatment with daratumumab have the option to continue to receive study treatment after the final OS analysis until the end of study.
Rationale: To clarify study assessments and data reporting requirements in relation to the final OS analysis cut-off until the end of study.	
Attachment 12 (new)	Attachment 12 added to clarify the study procedures for subjects who continue to receive daratumumab after the final OS analysis cut-off.
Time and Events Schedule Overview; Time and Events Schedule, Dose Administration; 9.1.9 Final OS Analysis till End of Study; 9.2.1.1 Response Categories; 9.8 Safety Evaluations; 12.3.2 Serious Adverse Events; 12.3.4 Pregnancy; 17.5 Case Report Form Completion; 17.9.1 Final OS analysis/End of Study	Reference to Attachment 12 was added (description of study procedures for all subjects after the final OS analysis cut-off.
3.1 Overview of Study Design; Figure 2	Footnote added to Figure 2 to clarify that after Study MMY3008 transitions to long-term survival follow-up, an end-of-treatment visit is no longer required.
Rationale: To clarify permitted/prohibited vaccinations.	
8.2 Permitted Therapies	Text was added indicating vaccinations are allowed per local guidelines with a reference to Section 8.3.
8.3 Prohibited Therapies	Text was added clarifying the restriction of live-attenuated and replication-competent viral vector vaccines.

Rationale: To incorporate changes from France and United Kingdom country-specific amendments into MMY3008 global Amendment 9.	
9.8 Safety Evaluations HBV Serology and DNA Testing	Text from Study MMY3008 France amendment added to specify that if the hepatitis B serologic status of a subject in the DRd arm is unknown, HBsAg, Anti-HBs, and Anti-HBc testing is recommended if the subject is still receiving daratumumab (or is within 6 months after the last dose).
10.2 Discontinuation of Study Treatment	Text revised to incorporate a country-specific requirement from Study MMY3008 UK amendment to specify that a subject's study treatment **will** ~~should~~ be discontinued if:
Rationale: To clarify the definition of medically important serious adverse events.	
12.1.1 Adverse Event Definitions and Classifications	Second primary malignancies added to medically important events.
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 8 (3 April 2020)

The overall reason for the amendment: The overall reason for the amendment is to provide flexibility for study investigators to prioritize the safety of their patients during the global coronavirus (COVID-19) pandemic. To ensure continuity of study treatment, while limiting subjects' time spent at the study center, subjects will be given the option to switch from daratumumab IV (16 mg/kg) to daratumumab subcutaneous (Dara-SC 1800 mg), at the discretion of the investigator.

Applicable Section(s)	Description of Change(s)
Rationale: To allow subjects currently receiving Dara-IV the option to switch to Dara-SC, at the discretion of the investigator.	
Synopsis; 3.1 Overview of Study Design	Text has been added to describe the option of daratumumab SC administration for subjects receiving daratumumab IV.
1.2.2.3 (new) Daratumumab Subcutaneous; 3.2 (new) Study Design Rationale for Daratumumab SC Dose Regimen	The following sub-sections and text have been added to support daratumumab SC dosing: background information regarding the SC formulation of daratumumab, rationale for daratumumab SC dose regimen, rationale for daratumumab fixed dose, and daratumumab SC administration.
Synopsis; Time & Events Schedules; 3.1 Overview of Study Design; 6 Dosage and Administration; 6.1.1 Daratumumab Preparation; 6.1.4.1 Pre-dose Medication; 6.1.4.2 Post-dose Medication; 6.1.5 Management of Infusion-related Reactions; 6.1.5.1 Infusion-Related Events of Grade 1 or Grade 2; 6.1.5.2 Infusion-Related Reactions of Grade 3 or Higher; 6.2 Lenalidomide (Arm A and Arm B); 6.3 Dexamethasone (Arm A and Arm B); 6.4.3 Dexamethasone Dose Modifications; 6.4.1.1 Daratumumab-Related Toxicity Management; 8 Concomitant Therapy; 11.4 Pharmacokinetic Analyses; 12.3.2 Serious Adverse Events; 16.1 Study-Specific Design Considerations; Attachment 9 The Family of Antihistamine Medications	Where text was specific to infusion(s) but applicable to both IV and SC administration, text was amended to remove "infusion" and/or add "dose" or "administration".
Synopsis; Sec 6.1.3 (new) Daratumumab SC Administration; 6.1.4.2 Post-dose Medication; 6.4.1.2 Daratumumab Interruption or Missed Doses; 9.1.1 Overview	Text has been added to describe daratumumab SC dose administration.

Applicable Section(s)	Description of Change(s)
Synopsis; Time & Events Schedules; 3.2 Study Design Rationale; 6 Dosage and Administration; 6.1.2 Daratumumab IV Administration; 6.1.4.1 Pre-dose Medication; 6.1.5 Management of Infusion-related Reactions; 6.1.5.1 Infusion-Related Events of Grade 1 or Grade 2; 6.1.5.2 Infusion-Related Reactions of Grade 3 or Higher; 8.4 Subsequent Therapies; 9.3.4 Immunogenicity Assessments (Antibodies to Daratumumab and rHuPH20)	Text has been added to clarify where text is applicable to both daratumumab IV and SC or to differentiate between daratumumab IV or SC administration, procedures, or requirements.
Synopsis; Time & Events Schedule Overview; 3.1 Overview of Study Design; 9.3.1 Evaluations; 9.3.4 Immunogenicity Assessments (Antibodies to daratumumab and rHuPH20)	Text has been added for pharmacokinetic and immunogenicity sampling requirements for subjects treated with daratumumab SC.
Rationale: Infusion-related reactions are systemic reactions related to daratumumab administration, regardless of route of administration.	
6.1.5 Management of Infusion-related Reactions	Text has been added to describe IRRs and the applicability to both daratumumab IV or SC administration.
Rationale: Subcutaneous administration of daratumumab is associated with local injection site reactions.	
6.1.4 Prevention of Infusion-Related and Injection-Site Reactions; 6.1.5.3 (new) Injection-Site Reactions	Text has been added to describe injection-site reactions and management of such events.
Rationale: Daratumumab SC is co-formulated with rHuPH20 and sorbitol.	
Synopsis; Time & Events Schedule Overview; 2.1 Objectives; 9.3.1 Evaluations; 9.3.2 Analytical Procedures; 9.3.4 Immunogenicity Assessments (Antibodies to Daratumumab and rHuPH20); 11.5 Immunogenicity Analyses	Text has been added to include the immunogenicity collection for analysis of rHuPH20 for those subjects treated with daratumumab SC.
Synopsis; 3.1 Overview of Study Design	Text has been added to specify that subjects with known allergies/intolerance to sorbitol will not be allowed to switch from daratumumab IV to daratumumab SC.
Rationale: Daratumumab IV has been shown to be safe and effective in patients with multiple myeloma, as such, immunogenicity sampling requirements for subjects receiving daratumumab IV have been amended to reduce patient and site burden.	
Time & Events Schedule Overview	Footnote added to T&E to clarify that pharmacokinetic and anti-daratumumab antibody sampling is no longer required for subjects in Treatment Arm B who remain on daratumumab IV therapy.
Synopsis; 9.1.6 (new) Assessments Following Implementation of Amendment 8; 9.3.1 Evaluations; 9.3.4 Immunogenicity Assessments (Antibodies to daratumumab and rHuPH20)	Text has been updated to remove pharmacokinetic and immunogenicity sampling for subjects who remain on daratumumab IV.
Rationale: Revisions made for clarity that align with daratumumab-wide program language.	

Applicable Section(s)	Description of Change(s)
6.1.5 Management of Infusion-related Reactions	Bolded text was added: Trained study staff at the clinic should be prepared to intervene in case of any infusion-related reactions 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**.
8.2 Permitted Therapies	New text was added: **Other symptoms may be managed according to institutional guidelines provided prohibited therapies are not administered (see Section 8.3).**
Rationale: Clarification of collection of laboratory samples.	
9.1.6 (new) Assessments Following Implementation of Amendment 8; 9.1.7 Assessments Following the Interim OS Analysis	New section added to specify that following the implementation of Amendment 8, disease evaluations are to be performed locally per the site's standard of care and quantitative immunoglobulin testing will be removed. rHuPH20 immunogenicity testing for Dara-SC subjects was added and pharmacokinetic and immunogenicity sampling for subjects who remain on daratumumab IV was removed.
Rationale: To provide physical description and guidance about packaging, labeling, preparation, handling, and storage for daratumumab SC.	
14.1 Physical Description of Study Drug; 14.2 Packaging; 14.3 Labeling; 14.4 Preparation, Handling and Storage	New text added about daratumumab SC.
Rationale: To allow sites flexibility in offering virtual visits due to COVID-19 pandemic.	
Time & Events Schedule; 9.1.1 Overview	Text added to specify that site visits may be replaced with virtual visits or other local arrangements in exceptional circumstances.
Rationale: Minor errors, editorial issues, or changes for clarity/consistency noted in the protocol were corrected.	
Abbreviations	Abbreviations for IPPI (Investigational Product Preparation Instruction), IRR (infusion-related reaction), ISR (injection-site reaction), and rHuPH20 (recombinant human hyaluronidase PH20) have been added.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 7 (17 January 2020)

The overall reason for the amendment: The overall reason for the amendment is to provide clarifications to study conduct and align with updates in all daratumumab protocols.

Applicable Section(s)	Description of Change(s)
Rationale: Clarification was added for the assessments performed after the interim overall survival (OS) analysis.	

Applicable Section(s)	Description of Change(s)
9.1.6 Assessments Following the Interim OS Analysis	Text was added to specify quantitative immunoglobulin testing is no longer required. Bold text added to clarify that confirmation of disease progression by sponsor is no longer required, **with the exception of subjects who progress on the Rd arm and then request subsequent therapy with daratumumab**. Bold text added to clarify that **all subjects must still meet IMWG criteria for progression (see Table 8)**, prior to initiation of subsequent anti-myeloma therapy. Text in ~~strikethrough~~ has been deleted: ~~For subjects who are continuing to receive study treatment at the time of the interim OS analysis, dosing data and safety information will be collected. Safety information will include adverse events during treatment and within 30 days after last dose, concomitant medications associated with a serious adverse event, and information on all second primary malignancies.~~
Rationale: Modified the list of anticipated events to remove any events that are known adverse drug reactions (ADRs) of daratumumab. Clarification that after unblinding of aggregate safety data by the sponsor's study team, there is no need for independent Safety Asessment Committee (SAC) review of anticipated events. Additional clarification of the reporting responsibilities for anticipated events to Health Authorities and IRBs/IECs. Changed name of committee to be in alignment with company procedures.	
Attachment 10 Anticipated Adverse Events	• Anemia, neutropenia, and thrombocytopenia were deleted from the anticipated events list. • The review and reporting requirements for anticipated events were clarified. • Revised "Anticipated Event Review Committee" (ARC) to "Safety Assessment Committee" (SAC).
Rationale: To eliminate the possibility of inconsistency between the NCI-CTCAE version numbering used in the protocol and the standard grade descriptions included in the protocol.	
12.1.3 Severity Criteria	Removed definitions of severity criteria as they are specified in NCI-CTCAE Version 4.03. Revised NCI-CTCAE version to 4.03.
Rationale: To further clarify the measures to mitigate the risk of embryo fetotoxicity associated with lenalidomide.	
4.3 Prohibitions and Restrictions 9.8 Safety Evaluations 10.2 Discontinuation of Study Treatment 12.3.4. Pregnancy Attachment 5 Lenalidomide Global Pregnancy Prevention Plan	Additional text regarding the pregnancy prevention plan for lenalidomide was added**.** Text regarding requirement of pregnancy test for women with regular and irregular menstrual cycles after last dose of lenalidomide was added.
Rationale: Minor errors were noted.	
9.5 Biomarkers	Bold text added to clarify testing on biomarker samples: Samples for biomarker evaluations will be collected as specified in the Time and Events Schedule **and may be used for additional biomarker testing that may arise at a later time point (see Section 16.2.5).**
Abbreviations	Abbreviation for Safety Assessment Committee (SAC) has been added.

Amendment 6 (12 June 2019)

The overall reason for the amendment: The overall reason for the amendment is in response to identification of a new important risk (hepatitis B virus [HBV] reactivation).

Applicable Section(s)	Description of Change(s)
Rationale: The text for identification of HBV reactivation, testing, and management of subjects with the potential for HBV reactivation was added or modified in response to identification of a new important risk (HBV reactivation).	
Time and Events Schedule – Overview	Added HBV DNA assessment at every 3 months during treatment ± 1 month until 6 months after last dose of daratumumab with the note 'Arm B subjects with known history of hepatitis B infection or positive hepatitis B serologies (HBsAg, Anti-HBc and/or Anti-HBs with exception of serologic findings suggestive of HBV vaccination [Anti-HBs positivity as the only serologic marker] and a known history of prior HBV vaccination)'.
8.1.7 Management of Hepatitis B Virus Reactivation	Added a new section for information for the management of HBV reactivation.
9.8 Safety Evaluations	Added information detailing the conduct of HBV serology and updated DNA tests
Rationale: To clarify the mode of subject monitoring post end-of-treatment (EOT).	
Time and Events Schedule – Overview (Disease Evaluations)	The following details clarifying subject monitoring post EOT were added – 'After EOT, subjects in both treatment arms prior to disease progression (PD) will continue to return for disease evaluations. After PD is documented, subjects will be followed for survival, time from randomization to progression on the next line of therapy or death, whichever comes first (PFS2), second primary malignancies, and subsequent anti-myeloma therapy. After the primary clinical cut-off date (24 September 2018), subject monitoring will be conducted as per Section 9.1.5. After the second interim OS analysis has occurred and the mPFS for DRd group has been confirmed, subject monitoring will be conducted according to Section 9.1.7'
Rationale: To provide a window for the 6-monthly collection of Eastern Cooperative Oncology Group (ECOG) and patient-reported outcome (PRO) assessments.	
Time and Events Schedule – Overview; 9.1.5: Assessments Following the Positive Second Interim Analysis of PFS	Added '±14 days' to the 6-monthly collection of ECOG and PRO assessments after completing the first year for these procedures.
Rationale: To clarify the guidance for delay in treatment.	
6.4.1.2 Daratumumab Interruption or Missed Doses	Text in bold added: A daratumumab dose that is held for more than the permitted time (Table 3) from the per-protocol administration date for any reason other than toxicities suspected to be related to daratumumab should be brought to the attention of the Sponsor at the earliest possible time. Subjects whose dose was delayed for more than 4 weeks (Cycle 1 to Cycle 6) or more than 6 weeks (Cycle 7 and beyond) should have study treatment discontinued, unless, upon consultation with the sponsor and the review of safety and efficacy, continuation is agreed upon. **Infusion-related reactions may occur upon re-initiation of daratumumab after a prolonged delay in treatment.**
Rationale: To provide additional details regarding the provision of daratumumab by the sponsor for subjects randomized to Arm A (Rd) who are receiving any subsequent line of therapy.	

Applicable Section(s)	Description of Change(s)
8.4. Subsequent Therapies	Added the sentence 'For these subjects, daratumumab should not be added to an ongoing subsequent therapy regimen until the subject has progressed on that regimen' and mentioned that safety management for and during the administration of daratumumab must be in accordance with local prescribing information and local regulations. Also clarified that second primary malignancy reporting should continue to end of study.
Rationale: To clarify the timing when disease evaluation will switch to local laboratories.	
9.1.6 Assessments Following the Interim OS Analysis	Text in ~~strikethrough~~ has been deleted, text in **bold** has been added: **Once the interim overall survival (OS) analysis has occurred and when the median progression free survival (PFS) is reached in the DRd arm, the sponsor will notify the investigators that from that point onward, disease evaluations are to** ~~For subjects without disease progression at the time of the interim OS analysis, disease assessments will continue but will~~ be performed locally per the **site's** standard of care.
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 5 (15 January 2019)

The overall reason for the amendment: Following review of data from the second interim analysis by the Independent Data Monitoring Committee (IDMC), the study is being amended to allow subjects in Arm A (lenalidomide and dexamethasone [Rd] alone) access to daratumumab after sponsor confirmation of disease progression (PD) per International Myeloma Working Group (IMWG) criteria.

Applicable Section(s)	Description of Change(s)
Rationale: Subjects randomized to Arm A (Rd) who have sponsor-confirmed disease progression may have the option to receive daratumumab provided by the sponsor (in any subsequent line of therapy) in the Follow-up phase, if recommended by the investigator. Eligibility for and administration of daratumumab must be in accordance with local prescribing information and local regulations.	
8.4. Subsequent Therapies	A new section has been added.
Rationale: To update the protocol following positive second interim analysis results.	
Synopsis, Overview of Study Design; Synopsis, Statistical Methods; 3.1. Overview of Study Design; 11.10. Interim Analysis	Details of IDMC reviews and planned interim analyses have been revised.
Synopsis, Overview of Study Design; Synopsis, Statistical Methods; 3.1. Overview of Study Design; 9.2.2. Endpoints;	It is explained that the interim PFS analysis will function as the primary PFS analysis of this endpoint, as the superiority of daratumumab plus Rd (DRd) over Rd alone was established at the second interim analysis.

Applicable Section(s)	Description of Change(s)
11.10. Interim Analysis	
Synopsis, Overview of Study Design; Time and Events Schedule, Overview; 3.1. Overview of Study Design	Removed text which referred to reduced data collection as described in Section 9.1.4. Where appropriate, added references to subject monitoring as described in the new Sections 9.1.5 (following positive second interim analysis of PFS) and 9.1.6 (following interim overall survival [OS] analysis).
Synopsis, Overview of Study Design; 3.1. Overview of Study Design; 11.10. Interim Analysis	Described that the second interim OS will now occur when approximately 260 deaths have occurred which will be about the same time the primary PFS analysis would have taken place.
9.1.4. Follow-up Phase	Removed the following text: A clinical cut-off will be established after the primary PFS analysis (390 PFS events). Following the clinical cut-off date, disease assessments will no longer be required and data collection will be limited to the following: • For subjects still receiving study treatment: study treatment administration, adverse events, SAEs, laboratory data associated with SAEs • For all subjects: all subsequent anticancer treatment, PFS2 (based on investigator judgment), second primary malignancies, and survival follow-up
9.1.5. Assessments Following the Positive Second Interim Analysis of PFS	A new section has been added.
9.1.6. Assessments Following the Interim OS Analysis	A new section has been added.
11.3. Efficacy Analyses	Described that the analysis of OS may be confounded by subjects from Arm A receiving daratumumab after disease progression. Exploratory analysis may be performed to adjust for the effect daratumumab exposure may have on OS for the subjects who were randomized to Arm A (Rd).
11.3. Efficacy Analyses	Text describing secondary endpoints was revised to align with the secondary endpoints which were planned to be sequentially tested at the second interim analysis.
Rationale: To clarify/emphasize the requirement to wait until confirmed PD prior to starting subsequent anti-myeloma therapy.	
Synopsis, Overview of Study Design; 3.1. Overview of Study Design	It is emphasized that for both Arm A (Rd) and Arm B (DRd), subjects entering the Follow-up Phase should not be started on subsequent anti-myeloma therapy 'until confirmed disease progression'.
8.3. Prohibited Therapies	Clarified that the prohibition on concomitant administration of any other antineoplastic therapy for the intention of treating multiple myeloma applies prior to confirmation of disease progression. Text in ~~strikethrough~~ has been deleted, text in **bold** has been added: ~~and other cancers not defined in the study protocol is prohibited~~

Applicable Section(s)	Description of Change(s)
	For management of second primary malignancies please see Section 10.2.
Synopsis, Overview of Study Design; 3.1. Overview of Study Design; 9.1.4. Follow-up Phase; 9.2.1.1. Response Categories	Cross-references to the new Section 8.4 Subsequent Therapies have been added.
Rationale: Clarification of the IDMC's role in data review following the interim PFS analysis.	
Synopsis, Overview of Study Design; Synopsis, Statistical Methods; 3.1. Overview of Study Design; 11.11. Data Monitoring Committee	It is noted that the IDMC will no longer review study data after the interim PFS analysis has been completed.
Rationale: To clarify the daratumumab pharmacokinetics (PK) and immunogenicity assessments specific to Arm B (DRd).	
Synopsis, Pharmacokinetic and Immunogenicity Evaluations; 9.3.1. Evaluations; 9.3.4. Immunogenicity Assessments (Antibodies to daratumumab)	Added text stating that in the Follow-up Phase, for all subjects in Arm B (DRd), samples for PK and immunogenicity assessments are to be collected 8 weeks after the last dose of daratumumab, regardless of whether there has been confirmed disease progression.
Time and Events Schedule, Overview	Within the rows describing daratumumab PK and immunogenicity assessments, text has been added to emphasize that these assessments apply only to subjects in Arm B.
Rationale: Clarification of visit time points to ensure consistent timing of assessments for both ECOG and ePRO and align with other daratumumab protocols.	
Time and Events Schedule, Overview	Text in ~~strikethrough~~ has been deleted, text in **bold** has been added: Within the ECOG and PRO rows: 'D1 of Cycle 3, 6, 9, 12 for year 1; every 6th **month** ~~cycle~~ thereafter until ~~EOT (~~PD~~)~~'
Rationale: Additional timepoints for MRD monitoring added to allow for MRD durability assessment.	
Time and Events Schedule, Overview	Text in ~~strikethrough~~ has been deleted, text in **bold** has been added: Within the bone marrow aspirate/biopsy row: 'To confirm CR/sCR, assess MRD, and evaluate PD (if feasible). Samples are requested at time of suspected CR/sCR and at 12, 18, 24**,** ~~and~~ 30**, 36, 48, and 60** months post C1D1 (+/-1 month).'
9.2.1.5. Bone Marrow Examination, Table 9	Text has been revised in the Bone Marrow Testing Table: During Treatment

Applicable Section(s)	Description of Change(s)
	1. Central Testing: A portion of bone marrow aspirates collected at time of suspected CR/sCR, and 12, 18, 24**,** ~~and~~ 30**, 36, 48, and 60** (+/-1) months post C1D1, will be analyzed for MRD*. Footnote: **Immunohistochemistry or immunofluorescence (both require kappa/lambda ratio from analysis of ≥100 **plasma** cells) or 2- to 4-color flow cytometry are acceptable methods to evaluate plasma cell clonality.
Rationale: To clarify visit time points for quantitative immunoglobulin (Ig) assessments.	
Time and Events Schedule, Overview	Text in ~~strikethrough~~ has been deleted, text in **bold** has been added: Within the quantitative Ig row, for 'Day 1 of each cycle (28-day cycles): every **16 weeks** ~~3 months~~
9.2.1.2. Myeloma Protein Measurements in Serum and Urine	• Serum quantitative immunoglobulins (QIgs) All subjects will be evaluated for IgG, IgA, IgM, IgE, and IgD at Screening. Every **16 weeks** ~~3 months~~ during treatment and at the EOT visit, subjects with IgD or IgE disease will be evaluated for IgG, IgA, IgM, IgE, and IgD and subjects with IgG, IgA, or IgM disease will be evaluated for IgG, IgA, and IgM.
Rationale: Widening of window for collection of visit time points for hematology and clinical chemistry assessments.	
Time and Events Schedule, Dose Administration	Text in ~~strikethrough~~ has been deleted, text in **bold** has been added: Within the hematology and clinical chemistry rows: 'For Cycle 1 Day 1, no need to repeat tests if they have been performed within the past 5 days. Testing may be performed up to **3** ~~2~~ days before other infusion days.'
Rationale: Additional text added to include Arm A cycle delays.	
6. Dosage and Administration	Text in **bold** has been added: **Subjects whose study treatment is delayed for more than 4 weeks (Cycle 1 to Cycle 6) or more than 6 weeks (Cycle 7 and beyond) should have study treatment discontinued, unless, upon consultation with the sponsor and the review of safety and efficacy, continuation is agreed upon.**
Rationale: Clarification that lenalidomide and dexamethasone doses can be re-escalated at the investigator's discretion.	
6.4.2. Lenalidomide Dose Reductions	Text in **bold** has been added: **In the event of a dose adjustment, lenalidomide doses maybe re-escalated at the investigator's discretion.**
6.4.3. Dexamethasone Dose Modifications	**In the event of a dose adjustment, dexamethasone doses maybe re-escalated at the investigator's discretion.**
Rationale: To clarify that Eastern Cooperative Oncology Group (ECOG) and patient-reported outcomes (PRO) assessments that occur at Week 8 and Week 16 post-PD should be scheduled relative to the date of laboratory confirmed disease progression.	
9.1.4. Follow-up Phase	Text in **bold** has been added: 'Every 16-week follow-up contacts**, as well as Week 8 and Week 16 post-PD ECOG and ePRO assessments,** should be scheduled from the date of confirmed progression **(ie, the date of the confirmatory laboratory assessment, not the date of confirmation by the sponsor)**.'
Rationale: Removed text that was not pertinent to subjects who achieved a partial response (PR) or disease progression (PD).	

Applicable Section(s)	Description of Change(s)
9.2.1.1. Response Categories, Table 8	Text has been deleted from the International Uniform Response Criteria Consensus Recommendations Table: Partial response (PR) • 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% Progressive disease (PD)† • 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%
Abbreviations	EBMT has been deleted from the list of abbreviations
Rationale: Replaced time qualifier of '1-3 weeks later' because in urgent situations, a repeat investigation may be needed sooner. 'At least 1 day later' is used to make clear that the confirmatory test cannot happen on the same day as the initial test.	
9.2.1.2. Myeloma Protein Measurements in Serum and Urine	Text in ~~strikethrough~~ has been deleted, text in **bold** has been added: 'Disease progression based on 1 of the laboratory tests alone must be confirmed by at least 1 repeat investigation performed **at least 1 day** ~~1 to 3 weeks~~ later'.
Rationale: To clarify definitions for study end.	
10.1. Completion	Text added that the study end is defined as when 330 deaths have occurred or 7 years after the last subject is randomized, whichever comes first.
Rationale: Alignment of text with recent protocol template changes.	
Title page	Added 'Janssen Pharmaceutica NV' to the list of legal entities.
12.3.1. All Adverse Events	Revised the text for expected disease progression not being recorded as an adverse event or a serious adverse event term. Noted that 'if determined by the investigator to be more likely related to the study treatment than the underlying disease, the clinical signs or symptoms of progression and the possibility that the study treatment is enhancing disease progression, should be reported per the usual reporting requirements see Section 12.1'.
17.3. Subject Identification, Enrollment, and Screening Logs	Text in ~~strikethrough~~ has been deleted, text in **bold** has been added: All reports and communications relating to the study will identify subjects by subject identification and **age at initial informed consent** ~~date of birth~~. In cases where the subject is not randomized into the study, the date seen and **age at initial informed consent** ~~date of birth~~ will be used.
17.11. Use of Information and Publication	Text in ~~strikethrough~~ has been deleted, text in **bold** has been added: 'key assessment parameters of the study will be used to determine a coordinating investigator **for the study'**. Changed the time for submitting combined results from the completed study for publication 'within **18 months after study end date** ~~12 months of the availability of the final data (tables, listings, graphs)~~' Revised the text beginning 'Authorship of publications...'
Abbreviations	ICMJE has been added to the list of abbreviations.
Rationale: Minor errors were noted	

Applicable Section(s)	Description of Change(s)
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.
Throughout the protocol	'anticancer' has been replaced with 'anti-myeloma'
Synopsis, Overview of Study Design; 3.1. Overview of Study Design	Text in **bold** has been added: Subjects who discontinue **study treatment** for reasons other than disease progression must continue to have disease evaluations according to the Time and Events Schedule until confirmed disease progression (PD) (see Section 8.4, Subsequent Therapies).
9.1.4. Follow-up Phase	Text in **bold** has been added: Subjects who discontinue **study treatment** before disease progression must continue to have disease evaluations.
10.3. Withdrawal from the Study	'When a subject withdraws before completing the study' has been revised to 'When a subject withdraws from the study'.
12.3.4. Pregnancy	Text in ~~strikethrough~~ has been deleted: Any subject who becomes pregnant during the study must discontinue further study treatment ~~and promptly be withdrawn from the study~~. Redundant text in ~~strikethrough~~ has been deleted: ~~Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required~~.

Amendment INT-4 (22 May 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: To allow subjects in Arm B (daratumumab + lenalidomide and dexamethasone [DRd]) to continue treatment with lenalidomide and dexamethasone (Rd) beyond the current protocol-specified 2 years.

Applicable Section(s)	Description of Change(s)
Rationale: Subjects in Arm B will continue treatment with lenalidomide and dexamethasone (Rd) until disease progression or unacceptable toxicity. Based on data from the FIRST study, lenalidomide treatment until disease progression is emerging as the standard of care and is also consistent with the approved lenalidomide package insert.	
Synopsis; Time and Events Schedule, Dose Administration; 3.1. Overview of Study Design; 6.2. Lenalidomide (Arm A and Arm B); 6.3. Dexamethasone (Arm A and Arm B) 6.2. Lenalidomide (Arm A and Arm B);	Subjects in both treatment arms will continue lenalidomide and dexamethasone (Rd) until disease progression or unacceptable toxicity.

Applicable Section(s)	Description of Change(s)
6.3. Dexamethasone (Arm A and Arm B) 3.2. Study Design Rationale	The following text is added to manage the implementation of this amendment**: Subjects in Arm B who discontinued treatment with Rd at 24 months may re-start treatment with Rd as per Amendment INT-4.** Text is added to support the modification of lenalidomide and dexamethasone dosing in Arm B.
Rationale: With the anticipated improved survival for subjects in Arm B (daratumumab, lenalidomide, and dexamethasone [DRd]), who with this amendment will receive continuous lenalidomide and dexamethasone (Rd) regimen, the end of study and long-term survival Follow-up Phase are extended from 5 to 7 years in order to reach 330 deaths as originally planned.	
Synopsis; 3.1. Overview of Study Design; 9.1.4. Follow-up Phase; 11.2. Sample Size Determination; 17.9.1. Study Completion	Text is changed from 5 to 7 years.
Rationale: Most infusion-related reactions will occur with the first infusion. Because antihistamines have side effects in the elderly population, the benefit-risk ratio of continued prophylaxis with antihistamines during subsequent infusions should be considered.	
6.1.3.1. Preinfusion Medication	The following text is added: After Cycle 6, if a subject has not developed an infusion-related reaction and is intolerant to antihistamines, modifications are acceptable as per investigator discretion.
Rationale: Clarify steroid administration.	
8.3. Prohibited Therapies	Clarify that steroids given for adverse events may exceed >10 mg prednisone if no other treatment options are available.
Rationale: Clarify the permitted treatments for second primary malignancies and follow up requirements.	
10.2. Discontinuation of Study Treatment	The following text regarding second primary malignancies was edited and modified: A subject who experiences a second primary malignancy that can~~not~~ be treated by surgery ~~alone must be withdrawn from the study. However, a subject who develops a malignancy that can be cured surgically~~ may continue to receive the assigned study treatment and **the subject** should continue to be followed for subsequent progression of multiple myeloma. **Subjects who require radiation therapy for treatment of second primary malignancy must have study treatment discontinued unless, upon consultation with the Sponsor and review of data, continuation is agreed upon. Subjects who require systemic treatment of a new malignancy must end study treatment but should continue to be followed for PFS2 and OS.**
Rationale: Update the recommended course of action regarding lenalidomide dose adjustment to treat thrombocytopenia and neutropenia to be more consistent with the current package insert.	
6.4.2.1. Thrombocytopenia (Table 4);	Thrombocytopenia (Table 4): Platelet Count: When count returns to ≥30 x 10^9/L after first fall to <30 x 10^9/L; Recommended Course of Action: Resume lenalidomide at ~~15 mg~~ **the next lower dose** Platelet Count: When count returns to ≥30 x 10^9/L for each subsequent drop in count to <30 x 10^9/L; Recommended Course of Action: Resume lenalidomide at the next lower dose. ~~level (10 mg or 5 mg) once daily. Do not decrease dose below 5 mg once daily.~~

Applicable Section(s)	Description of Change(s)
6.4.2.2. Neutropenia (Table 5)	Neutropenia (Table 5): Neutrophil Count: When count first falls to <1.0 x 10^9/L; Recommended Course of Action: Interrupt lenalidomide treatment, ~~start~~ **consider** G-CSF treatment,~~-~~follow complete blood count weekly; Neutrophil Count: When count returns to ≥1.0 x 10^9/L and neutropenia is the only observed toxicity; Recommended Course of Action: Resume lenalidomide at 25 mg ~~once~~ daily **or initial starting dose** Neutrophil Count: When count returns to ≥1.0 x 10^9/L and dose-dependent hematological toxicities other than neutropenia are observed; Recommended Course of Action: Resume lenalidomide at ~~15 mg once daily~~ **the next lower dose** Neutrophil Count: When count returns to ≥1.0 x 10^9/L for each subsequent drop in count to <1.0 x 10^9/L; Recommended Course of Action: Resume lenalidomide at the next lower dose level ~~(15 mg, 10 mg, or 5 mg) once daily. Do not decrease dose below 5 mg once daily.~~
Rationale: Clarify that preinfusion medications are required.	
6.1.3. Prevention of Infusion Reactions	Remove 'guidelines' from Section 6.1.3 header to clarify that preinfusion medications are required.
Rationale: Align text with Amendment INT-3 which removed the whole blood sample for MRD assessment.	
Synopsis; 3.1. Overview of Study Design; 9.5. Biomarkers	The following text is modified: An assessment of MRD will be conducted on ~~whole blood and~~ bone marrow samples. The following text is modified: In addition to planned bone marrow aspirate assessments, a whole blood sample will be collected from subjects as outlined in the Time and Events Schedule ~~for assessment of MRD and~~ for processing to plasma and PBMCs.
Rationale: Clarify the requirements to meet the primary endpoint of progression-free survival.	
9.1.3. Treatment Phase	Text is added: If disease progression has not occurred at the time of the End-of-Treatment visit, disease evaluations must continue until disease progression is confirmed. Subsequent anti-myeloma treatment will not be started until after disease progression is confirmed by the Sponsor.
Rationale: Clarify MRU procedures.	
Time and Events Schedule Overview; 9.6. Medical Resource Utilization	MRU is added to the Disease Evaluation portion of the Time and Events Schedule Overview. Text is modified: ~~Medical resource utilization (MRU) data, principally number of hospitalizations, will be derived from data collected in the eCRF for all subjects throughout the study.~~ **Medical resource utilization (MRU) data, including primary non-protocol driven hospitalizations, outpatient visits, and emergency room visits, should be collected in the eCRF (Hospitalization/Outpatient Visits CRF) by the Investigator and study-site personnel for all subjects throughout the study. Please see CRF completion guidelines.**
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment INT-3 (2 November 2016)

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 International Myeloma Working Group (IMWG) has recently defined new categories of minimal residual disease (MRD)–negativity and has clarified several aspects of disease response assessment along with clinical trial endpoints (Kumar, 2016[16]). In order to align with the new categories of MRD-negativity, the timepoints for collection of bone marrow and whole blood for MRD assessment are revised.

Applicable Section(s)	Description of Change(s)
Rationale: Revision of the timepoints for the assessment of MRD-negativity required to align with newly defined IMWG categories	
Time & Events Schedule (Bone marrow aspirate/biopsy; Blood sample for MRD) 9.2.1.5 Bone Marrow Examination (Table 9); 9.2.1.6 Minimal Residual Disease Assessment; 9.2.2 Endpoints	Text is revised and added to clarify sample timing for MRD assessment: To confirm CR/sCR, assess MRD, and evaluate PD (if feasible). Samples are requested at time of suspected CR/sCR and at 12, 18, 24 and 30 months post C1D1 (+/-1 month). If one of these time points occurs within 1 month of suspected CR, a repeat bone marrow will not be requested. These bone marrow tests will only be required if patient's response is near CR or better by blood and urine evaluations. See Section 9.2.1.5 for additional information including timepoints. The whole blood sample for MRD assessment is removed from the protocol; text is deleted to align with other daratumumab protocols. The following text is modified in Section 9.2.1.5: Additional bone marrow aspirates ~~or biopsies (or both)~~ will be performed to confirm sCR **and** CR~~, or relapse from CR~~ (only one analysis is required, with either IHC or immunofluorescence or 2- to 4- color flow cytometry included in the analysis) and to monitor for MRD **at time points detailed in Table 9**. ~~An additional bone marrow aspirate will be obtained 6, 12, and 18 months +/- 1 month after the achievement of CR to monitor for MRD.~~
Rationale: Secondary objectives modified for consistency with other daratumumab protocols.	
Synopsis; 2. Objectives and Hypothesis; 9.2.2 Endpoints; 11.3 Efficacy Analyses	Time to response is added to objectives and endpoints. This objective is modified: ~~To assess the minimal residual disease (MRD) negative rate after treatment~~ Changed to: **MRD negativity rate** This corresponding endpoint is added: To assess MRD negativity rate, defined as the proportion of subjects assessed as MRD negative, at any timepoint after the date of randomization. Durability of MRD negativity is added to exploratory objectives and endpoints. The order of secondary objectives and efficacy endpoints has been modified for consistency with other daratumumab protocols
Rationale: Criteria modified for the timing of contraception, sperm donation, pregnancy, and fathering a child for consistency across daratumumab protocols.	
4.1 Inclusion Criteria; 4.2 Exclusion Criteria; 4.3 Prohibitions and Restrictions	Inclusion criterion 6: Contraception must continue for **3** months after the last dose of daratumumab. Inclusion criterion 7: Men must not donate sperm for **3** months after the last dose of daratumumab. Exclusion criterion 15: Revised pregnancy timing and for men not to father a child for **3** months after last dose of daratumumab. The change to 3 months is also revised in Prohibition and Restriction 1 and 3.
Rationale: Minor clarification regarding use of dexamethasone.	

Applicable Section(s)	Description of Change(s)
4.2 Exclusion Criteria	Exclusion criterion 3: the following text is revised: (equivalent of dexamethasone 40 mg/day for ~~a maximum~~ 4 days)
Rationale: Clarifications in the Dosage and Administration section	
6. Dosage and Administration	In Figure 4 Schematic Overview Study Treatment Administration, the parenthetical phrase is deleted for dexamethasone "For 1 yr, 20 mg thereafter" is removed from dexamethasone to align figure with text.
6.1.3.1 Preinfusion Medication	Text in the third bullet regarding dexamethasone is revised: Dexamethasone 40 mg IV (**preferred**) or PO ~~(only if IV is not available)~~, approximately 1 hour or less prior to daratumumab infusion. For subjects older than 75 years or underweight (body mass index [BMI] <18.5), dexamethasone 20 mg may be administered as appropriate (see Section 6.3). An equivalent intermediate-acting or long-acting corticosteroid may substitute (see Attachment 6 for conversion table). On days when subjects receive this dose of dexamethasone in the clinic, dexamethasone will not be self-administered at home. **If weekly dexamethasone dosing has been reduced below 10 mg due to adverse events during study, a minimum of dexamethasone 10 mg IV should continue to be administered prior to daratumumab infusions.**
6.2 Lenalidomide (Arm A and Arm B)	The following text is modified: On daratumumab infusion days, **it is recommended that lenalidomide should** be administered either prior to or at the same time (preferred) as the premedications. ~~The daratumumab infusion should begin approximately 1 hour after the lenalidomide administration~~.
6.4.1.1 Daratumumab-Related Toxicity Management	The following text is modified: **Other than on Day 1 of a cycle**, if a daratumumab administration does not commence within the prespecified window (Table 3) of the scheduled administration date, then the dose will be considered a missed dose. **Day 1 of a cycle should not be skipped; however**, ~~If~~ Day 1 of a cycle ~~is~~ **may be** delayed, and Day 1 of subsequent cycles should be adjusted accordingly to maintain the 28-day cycle duration.
6.4.2 Lenalidomide Dose Reductions	The following text is added: After initiation of lenalidomide, subsequent lenalidomide dose adjustment is based on individual subject treatment tolerance. If the investigator determines that an adverse event may be related to lenalidomide, dose adjustment can be done even if not specified in this protocol.
6.4.2.3 Renal Impairment (Table 6, footnote a); Attachment 3 Calculated and Measured Creatinine Clearance	Text is added to specify that calculation of CrCl should be adjusted for body weight in subjects with a body mass index >30 kg/m^2.
6.4.2.4 Other Grade 3 or 4 Adverse Events	Heading is modified to remove "Grade 3 or 4" and the following text is added: Note that the dose modifications above are suggested, but physician discretion and clinical judgment should prevail.
6.4.3 Dexamethasone Dose Modifications	The following text is added: For other Grade 3 or 4 non-hematologic and non-renal toxicities judged by the investigator to be related to dexamethasone alone, treatment with dexamethasone should be interrupted and restarted at the next lower dose level once the toxicity has resolved to Grade 2 or less. Treatment with daratumumab and lenalidomide may continue. For complete details on dexamethasone, refer to the most current local product prescribing information. If weekly dexamethasone dosing has been reduced below 10 mg due to adverse events during study, a minimum of dexamethasone 10 mg IV should continue to be administered prior to daratumumab infusions.

Applicable Section(s)	Description of Change(s)
Rationale: Text is added to clarify timing of urine collection for M-protein analysis.	
9.2.1.2 Myeloma Protein Measurements in Serum and Urine	The following text is added: If the 24-h urine collection (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.
Rationale: Text is modified to clarify imaging assessments for lytic disease.	
9.2.1.7 Assessment of Lytic 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~~ locally ~~laboratory~~ by X-ray ~~roentgenography or the local standard of care imaging, eg,~~ or low-dose CT during the Screening Phase. Magnetic resonance imaging (MRI) may be included as an additional assessment at the discretion of the investigator; however, focal lesions identified by MRI alone cannot be counted as lytic disease.
Rationale: A list of anticipated events is added, consistent with other daratumumab studies.	
12.3.1 All Adverse Events; Attachment 10 Anticipated Adverse Events	Standard text on reporting of anticipated adverse events is added. The list of events is added to Attachment 10.
Rationale: Clarifications regarding CRAB criteria eligibility	
Attachment 1 Modified IMWG Diagnostic Criteria for Multiple Myeloma	The following text is added: Note: Subjects only meeting SLiM CRAB are not eligible. c) Hemoglobin measurement performed as part of standard of care within 42 days before randomization is acceptable for screening for CRAB criteria; but must be performed within 21 days before randomization for other eligibility requirements.
Rationale: Additional minor clarifications.	
Time & Events Schedule; 9.1.4 Follow-up Phase	In Follow-up, a window of ±2 weeks is added for after PD (Q16 wks). The following text is added to the first paragraph in 9.1.4: Every 16-week follow-up contacts should be scheduled from the date of confirmed progression. In subjects for whom disease progression will not be documented (eg, received subsequent anticancer treatment or refused disease evaluations, but agreed to follow-up contacts), the every 16-week follow-up should be scheduled from the date of the End of Treatment Visit.
8.1.5 Prophylaxis for Herpes Zoster Reactivation	Standard text for herpes zoster reactivation text is added. The following is revised: Prophylaxis for herpes zoster reactivation **is recommended during the Treatment Phase, as per institutional guidelines** ~~may be used at the discretion of the investigator.~~
9.2.1.1 Response Categories	The following text is added: For patients with measurable disease by SPEP or UPEP at baseline, increases in serum free light chains (FLC) or the FLC ratio alone do not meet criteria for progressive disease
9.8 Safety Evaluations	Minor changes in the serum chemistry panel: -blood urea nitrogen (BUN) **or urea** -total; direct bilirubin **(not required except in case of congenital bilirubinemia, such as Gilbert disease)** *New footnote*: *Sodium and potassium assessment were added in Protocol Amendment 2; however, collection of sodium and potassium results will be done retrospectively from the date of subject consent for the duration of the study, if collected as part of routine care

Applicable Section(s)	Description of Change(s)
9.8 Safety Evaluations; 11.9 Safety Analyses; Time & Events Schedule	Text is modified to clarify vital signs: Descriptive statistics of **baseline** temperature, pulse/**heart rate**, and blood pressure (systolic and diastolic) values ~~and changes from baseline~~ will be summarized.
17.5 Case Report Form Completion	Template text is revised based on the current Janssen global protocol template.
References	New references are added: Chapuy 2016 Kumar 2016
Attachment 7 Asthma Guidelines	Typo corrected for Persistent, Mild: >2 days/week but not daily.
Attachment 8 International Staging System	Typo corrected for Stage III: Serum $ß_2$ microglobulin ≥5.5 mg/L Typo corrected for Note 2: Serum $ß_2$ microglobulin 3.5 – 5.**4** mg/L
Title page	Janssen Sciences Ireland UC is added and Janssen Infectious Diseases BVBA is removed per the protocol template.
Abbreviations	SLiM is defined
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment INT-2 (26 August 2015)

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: To incorporate Indirect Antiglobulin (Coombs) Testing (IAT) during the Screening Phase due to the risk of daratumumab interference with blood typing, as well as make updates throughout the protocol to align with the other daratumumab Phase 3 protocols and to incorporate regulatory agency feedback.

Applicable Section(s)	Description of Change(s)
Rationale: Due to risk of daratumumab interference with IAT testing, in addition to blood typing, subjects must also have IAT performed at screening.	
Time and Events Schedule Overview;	Blood type assessment **(ABO, Rh) and IAT** must be performed at screening and at C1D1 predose in Arm B only.
4.3 Prohibitions and Restrictions, Criterion #7	Removed the text pertaining to blood typing from here as this information is provided in Section 9.8 Safety Evaluations.
9.8 Safety Evaluations	Updated the requirement for blood typing and IAT results to align with other Phase 3 daratumumab protocols.
Rationale: Updated inclusion and exclusion criteria for clarity, to align with IMWG criteria, and to align with other Phase 3 daratumumab protocols.	
4.1 Inclusion Criteria Criterion #2, bullet 2.1	**Criterion modified as per Amendment INT-2:** 2.1 Subject must have documented multiple myeloma satisfying the CRAB **(calcium elevation, renal insufficiency, anemia and bone abnormalities)** criteria (see

Applicable Section(s)	Description of Change(s)
	Attachment 1), **monoclonal plasma cells in the bone marrow ≥10% or presence of a biopsy proven plasmacytoma,** and measurable disease. • Measurable disease, **as assessed by central laboratory**, defined by any of the following: – IgG 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 serum or urine:** Serum immunoglobulin free light chain ≥10 mg/dL and abnormal serum immunoglobulin kappa lambda free light chain ratio.
Criterion #5, bullet g1	Creatinine clearance ≥30 mL/min (for lenalidomide dose adjustment for subjects with creatinine clearance 30-**50** mL/min, refer to Section 6.2). Creatinine clearance can be calculated using the Cockcroft-Gault formula provided in Attachment 3; **or for subjects with over- or underweight, creatinine clearance may be measured from a 24-hours urine collection using the formula provided in Attachment 3**;--
Criterion #5, bullet h1	corrected serum calcium ≤14 mg/dL (≤3.5 **mM/L**); or free ionized calcium **≤6.5 mg/dL (≤1.6 mM/L)** (Attachment 4)
Criterion #6, bullet 6.1	Women of childbearing potential must commit to either abstain continuously from heterosexual sexual intercourse or to use 2 methods of reliable birth control simultaneously. This includes one highly effective form of contraception (tubal ligation, **intrauterine device [IUD], hormonal [progesterone-only birth control pills or injections** or partner's vasectomy) and one additional effective contraceptive method (male latex or synthetic condom, diaphragm, or cervical cap). Contraception must begin 4 weeks prior to dosing **and must continue for 4 months after the last dose of daratumumab.** Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy or bilateral oophorectomy. **(Also see Attachment 5: Lenalidomide Global Pregnancy Prevention Plan).**
4.2 Exclusion Criteria Criterion #8.1a and Criterion #8. 1b	Modified the criteria pertaining to subjects with COPD and severe persistent asthma to align with other Phase 3 daratumumab protocols. **8.1a) Subject has 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 <50% of predicted normal.** **8.1b) Subject has had known moderate or severe persistent asthma within the last 2 years (see Attachment 7), or currently has uncontrolled asthma of any classification. (Note that subjects who currently have controlled intermittent asthma or controlled mild persistent asthma are allowed in the study).** **Attachment 7: Asthma Guidelines was added.**
Criterion #9.1	Subject is known to be seropositive for human immunodeficiency virus (HIV) or hepatitis B **(defined by a positive test for hepatitis B surface antigen [HBsAg] or antibodies to hepatitis B surface and core antigens [anti-HBs and anti-HBc, respectively])** or hepatitis C (**anti-HCV antibody positive or HCV-RNA quantitation positive).**
Rationale: Clarified that the visit window is not intended for all study visits, only intended for the start of a treatment cycle	

Applicable Section(s)	Description of Change(s)
Time and Events Schedule Overview	Modified the second sentence: Study treatment should be initiated within 72 hours after randomization. **Day 1 of each cycle** ~~Each study visit~~ may occur ±3 days of the scheduled day in order to accommodate the schedule of the site or subject.
Rationale: Clarified that if a full chest CT has been done, it is not necessary to perform an additional chest X-ray	
Time and Events Schedule Overview 9.1.2 Screening	Modified Procedures: Chest X-ray **(or full chest CT scan)**
Rationale: To clarify the timing of daratumumab PK sample collection on infusion days.	
Time and Events Schedule Overview 6.1.2 Daratumumab Administration	Modified Laboratory Assessments for Daratumumab PK sampling: Arm B only. On dara infusion days, 1 sample to be collected before **infusion start** (window -2 hrs) and 1 sample **to be collected** after **end of infusion** (window +2 hrs).~~infusion~~ As noted in the Time and Events Schedule, vital signs should be monitored extensively on Cycle 1 Day 1 before, during, and after the first infusion of daratumumab. For all other 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.
Rationale: To clarify that vital signs 2 hours post end of infusion are not necessary	
Time and Events Schedule, Dose Administration	Modified Vital Signs Notes: On Cycle 1 Day 1: Immediately before the start of dara infusion; at 0.5, 1, 1.5, 2, 3.5 hrs after the start of the infusion; at end of infusion; and 0.5, **and** 1 hr after end of infusion.
Rationale: To allow for flexibility if preinfusion medications are administered orally.	
6.1.3.1 Time and Events Schedule, Dose Administration, Pre-infusion medications	• **An antihistamine (diphenhydramine 25-50 mg IV or PO, or equivalent but avoid IV use of promethazine) approximately 1 hour prior to infusion (see Attachment 9 for list of antihistamines that may be used)** Added the sentence: **If necessary, all PO preinfusion medications may be administered outside of the clinic on the day of the infusion, provided they are taken within 3 hours before the infusion.**
Rationale: Removed the requirement that tracheostomy equipment needs to be available in case of infusion-related reactions.	
6.1.4 Management of Infusion Related Reactions	Trained study staff at the clinic should be prepared to intervene in case of any infusion reactions 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**~~. Attention to staffing should be considered when multiple subjects will be dosed at the same time.
Rationale: To reflect current practice, updated management of infusion-related reactions section to indicate that the infusion will be paused (not interrupted or slowed down) if an infusion-related reaction occurs.	
6.1.4 Management of Infusion Related Reactions	If an infusion-related reaction develops, then the infusion should be **paused** ~~temporarily interrupted or slowed down~~. If an infusion is **paused** ~~or the infusion rate is decreased~~, then a longer-than-anticipated infusion time may occur.

Applicable Section(s)	Description of Change(s)
Rationale: FEV1 measurement is not relevant for asthma assessment.	
Time and Events Schedule Overview; 9.8 Safety Evaluations	For subjects with COPD ~~and/or asthma~~a, FEV1 should be measured at baseline.
6.1.3.2 Postinfusion Medications	For subjects with higher risk of respiratory complications (ie, subjects **with mild asthma, or subjects with COPD** who have a FEV1 <80%), the following postinfusion medications should be considered.
Rationale: Updated protocol to align with Revlimid US Package Insert and EU SmPC	
1.3 Lenalidomide	Added: **REVLIMID® (lenalidomide) in combination with dexamethasone was approved by both U.S. Food and Drug Administration and the European Commission for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant, on 18 February 2015 and 20 February 2015, respectively.**
6.2 Lenalidomide (Arm A and Arm B) 6.4.2.3 Renal Impairment	Lenalidomide will be self-administered at a dose of 25 mg PO each day on Days 1 through 21 of each 28 day cycle for subjects with creatinine clearance **>50** mL/min. If creatinine clearance is between 30 and **50** mL/min, the dose of lenalidomide will be 10 mg every 24 hours. Once the creatinine clearance is **>50** mL/min during the course of the treatment, lenalidomide can be increased to 25 mg. Lenalidomide dose adjustment should be instituted for subjects with a creatinine clearance of **50 mL/minute** or less. The recommended doses for subjects with multiple myeloma and renal impairment are shown in Table 6. **Table 6: Lenalidomide Dose Adjustment for Renal Impairment** **Category** / **Renal Function** / **Dose** Moderate renal impairment / CrCl 30-50 mL/min / 10 mg every 24 hours Severe renal impairment / CrCl <30 mL/min (not requiring dialysis) / 15 mg every 48 hours
Rationale: To provide guidance on management of missed lenalidomide doses	
6.2 Lenalidomide (Arm A and Arm B)	Added the following 3rd paragraph: If a daily lenalidomide dose is missed, it may be taken if <12 hours have elapsed since the time that it should have been taken. If the next dose is scheduled to be taken within 12 hours, the missed lenalidomide dose should be skipped.
Rationale: Aligned language to be consistent with criteria in other Phase 3 protocols.	
6.4.1.1 Daratumumab-Related Toxicity Management	The criteria for dose delay due to hematologic toxicity have been revised. • Grade 4 **hematologic toxicity** ~~thrombocytopenia or~~ • Grade 3 thrombocytopenia with bleeding • ~~**Grade 4 neutropenia, if this is the second occurrence despite growth factor support**~~ • Febrile neutropenia ~~of any grade~~ ----- ----**A missed dose will not be made up.**--- ---Doses of daratumumab may be delayed up to 4 weeks (Cycle 1 to Cycle 6) or up to 6 weeks **(Cycle 7 and beyond). If Day 1 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 is delayed, then the dates of the subsequent within-cycle doses should not be adjusted.** Any adverse event deemed to be related to daratumumab **that requires a dose hold of more than 4 weeks (Cycle 1 to Cycle**

Applicable Section(s)	Description of Change(s)
	6) or more than 6 weeks (Cycle 7 and beyond) will result in permanent discontinuation of daratumumab.----
6.4.1.2 Daratumumab Interruption or Missed Doses	Subjects whose dose was delayed for more than 4 weeks **(Cycle 1 to Cycle 6) or more than 6 weeks (Cycle 7 and beyond)** should have study treatment discontinued, unless, upon consultation with the sponsor and the review of safety and efficacy, continuation is agreed upon.

Rationale: Changed per Irish Regulatory Authority request (aligned with lenalidomide SmPC and US Package Insert

6.4.2.2. Neutropenia — Modified Table 5 as below:

Neutrophil Count	**Recommended Course of Action**
• When count first falls to $<1.0 \times 10^9$/L • When count returns to $\geq 1.0 \times 10^9$/L and neutropenia is the only observed toxicity	• Interrupt lenalidomide treatment, start G-CSF treatment, follow complete blood count weekly • Resume lenalidomide at 25 mg once daily
• **When count returns to $\geq 1.0 \times 10^9$/L and dose-dependent hematological toxicities other than neutropenia are observed**	• Resume lenalidomide at 15 mg once daily
• For each subsequent drop in count to $<1.0 \times 10^9$/L • When count returns to $\geq 1.0 \times 10^9$/L	• Interrupt lenalidomide treatment • Resume lenalidomide at the next lower dose level (15 mg, 10 mg, or 5 mg) once daily. Do not decrease dose below 5 mg once daily

Rationale: Updated recommended therapies to prevent deep vein thrombosis and pulmonary embolism to align with IMWG criteria.

8.1.1 Prevention of Deep Vein Thrombosis and Pulmonary Embolism — Text in Section 8.1.1 reworded.

Lenalidomide has been associated with increased incidence of deep vein thrombosis and pulmonary embolism. **Therefore, prophylaxis of venous thromboembolism (VTE) for all subjects is recommended according to IMWG guidelines as well as at the investigator's discretion (Palumbo 2008). Both individual and myeloma-related risks of VTE should be taken into account in determining the type of thromboprophylaxis. In summary:**

- **If no risk factor, or any one risk factor is present, aspirin 81-325 mg once daily is recommended or dose per institutional standards**
- **If 2 or more risk factors are present, low molecular weight heparin (LMWH) (equivalent of enoxaparin 40 mg once daily) or full-dose warfarin, international normalized ratio (INR) 2-3, is recommended**
- **If any myeloma therapy-related risk factor is present, then LMWH (equivalent of 40 mg enoxaparin once daily) or full-dose warfarin (target INR 2-3) is recommended**

Applicable Section(s)	Description of Change(s)
	~~all subjects should be prophylactically treated with aspirin at a dose of 100 to 150 mg PO daily. Subjects at increased risk of thromboembolic events (based on their medical history) should be treated with enoxaparin at a dose of 40 mg subcutaneously daily (or other low molecular heparin with equivalent dose and frequency for prophylaxis indication). The injection should be handled according to local practice.~~
Rationale: Clarification of the use of bisphosphonate after Cycle 1	
8.1.2 Bisphosphonate Therapy	After Cycle 1, investigators should not prescribe bisphosphonates to subjects who have not received it before, **unless it has been discussed with sponsor and there is no** sign of disease progression.
Rationale: Modification of the dexamethasone dose in both treatment arms and provides guidance on management of missed doses.	
Synopsis: Dosage and Administration 6.3 Dexamethasone (Arm A and Arm B)	Added sentence: **If a weekly dexamethasone dose is missed, it may be taken if <4 days have elapsed since the time that it should have been taken. If the next dose is scheduled to be taken within 3 days, the missed dexamethasone dose should be skipped.**
Rationale: Allows for flexibility in scheduling	
6 Dosage and Administration; 9.1.3 Treatment Phase	Inserted following sentence in 1st paragraph: **In Cycles 1 through 6, weekly or bi-weekly daratumumab infusions may be given within ±1 day of the scheduled day in order to accommodate the schedule of the site or subject. In all cycles, weekly dexamethasone doses may be given within ±1 day of the scheduled day in order to accommodate the schedule of the site or subject. Changes to within-cycle dosing should not impact Day 1 of the next cycle.** Also inserted new **Figure 4: Schematic Overview Study Treatment Administration** in Section 6
Rationale: Clarification of bone marrow examination requirements. Clinical staging must be done locally; no option for this to be done centrally.	
9.2.1.5 Bone Marrow Examination	Bone marrow aspirate or biopsy will be performed at Screening for clinical **characterization** (morphology, **IHC or immunofluorescence or 2- to 4- color flow cytometry,** and cytogenetics), to establish baseline **multiple myeloma clonality** to monitor for MRD and to perform molecular subtyping to monitor daratumumab activity in high-risk molecular subgroups. Good quality slides are required for morphological examination to determine plasma cell percentage in the bone marrow. Assessment by flow cytometry alone is not sufficient. **Bone marrow examination for disease assessment ~~Clinical staging may~~ will be** performed locally; however, a portion of the bone marrow aspirate must be sent to the central **laboratory** for analysis of MRD and molecular subtyping. A fresh bone marrow aspirate at screening is required if at all possible, by exception non-decalcified diagnostic tissue (bone marrow aspirate slides or FFPE tissue) may be supplied for MRD assessment instead. Additional bone marrow aspirates or biopsies (or both) will be performed to confirm sCR, CR, or relapse from CR **(only one analysis is required, with either** IHC or immunofluorescence **or 2- to 4- color flow cytometry included in the analysis)** and to monitor for **MRD. An** additional bone marrow aspirate will be obtained 6, 12, and 18 months +/- 1 month after the achievement of CR to monitor for MRD. If feasible, a bone marrow aspirate may be collected from subjects at disease progression to evaluate mechanisms of daratumumab resistance. **Inserted Table 9. Bone Marrow Testing**
Rationale: Description of Daratumumab interference with Indirect Antiglobulin Test (IAT) results.	

Applicable Section(s)	Description of Change(s)
9.8 Safety Evaluations	Inserted the following: **Daratumumab Interference with Indirect Antiglobulin Test (IAT) results:** **Daratumumab interferes with the Indirect Antiglobulin Test (IAT), which is a routine pre-transfusion test performed to identify a patient'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) 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 IAT interference by treating reagent RBCs with dithiothreitol (DTT) (Chapuy 2015).** Possible methods for blood banks to provide safe RBCs for transfusion to subjects receiving daratumumab include: a) Providing ABO/RhD compatible, phenotypically or genotypically matched units b) Providing ABO/RhD compatible, K-negative units after ruling out or identifying alloantibodies using dithiothreitol (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 IB. ~~Blood type assessment CD38 is expressed on erythrocytes to a minor extent. Hemolysis could occur following the infusion of daratumumab, which would confound the blood type assessment. To be cautious and in case of urgent need for blood transfusion, the subject's blood type, including minor group, will be assessed before the first infusion of daratumumab. Subjects in Arm B should at all times carry a card with their blood type during the study.~~
Rationale: Inserted information per Irish Regulatory request	
12.1.1 Adverse Event Definitions and Classifications	Inserted: **Suspected Unexpected Serious Adverse Reactions (SUSARs)** **If a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the study treatment 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). Refer to Section 12.3.3 for SUSAR Reporting Requirements.** ~~If a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the study treatment 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).~~
12.3.3 Suspected Unexpected Serious Adverse Reactions	Added Section. **The sponsor assumes responsibility for appropriate reporting of all Suspected Unexpected Serious Adverse Reactions (SUSAR) [serious adverse events that are unlisted (unexpected) and associated with the use of the study drug] to the regulatory authorities in accordance with GCP. The sponsor will also report to the investigator (and the head of the investigational institute where**

Applicable Section(s)	Description of Change(s)
	required) all serious adverse events that are unlisted (unexpected) and associated with the use of the study drug. The investigator (or sponsor where required) must report these events to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.
Rationale: Attachment 1 was updated to be consistent with other Daratumumab protocols	
Attachment 1: Modified IMWG Diagnostic Criteria for Multiple Myeloma	Entire attachment updated to be consistent with other Daratumumab protocols
Rationale: Added for convenience by clinical operations (logistical purposes)	
Time and Events Schedule, Overview: Blood sample for MRD	For subjects who maintain CR, whole blood sample will also be obtained at 6, 12, and 18 months **± 1 month** after confirmed CR.
Rationale: Clarification of disease evaluation testing in Screening Phase	
Time and Events Schedule, Overview:	Added clarification on serum and urine disease evaluation at Screening in the Disease Evaluation section: Serum disease evaluations (SPEP): **X (Repeat on C1D1 if not within 14 days prior to C1D1)** Urine disease evaluations (UPEP): **X (Repeat on C1D1 if not within 14 days prior to C1D1)** Calcium, albumin, β_2-microglobulin: **X (Repeat calcium and albumin on C1D1 if not within 14 days prior to C1D1); don't repeat β_2-microglobulin**
Rationale: Miscellaneous updates for clarity.	
Time and Events Schedule, Dose Administration	Removed the requirement to measure vital signs 2 hours after the end of infusion.
6.1.3.1 Preinfusion Medication	Change to bullet 3: An equivalent **intermediate-acting or** long-acting corticosteroid may substitute (see Attachment 6 for conversion table).
6.1.3.2 Postinfusion Medication	Control medications for lung disease (eg, inhaled corticosteroids ± long-acting β_2 adrenergic receptor agonists for subjects with asthma; long-acting bronchodilators such as tiotropium or ~~salbumatol~~ **salmeterol** ± inhaled corticosteroids for subjects with COPD)
8.3 Prohibited Therapies	Concomitant administration of any other antineoplastic therapy for the intention of treating multiple myeloma **and other cancers** not defined in the study protocol is prohibited. Nonsteroidal anti-inflammatory agents should be **used with caution in order** to prevent myeloma-related kidney disease.
9.2.1.8 Documentation of Extramedullary Plasmacytomas	To qualify for PR, the sum of products of the perpendicular diameters of the existing extramedullary plasmacytomas must have decreased by at least 50% ~~or 25%, respectively~~, and new plasmacytomas must not have developed (see the disease response criteria in Table 8).
9.5 Biomarkers	Biomarker assessments will focus on 2 main objectives including evaluating the ability of daratumumab + Rd to reduce MRD in subjects who achieve a complete

Applicable Section(s)	Description of Change(s)
	response (compared to Rd alone) and to determine the clinical benefit (ORR, PFS, and OS) of daratumumab + Rd in high-risk molecular subtypes (del17p, t(4;14), **t(14;16)**, specific gene signatures, specific mutations).
Attachment 3: Calculated and Measured Creatinine Clearance	Added the formula to measure CrCL to the attachment:
5 Treatment Allocation and Blinding	Eligible subjects will be stratified by **International Staging System (I vs II vs III see Attachment 8),** region (North America vs Other), and age (<75 vs ≥75) and then randomized to treatment in a 1:1 ratio to either Treatment Arm A (Rd alone) or Treatment Arm B (daratumumab+Rd [DRd]). **A new Attachment 8 was added.**
6.1.3.1 Preinfusion Medication	**An antihistamine (diphenhydramine 25-50 mg IV or PO, or equivalent but avoid IV use of promethazine) approximately 1 hour prior to infusion (see Attachment 9) for list of antihistamines that may be used).** Added Attachment 9.
9.2.2 Endpoints, Secondary Endpoints	• Endpoints Overall response rate (ORR), defined as the proportion of subjects who achieve **PR or better**, according to the IMWG criteria, during or after the study treatment. • Duration of response, calculated from the date of initial documentation of a response **(PR or better)** to the date of first documented evidence of progressive disease, as defined in the IMWG criteria. For subjects who have not progressed, data will be censored at the last disease evaluation before the start of any subsequent anti-myeloma therapy.
12.3.1 All Adverse Events	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 **and for at least 6 months after treatment ends** indicating the following: ---
Rationale: Hydrocortisone is not an adequate substitute for a glucocorticosteroid as it is a short acting corticosteroid. Per request of Swedish HA, hydrocortisone has been replaced with betamethasone as an acceptable substitute for pre-medication with dexamethasone, due to the short duration of action of hydrocortisone. Attachment 6 is modified accordingly.	
Attachment 6: Conversion Table for Glucocorticosteroid Dose	Removed hydrocortisone (20 mg) because it is short-acting and therefore not an adequate substitution.

Generic Name	**Oral or Intravenous Dose (mg)**
Dexamethasone	0.75
~~Hydrocortisone~~	~~20~~
Methylprednisolone	4
Prednisolone	5
Prednisone	5
Betamethasone	**0.6**

Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, abbreviations or spelling changes were made.

Amendment INT-1 (29 October 2014)

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: To incorporate investigator feedback into the protocol and to further clarify MRD monitoring.

Applicable Section(s)	Description of Change(s)
Rationale: To clarify that when a subject discontinues lenalidomide/dexamethasone study treatment on Arm B, they would still continue to receive dexamethasone as premedication.	
Synopsis, Overview of Study Design; 3.1 Overview of Study Design; 6.3 Dexamethasone (Arm A and Arm B)	Text was added to indicate that subjects will continue to receive dexamethasone as a premedication for daratumumab administration even after the lenalidomide/dexamethasone treatment is discontinued.
Rationale: To allow for a bone marrow biopsy or aspirate (or both) to confirm CR.	
Time and Events Schedule Overview; 9.2.1.5 Bone Marrow Examination	Additional bone marrow aspirates or biopsies (or both) will be performed to confirm sCR, CR, or relapse from CR (IHC or immunofluorescence) and to monitor for MRD. Only 1 bone marrow sample is required, with either IHC or immunofluorescence included in the analysis. For subjects who maintain CR, fresh aspirate will also be obtained at 6 and 12 months +/- 1 month after confirmed CR to monitor for MRD. A portion of all bone marrow tissues may be used for other biomarker assessments
Rationale: To allow for the possibility of stopping treatment ≥24 months based on MRD status, an additional time point of 18 months was added for collection of fresh aspirate and a whole blood sample after confirmed CR to monitor MRD.	
Synopsis, Efficacy Evaluations/Endpoints; Time and Events Schedule Overview; 9.2.1.5 Bone Marrow Examination; 9.2.1.6 Minimal Residual Disease Assessment; 9.2.2 Endpoints	Text was added to indicate that for subjects with confirmed CR, an additional bone marrow aspirate and whole blood sample will be obtained 6, 12, and **18** months +/- 1 month to monitor for MRD.
Rationale: To indicate that bone marrow aspirate or biopsy performed at Screening for clinical staging will be analyzed for morphology and via cytogenetics, only.	
9.2.1.5 Bone Marrow Examination	Bone marrow aspirate or biopsy will be performed at Screening for clinical staging (morphology and cytogenetics~~, and immunohistochemistry [IHC] or immunofluorescence or flow cytometry~~) to establish baseline multiple myeloma clonality, to monitor for MRD, and to perform molecular subtyping to monitor daratumumab activity in high-risk molecular subgroups.
Rationale: To clarify that good quality slides are required for morphological examination to determine plasma cell percentage in the bone marrow.	
9.2.1.5 Bone Marrow Examination	Good quality slides are required for morphological examination to determine plasma cells percentage in the bone marrow. Assessment by flow cytometry alone is not sufficient

Applicable Section(s)	Description of Change(s)
Rationale: To include clarithromycin as a prohibited therapy because it may have potential anti-multiple myeloma effects when combined with lenalidomide and dexamethasone.	
8.3 Prohibited Therapies	Added clarithromycin as a prohibited therapy.
Rationale: To exclude subjects with uncontrolled cardiac arrhythmias (thereby allowing participation of subjects with controlled cardiac arrhythmias).	
4.2 Exclusion Criteria	Subject has clinically significant cardiac disease, including: • myocardial infarction within 1 year before randomization, or an unstable or uncontrolled disease/condition related to or affecting cardiac function (eg, unstable angina, congestive heart failure, New York Heart Association Class III IV • **uncontrolled** cardiac arrhythmia (NCI CTCAE Version 4 Grade ≥2) or clinically significant ECG abnormalities • screening 12-lead ECG showing a baseline QT interval as corrected by Fridericia's formula (QTcF) >470 msec
Rationale: To clarify that the secondary objective and secondary endpoint is to assess the MRD negative rate.	
Synopsis, Secondary Objectives; 2.1 Objectives	To assess the MRD negative rate after treatment
Synopsis, Efficacy Evaluations/Endpoints; 9.2.2 Endpoints	Assess MRD negative rate, as measured in subjects who achieve CR/sCR, at 6 and 12 months after confirmed CR.
Rationale: To align PRO and ECOG performance status evaluations with study visits.	
Time and Events Schedule Overview	Evaluations will be conducted on D1 of Cycle 3, 6, 9, 12 for year 1; every 6th cycle thereafter until EOT (PD). Post-PD evaluations will be collected at Weeks 8 and 16.
Rationale: Added a PRO evaluation at Screening which will allow the PRO assessment conducted during the study to be compared with baseline.	
Time and Events Schedule Overview	Added an assessment during the Screening Phase for the PROs: EORTC-QLQ-30, EQ-5D-5L.
Rationale: To clarify that all PRO measures will be collected via an electronic device (ePRO) and the mode of data transfer.	
Time and Events Schedule Overview; 9.7 Patient Reported Outcomes	All PRO measures will be collected via an electronic device (ePRO).
17.6 Data Quality Assurance/Quality Control	PRO data will be transmitted to the ePRO vendor database and then to the sponsor's database.
Rationale: To clarify the administration schedule of daratumumab, in particular, starting at Cycle 7 and beyond, treatment will be every 4 weeks rather than monthly.	
Synopsis, Overview of Study Design; 3.1 Overview of Study Design	For subjects assigned to DRd, daratumumab will be administered weekly for the first 8 weeks (Cycles 1-2) of treatment and then every other week for 16 weeks (Cycles 3-6), then every 4 weeks (from Cycle 7 and beyond) until disease progression or unacceptable toxicity.

Applicable Section(s)	Description of Change(s)
Rationale: To revise the inclusion criteria to align with the other protocols in the daratumumab program.	
4.1 Inclusion Criteria	total bilirubin ≤**2.0** x ULN, except in subjects with congenital bilirubinemia, such as Gilbert syndrome **(direct bilirubin ≤2.0 x ULN);** corrected serum calcium ≤14 mg/dL (≤3.5 **mM/L**); or free ionized calcium **<6.5 mg/dL (<1.6 mM/L)**
Rationale: To align the creatinine clearance calculation with the other protocols in the daratumumab program.	
4.1 Inclusion Criteria	g) Creatinine clearance ≥30 mL/min (for lenalidomide dose adjustment for subjects with creatinine clearance 30-60 mL/min, refer to Section 6.2). Creatinine clearance may be calculated using the Cockcroft-Gault formula provided in Attachment 3
Attachment 3	Added the Cockcroft-Gault formula for Calculated Creatinine Clearance.
Rationale: To align the criteria for a dose delay with the other protocols in the daratumumab program.	
6.4.1.1 Daratumumab-Related Toxicity Management	Grade 4 thrombocytopenia was added to the criteria for a dose delay.
Rationale: To further clarify procedures not considered to be major surgeries.	
4.2 Exclusion Criteria	Included vertebroplasty as a procedure that is not considered to be a major surgery.
Rationale: To specify the timing of lenalidomide administration and to align with other protocols in the daratumumab program.	
6.2 Lenalidomide (Arm A and Arm B)	On daratumumab infusion days, lenalidomide will be administered at the same time as the premedications. The daratumumab infusion should begin approximately 1 hour after the lenalidomide administration.
Rationale: Fixed typographical errors whereby the sample size remained the same, but the assumptions were corrected.	
Synopsis, Statistical Methods; 11.2 Sample Size Determination	The sample size calculation is performed on the basis of the following assumption. Based on the published data, the median PFS for Rd arm is assumed to be approximately **24** ~~6~~ months. Assuming that DRd can reduce the risk of the disease progression or death by 25%, ie, assuming the hazard ratio (DRd vs Rd) of **0.75** ~~0.724~~, a total of 390 PFS events is needed to achieve a power of **80%** ~~85%~~ to detect this hazard ratio with a log-rank test (two-sided alpha is 0.05). With a 21-month accrual period and an additional 24-month follow-up, the total sample size needed for the study is approximately 730 (365/arm) subjects. The sample size calculation has taken into consideration an annual dropout rate of 5%.
Rationale: Because dexamethasone in IV formulation is not available in some countries, the PO administration of dexamethasone is permitted (only when IV is not available).	
Time and Events Schedule, Dose Administration; 6.1.3.1 Preinfusion Medication	Dexamethasone 40 mg **IV or PO (only if IV is not available)**
Rationale: To make the administration of drug medication more convenient for patients.	
6.2 Lenalidomide (Arm A and Arm B)	On daratumumab infusion days, lenalidomide will be administered **either prior to or** at the same time **(preferred)** as the premedications.

Applicable Section(s)	Description of Change(s)
Rationale: To align with other protocols in the daratumumab program.	
14.4 Preparation, Handling, and Storage	Clarified that daratumumab must be protected from light. Clarified that daratumumab infusion solution prepared for administration does not need to be stored in a refrigerator. Clarified that the daratumumab infusion solution does not need to be kept at room temperature for approximately 1 hour before the start of infusion and that the infusion does not have to be completed within 24 hours of preparation. Added that daratumumab will be diluted in a sterile, pyrogen-free physiological saline solution (0.9%NaCl) prior to IV administration. Included that additional guidance can be found in the Investigational Product Preparation Instructions and Investigational Product Procedures Manual.
6.1.3.1 Preinfusion Medication	Preinfusion medications for subjects receiving daratumumab will be administered as described in the Time and Events Schedules. On daratumumab infusion days, subjects will receive the following medications prior to infusion: • Acetaminophen (paracetamol) 650-1000 mg IV or orally (PO) **approximately** 1 hour or less prior to daratumumab infusion • An antihistamine (diphenhydramine 25-50 mg IV or PO, or equivalent) approximately ~~12 hours prior and again approximately~~ 1 hour prior to infusion ~~on Cycle 1 Day 1, for all subsequent infusions approximately 1 hour prior~~ • Dexamethasone 40 mg IV or PO, **approximately**1 hour or less prior to daratumumab infusion. Dexamethasone 20 mg may be administered as appropriate [see Section 6.3]. An equivalent long-acting corticosteroid may substitute [see Attachment 6 for conversion table]. On days when subjects receive this dose of dexamethasone in the clinic, dexamethasone will not be self-administered at home.
Rationale: Miscellaneous grammatical, formatting, or spelling changes were made for consistency and clarification.	
Time and Events Schedule, Dose Administration; 6.1.3.1 Preinfusion Medication	For consistency with other parts of the protocol, added the below bolded text and removed the text in strikeout. Administer **approximately** 1 hour before daratumumab infusion. • Dexamethasone 40 mg IV or PO **(only if IV is not available)**. **For subjects older than 75 years or underweight (BMI <18.5), see Section 6.3**. Substitutions for dexamethasone allowed, see Attachment 6. • An antihistamine (diphenhydramine 25-50 mg **IV or PO**, or equivalent) ~~on C1D1 administer 12 hours before infusion and again 1 hr before infusion~~ • Acetaminophen (paracetamol) 650-1000 mg **IV or PO**
Synopsis, Overview of Study Design; 3.1 Overview of Study Design; 5 Treatment Allocation	Amended the stratification factor wording to "International ~~Scoring~~ **Staging** System" to be consistent with the proper nomenclature.
6.4.1.1 Daratumumab-Related Toxicity Management	To emphasize the criteria when to stop daratumumab, bolded and underlined the following sentence: **ONLY if any of the following criteria are met, and the event cannot be ascribed to lenalidomide, the daratumumab infusion must be held to allow for recovery from toxicity**. Clarified that any adverse event deemed to be related to daratumumab **and unrelated to lenalidomide** that requires a dose hold of more than 4 weeks will result in permanent discontinuation of daratumumab.

Applicable Section(s)	Description of Change(s)
Time and Events Schedule Overview	Clarified that both PRO questionnaires and ECOG performance status must be administered and completed prior to any other study procedures or assessments for that study visit. Clarified that β_2-microglobulin will be evaluated at screening only. Clarified that EOT is part of the Treatment Phase of the study.
4.2 Exclusion Criteria	Removed intolerance to lenalidomide from exclusion criteria 12 because subjects in this study are newly diagnosed multiple myeloma patients and have never been exposed to lenalidomide.
Synopsis, Overview of Study Design; Time and Events Schedule, Dose Administration; 3.1 Overview of Study Design; 6.1.3.1 Preinfusion Medication	Provided the generic name for paracetamol (acetaminophen), as this is a global study
14.2 Physical Description of Study Drug	Clarified that the daratumumab supplied for this study is a colorless to ~~slightly~~ yellow liquid and sterile concentrate of 20 mg/mL in a vial.
1.1.3 Transplant-ineligible Population; 1.3 Lenalidomide; 3.2 Study Design Rationale	Updated the reference to the Frontline Investigation of Revlimid and Dexamethasone versus Standard Thalidomide (FIRST) study (previously referred to in protocol as MM-020 study), with citation to the recently published NEJM publication.
Synopsis, Overview of Study Design; Time and Events Schedule, Dose Administration; 3.1 Overview of Study Design; 3.2 Study Design Rationale; 6.2 6.2 Lenalidomide (Arm A and Arm B); 6.3 Dexamethasone (Arm A and Arm B)	To be consistent throughout the protocol, text was added that treatment would continue until disease progression **or unacceptable toxicity**.
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

SYNOPSIS

A Phase 3 Study Comparing Daratumumab, Lenalidomide, and Dexamethasone (DRd) vs Lenalidomide and Dexamethasone (Rd) in Subjects with Previously Untreated Multiple Myeloma who are Ineligible for High Dose Therapy

Daratumumab is a human IgG1κ monoclonal antibody (mAb) that binds with high affinity to a unique epitope on CD38, a transmembrane glycoprotein. It is a targeted immunotherapy directed towards tumor cells that express high levels of CD38, such as plasma cells from patients with multiple myeloma. This target is distinct from those of other approved agents for multiple myeloma therapy.

OBJECTIVES AND HYPOTHESIS

Primary Objective

The primary objective is to compare the efficacy of daratumumab when combined with lenalidomide and dexamethasone (DRd) to that of lenalidomide and dexamethasone (Rd), in terms of progression-free survival (PFS) in subjects with newly diagnosed myeloma who are not candidates for high dose chemotherapy and autologous stem cell transplant.

Secondary Objectives

The secondary objectives are:

- To evaluate clinical outcomes including:
  - Time to disease progression (TTP)
  - CR rate
  - MRD negativity rate
  - PFS2 (defined as time from randomization to progression on the next line of therapy or death, whichever comes first)
  - Overall survival
  - Time to next treatment
  - Stringent CR (sCR) rate
  - Overall response rate (partial response [PR] or better)
  - Proportion of subjects who achieve very good partial response (VGPR) or better
  - Time to response
  - Duration of response
- To assess the safety and tolerability of daratumumab when administered in combination with Rd.
- To assess the pharmacokinetics of daratumumab in combination with Rd.
- To assess the immunogenicity of daratumumab in Arm B subjects and the immunogenicity of rHuPH20 in subjects receiving daratumumab SC.
- To evaluate treatment effects on patient reported outcomes and heath economic/resource utilization
- To evaluate the clinical efficacy of daratumumab combination with Rd in high-risk molecular subgroups

Exploratory Objectives

- To explore biomarkers predictive of response or resistance to therapy
- To assess durability of MRD negativity

Hypothesis

The primary hypothesis of this study is that daratumumab in combination with Rd will prolong PFS as compared with Rd alone in subjects with newly diagnosed multiple myeloma who are ineligible for high dose chemotherapy and autologous stem cell transplant.

OVERVIEW OF STUDY DESIGN

This is a randomized, open-label, active controlled, parallel-group, multicenter study in subjects at least 18 years of age with newly diagnosed multiple myeloma who are not candidates for high dose chemotherapy and ASCT. Approximately 730 subjects will be enrolled in this study with 365 subjects planned per treatment arm.

Subject participation will include a Screening Phase, a Treatment Phase, and a Follow-up Phase. The Screening Phase will be up to 21 days before Cycle 1, Day 1. The Treatment Phase will extend from Day 1 of Cycle 1 until discontinuation of all study treatment. For subjects assigned to DRd, daratumumab will be administered weekly for the first 8 weeks (Cycles 1-2) of treatment and then every other week for 16 weeks (Cycles 3-6), then every 4 weeks (from Cycle 7 and beyond) until disease progression or unacceptable toxicity. This will equate to 9 consecutive weeks of dosing at the start of the study and a total of 23 doses in the first year. Lenalidomide will be administered at a dose of 25 mg orally (PO) on Days 1 through 21 of each 28-day cycle, and dexamethasone will be administered at a dose of 40 mg once a week. Subjects in both treatment arms will continue lenalidomide and dexamethasone until disease progression or unacceptable toxicity. Subjects in the DRd arm will continue on daratumumab until disease progression or unacceptable toxicity. Randomization will be stratified by International Staging System (I vs II vs III), region (North America vs Other), and age (<75 vs ≥75), using an equal allocation ratio of 1:1.

Measures to prevent infusion-related reactions will include pre-dose medication with dexamethasone, acetaminophen (paracetamol), and an antihistamine before each daratumumab administration.

All subjects randomized to Treatment Arm B in this study initially received daratumumab IV formulation; however, following implementation of protocol amendment 8, subjects still receiving treatment with daratumumab IV will have the option to switch to daratumumab SC on Day 1 of any cycle, at the discretion of the investigator. Subjects with a known allergy/intolerance to any of the components of the SC formulation, including sorbitol, will not be eligible to switch to daratumumab SC. Note: throughout this document, text has been added to highlight any differences between daratumumab IV and daratumumab SC dosing, and where there is no clarification, it is implied that the descriptions are the same for daratumumab IV and daratumumab SC.

The Follow-up Phase will begin once a subject discontinues all study treatments. Subjects who discontinue study treatment for reasons other than disease progression must continue to have disease evaluations according to the Time and Events Schedule until confirmed disease progression (PD) (see Section 8.4, Subsequent Therapies). After PD is documented, follow-up will be obtained at least every 16 weeks. Subsequent anti-myeloma therapy, PFS2 (per investigator judgment), second primary malignancies, and survival will be recorded. The Follow-up Phase will continue until death, lost to follow up, consent withdrawal, or study end, whichever occurs first.

Two interim analyses are planned. The first interim analysis, with a purpose to evaluate safety, will be performed after a total of approximately 100 subjects have been treated for at least 8 weeks or discontinued the study treatment. The second interim analysis will be performed when 234 PFS events, which are 60% of the total planned events, have been accumulated. The purpose of this interim analysis is to evaluate

cumulative interim safety and efficacy data. The significance level at this interim analysis to establish the superiority of DRd over Rd with regard to PFS will be determined 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. If the experimental arm (DRd) is numerically worse than the control arm in terms of PFS (observed hazard ratio >1 favoring the control arm), then the study may be terminated for futility.

As the superiority of DRd over Rd alone with respect to PFS was established at the second interim analysis, the interim PFS analysis will serve as the primary PFS analysis, which otherwise was to occur when approximately 390 PFS events had been observed. The first interim OS analysis was performed at the interim PFS analysis. The second interim OS analysis occurred when 273 deaths had occurred and demonstrated superiority of DRd over Rd alone for OS. The median OS was not reached.

The date established for the primary PFS analysis (24 September 2018) will serve as the clinical cut-off date, after which subject monitoring in the study will be conducted as per Section 9.1.5. After the second interim OS analysis (19 February 2021) subject monitoring will be conducted according to Section 9.1.7.

Following the positive second interim OS analysis that established the superiority of DRd over Rd alone for OS, the final CSR analysis will be performed approximately 5 years after the last subject was randomized. The final CSR analysis will provide updates to the primary CSR analysis for both efficacy and safety. The sponsor will communicate the clinical cut-off date for the final CSR analysis to sites. At the time of this clinical cut-off, the study will transition to long-term survival follow-up.

The clinical cut-off of the final OS analysis will occur when approximately 390 deaths have occurred. No additional eCRF data will be collected after the final OS analysis. Data collected up to this timepoint will be included in the final OS analysis and reported in a separate addendum to the clinical study report.

The sponsor will ensure that subjects who are benefiting from treatment with daratumumab can continue to receive daratumumab after the final OS analysis through end of study. For these subjects, treatment with daratumumab will be available through continued access within the current study until it is available through another source such as commercial availability, continued access through a long-term extension study, a patient access program, when all subjects have discontinued daratumumab treatment, or until 31 January 2026, whichever occurs first.

An Independent Data Monitoring Committee (IDMC) will be commissioned for this study to review efficacy and safety results at the planned interim analyses. After the interim review, they will make recommendations regarding the continuation of the study. In addition, the IDMC may also review cumulative safety data every 6 months besides the 2 interim analyses. The IDMC will no longer review study data after the interim PFS analysis has been completed.

Assessment of tumor response and disease progression will be conducted in accordance with the International Myeloma Working Group (IMWG) response criteria. An assessment of MRD will be conducted on bone marrow samples. Safety evaluations will include adverse event monitoring, physical examinations, electrocardiogram (ECG) monitoring, clinical laboratory parameters (hematology and chemistry), vital sign measurements, and Eastern Cooperative Oncology Group (ECOG) performance status. Blood samples will be drawn for assessment of pharmacokinetic parameters.

Following the positive second interim analysis that established the superiority of DRd over Rd alone with respect to the primary endpoint (PFS), the sponsor will provide access to daratumumab for subjects randomized to Arm A (Rd) who have sponsor-confirmed disease progression (see Section 8.4, Subsequent Therapies), if recommended by the investigator. After the cut-off for the final CSR, sponsor confirmation of PD is no longer required and will be based on investigator assessment of PD.

SUBJECT POPULATION

Key eligibility criteria include the following: subjects who are ≥18 years of age, have a confirmed diagnosis of symptomatic multiple myeloma and measurable secretory disease, an ECOG performance status score of 0, 1, or 2, must be newly diagnosed and not considered candidates for high-dose chemotherapy with stem cell transplantation (SCT).

DOSAGE AND ADMINISTRATION

Daratumumab IV (16 mg/kg) or daratumumab SC (1800 mg fixed dose) will be administered to subjects assigned to Arm B initially once every week for 8 weeks; then once every other week for 16 weeks; thereafter once every 4 weeks until documented progression, unacceptable toxicity, or study end.

Lenalidomide will be self-administered at a dose of 25 mg PO each day on Days 1 through 21 of each 28-day cycle.

Dexamethasone (or equivalent in accordance with local standards; see Attachment 6 for conversion table) will be administered at a total dose of 40 mg weekly.

EFFICACY EVALUATIONS/ENDPOINTS

Disease evaluations must be performed every 28 days for the first 2 years and then every 8 weeks until disease progression (or other reasons as per Section 10). A window of ±7 days is allowed. If treatment has been delayed for any reason, the disease evaluations must be performed according to schedule, regardless of any changes to the dosing regimen.

The primary endpoint is PFS, which is defined as the duration from the date of randomization to either progressive disease, or death, whichever occurs first. Disease progression will be determined according to the IMWG criteria.

The secondary efficacy endpoints include:

- Time to disease progression (TTP) is defined as the time from the date of randomization to the date of first documented evidence of PD, as defined in the IMWG criteria. For subjects who have not progressed, data will be censored at the date of the disease evaluation before the start of any subsequent anti-myeloma therapy.
- CR rate, defined as the percentage of subjects achieving CR, as defined:

  Negative immunofixation of serum and urine, and

  Disappearance of any soft tissue plasmacytomas, and

  <5% plasma cells (PCs) in bone marrow

  For those subjects with negative serum M-protein quantitation by electrophoresis (SPEP) and suspected daratumumab interference on immunofixation, a reflex assay using anti-idiotype antibody will be utilized to confirm daratumumab interference and rule out false positive immunofixation. Patients who have confirmed daratumumab interference, but meet all other clinical criteria for CR or sCR, will be considered CR/sCR.
- MRD negativity rate, defined as the proportion of subjects assessed as MRD negative, at any timepoint after the date of randomization.
- Progression-free Survival on Next line of Therapy (PFS2), defined as the time from randomization to progression on the next line of treatment or death, whichever comes first. Disease progression will be based on investigator judgment. For those subjects who are still alive and not yet progressed on the next line of treatment, they will be censored on the last date of follow-up.

- Overall survival (OS), measured from the date of randomization to the date of the subject's death. If the subject is alive or the vital status is unknown, then the subject's data will be censored at the date the subject was last known to be alive.
- Time to next treatment, defined as the time from randomization to the start of the next-line treatment.
- sCR rate, defined as the percentage of subjects achieving CR in addition to having a normal free light chain (FLC) ratio and an absence of clonal cells in bone marrow by immunohistochemistry, immunofluorescence, 2-4 color flow cytometry
- Overall response rate (ORR), defined as the proportion of subjects who achieve PR or better, according to the IMWG criteria, during or after the study treatment.
- Proportion of subjects who achieve VGPR or better, defined as the proportion of subjects achieving VGPR and CR (including sCR) according to the IMWG criteria during or after the study treatment at the time of data cut-off.
- Time to response, defined as the time between the randomization and the first efficacy evaluation that the subject has met all criteria for PR or better. For subjects without response, data will be censored either at the date of progressive disease or, in the absence of progressive disease, at the last disease evaluation before the start of subsequent anti-myeloma therapy.
- Duration of response, calculated from the date of initial documentation of a response (PR or better) to the date of first documented evidence of progressive disease, as defined in the IMWG criteria. For subjects who have not progressed, data will be censored at the last disease evaluation before the start of any subsequent anti-myeloma therapy.
- To evaluate clinical efficacy of DRd in high risk molecular subgroups compared to Rd alone.
- To evaluate the impact of DRd compared to Rd on patient-reported perception of global health.

PHARMACOKINETIC AND IMMUNOGENICITY EVALUATIONS

Samples to assess both the serum concentration (pharmacokinetics) of daratumumab and the generation of antibodies to daratumumab and rHuPH20 (immunogenicity) will be obtained in the D-Rd group according to the Time and Events Schedule. Following amendment 8, subjects in Treatment Arm B who continue to receive daratumumab IV no longer require pharmacokinetic and immunogenicity sampling, however subjects in Treatment Arm B who switch to daratumumab SC will require pharmacokinetic and immunogenicity samples as specified in the Time and Events Schedule.

BIOMARKER EVALUATIONS

Bone marrow aspirates will be collected at screening and following treatment as outlined in the Time and Events Schedule. Baseline bone marrow aspirate samples will be subjected to DNA and RNA sequencing in order to classify subjects into high-risk molecular subgroups and to establish the myeloma clone for MRD monitoring.

In addition to planned bone marrow aspirate assessments, a whole blood sample will be collected from subjects as outlined in the Time and Events Schedule for processing to plasma and PBMCs.

SAFETY EVALUATIONS

Safety will be measured by adverse events, laboratory test results, ECGs, vital sign measurements, physical examination findings, and assessment of ECOG performance status score.

STATISTICAL METHODS

The sample size calculation is performed on the basis of the following assumption. Based on the published data, the median PFS for Rd arm is assumed to be approximately 24 months. Assuming that DRd can reduce the risk of the disease progression or death by 25%, ie, assuming the hazard ratio (DRd vs Rd) of 0.75, a total of 390 PFS events is needed to achieve a power of 80% to detect this hazard ratio with a log-rank test (two-sided alpha is 0.05). With a 21-month accrual period and an additional 24-month follow-up, the total sample size needed for the study is approximately 730 (365/arm) subjects. The sample size calculation has taken into consideration an annual dropout rate of 5%.

Long-term survival follow-up was originally planned to continue until 330 deaths had been observed or 7 years after the last subject was randomized. Therefore, this study would achieve approximately 80% power to detect a 27% reduction in the risk of death (hazard ratio = 0.73) with a log-rank test (two-sided alpha = 0.05). However, after reaching the statistical significance at the second interim OS, the long-term survival follow-up will be extended to approximately 390 deaths when the median survival for the DRd group has likely been reached.

Response to study treatment and progressive disease will be evaluated by a computer algorithm. 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 arms. 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.

Details of the 2 planned interim analyses are provided in the Synopsis, Overview of Study Design. After each interim review, the IDMC will make recommendations regarding the continuation of the study. The IDMC will no longer review study data after the interim PFS analysis has been completed.

As the superiority of daratumumab combined with Rd over Rd alone with respect to PFS was established at the second interim analysis, the interim PFS analysis will serve as the primary PFS analysis, which otherwise was to occur when approximately 390 PFS events had been observed.

TIME AND EVENTS SCHEDULE OVERVIEW

Note: Refer to Attachment 11 for a description of study procedures and data collection during the long-term survival follow-up and Attachment 12 for study procedures after final OS analysis.

	Notes	Screening Phase	Treatment Phase		Follow-up Phase	
		within 21 days before randomization	Day 1 of each cycle (28-day cycles)	EOT within 30 days of last dose	Prior to PD	After PD (Q16wks) ±2 wks
Study treatment should be initiated within 72 hours after randomization. Day 1 of each cycle may occur ±3 days of the scheduled day in order to accommodate the schedule of the site or subject. After EOT, subjects in both treatment arms prior to PD will continue to return for disease evaluations. After PD is documented, subjects will be followed for survival, PFS2, second primary malignancies, and subsequent anti-myeloma therapy. After the primary clinical cut-off date (24 September 2018), subject monitoring will be conducted as per Section 9.1.5. After the second interim OS analysis and mPFS for DRd group has been confirmed, subject monitoring will be conducted according to Section 9.1.7. With the implementation of Amendment 8, site visits may be replaced with virtual visits or other local arrangements in exceptional circumstances, with site visits resuming as soon as possible thereafter.						
Procedures						
Informed consent	ICF must be signed before any study-related procedures					
Eligibility criteria		X				
Demography/ Medical History		X				
Height		X				
Chest X-ray (or full chest CT scan)	Acceptable for screening if performed as part of SOC within 42 days before randomization	X				
PFT	For subjects with COPD, FEV1 should be measured	X				
ECOG	Prior to any other study procedures planned for the same day	X	D1 of Cycle 3, 6, 9, 12 for year 1; every 6th month ±14 days thereafter until PD. Post-PD collect at Wks 8 and 16.			
12-lead ECG	Acceptable for screening if performed as part of SOC within 42 days before randomization	X	C3D1, C6D1	X		
Physical exam	including neurological exam	X	symptom and disease directed exam as clinically indicated			
Vital signs, weight		X	Please see following table for details.			
Blood type and IAT	ABO, Rh, and IAT. A wallet card with the subject's blood type and IAT will be provided to subjects randomized to Arm B.	X	C1D1 predose, Arm B only			
Laboratory Assessments						
Pregnancy test	For women of childbearing potential only. During screening, within 10-14 days prior to first dose and again within 24 hrs prior to first dose. Minimum testing requirements during study: weekly during Cycle 1 and then monthly in women with regular menstrual cycles or every 2 weeks in women with irregular menstrual cycles. Please refer to Section 9.8 for details.			X		

	Notes	Screening Phase	Treatment Phase		Follow-up Phase	
		within 21 days before randomization	Day 1 of each cycle (28-day cycles)	EOT within 30 days of last dose	Prior to PD	After PD (Q16wks) ±2 wks
Hematology		X	Please see following table for details.	X		
Serum chemistry		X	Please see following table for details.	X		
HBV DNA Testing	Arm B subjects with known history of hepatitis B infection or positive hepatitis B serologies (HBsAg, Anti-HBc and/or Anti-HBs with exception of serologic findings suggestive of HBV vaccination [Anti-HBs positivity as the only serologic marker] and a known history of prior HBV vaccination).		Every 3 months during treatment ± 1 month until 6 months after last dose of daratumumab.			
Daratumumab PK	Arm B only. On dara administration days, 1 sample to be collected before administration start (window -2 hrs) and 1 sample to be collected after end of administration (window +2 hrs). Samples to be sent to central laboratory.		C1D1, C6D1, C12D1	X **Arm B ONLY**[a]	8 wks after last dara dose **Arm B ONLY**[a]	
rHuPH20 immunogenicity	Following implementation of Amendment 8, Arm B subjects who switch to daratumumab SC only: Plasma sample will be collected. If an infusion-related reaction occurs, obtain unscheduled plasma sample as soon as possible.			X **Arm B ONLY**	8 wks after last dara dose **Arm B ONLY**	
Daratumumab immunogenicity	Arm B only. No additional sample needed; will be taken from PK sample. If an infusion reaction occurs, obtain unscheduled blood sample as soon as possible.		predose C1D1 only	X **Arm B ONLY**[a]	8 wks after last dara dose **Arm B ONLY**[a]	
Whole blood	Plasma or PBMC biomarker assessments		predose C1D1 only	X		
Disease Evaluations: Every effort should be made to conduct disease evaluations as per schedule (window ± 7 days). Refer to Section 9.2 for details on efficacy evaluations After EOT, subjects in both treatment arms prior to PD will continue to return for disease evaluations. After PD is documented, subjects will be followed for survival, PFS2, second primary malignancies, and subsequent anti-myeloma therapy. After the primary clinical cut-off date (24 September 2018), subject monitoring will be conducted as per Section 9.1.5. After the second interim OS analysis has occurred and the mPFS for DRd group has been confirmed, subject monitoring will be conducted according to Section 9.1.7.						
Serum disease evaluations (SPEP)	Sample to be sent to central laboratory. IFE and FLC when CR is suspected or maintained. FLC every cycle for subjects with light chain only myeloma.	X (Repeat on C1D1 if not within 14 days prior to C1D1)	X (for first 2 years and then every 8 wks until PD)			
Urine disease evaluations (UPEP)	Sample to be sent to central laboratory. IFE when CR is suspected or maintained.	X (Repeat on C1D1 if not within 14 days prior to C1D1)	X (for first 2 years and then every 8 wks until PD)			
Calcium, albumin, β_2-microglobulin	Sample to be sent to central laboratory. β_2-microglobulin at screening only.	X (Repeat calcium and albumin on	calcium/albumin every cycle for first 2 years and then every 8wks until PD			

	Notes	Screening Phase	Treatment Phase		Follow-up Phase	
		within 21 days before randomization	Day 1 of each cycle (28-day cycles)	EOT within 30 days of last dose	Prior to PD	After PD (Q16wks) ±2 wks
		C1D1 if not within 14 days prior to C1D1); don't repeat β2-microglobulin				
Bone marrow aspirate/biopsy	For screening (up to 42 days before randomization) fresh aspirate or biopsy preferred. If not available, obtain non-decalcified tissue according to Section 9.2.1.5 Table 9 and/or FFPE tissue. Fresh biopsy or aspirate (or both) required to confirm CR/sCR. Samples for biomarker analysis to be sent to central laboratory	X	To confirm CR/sCR, assess MRD, and evaluate PD (if feasible). Samples are requested at time of suspected CR/sCR and at 12, 18, 24, 30, 36, 48, and 60 months post C1D1 (+/-1 month). If one of these time points occurs within 1 month of suspected CR, a repeat bone marrow will not be requested. These bone marrow tests will only be required if patient's response is near CR or better by blood and urine evaluations. See Section 9.2.1.5 for additional information including timepoints.			
Quantitative Ig	See Section 9.2.1.2	X	every 16 weeks	X		
Assessment of lytic disease	Acceptable for screening if performed within 42 days before randomization	X	As clinically indicated, using the same methodology as used at screening			
Extramedullary plasmacytomas	Subjects with history of plasmacytoma; acceptable for screening if performed within 42 days before randomization	X	If applicable, by physical exam every 4 wks, by radiologic exam (if required) every 12 wks using same methodology as used at screening; for subjects with history of plasmacytoma assessed by physical exam, repeat assessment on C1D1 if not done within 14 days prior to randomization			
PRO	EORTC-QLQ-30, EQ-5D-5L Both questionnaires must be administered and completed prior to any other study procedures or assessments for that study visit. All PRO measures will be collected via an electronic device (ePRO).	X	D1 of Cycle 3, 6, 9, 12 for year 1; every 6th month ± 14 days thereafter until PD. Post-PD collect at Wks 8 and 16.			
MRU			Continuous from C1D1 until End of Treatment (see Section 9.6)			
Follow-up						
Survival, PFS2, second primary malignancy, subsequent anti-myeloma therapy						Q16wk
Ongoing Subject Review						
Adverse Events	See Section 12 for detailed instructions.	continuous from the time of signing of ICF until 30 days after last dose of last study drug				
Concomitant Medications	See Section 8 for detailed instructions.	continuous from the time of signing of ICF until 30 days after last dose of last study drug				

		Screening Phase	Treatment Phase		Follow-up Phase	
	Notes	within 21 days before randomization	Day 1 of each cycle (28-day cycles)	EOT within 30 days of last dose	Prior to PD	After PD (Q16wks) ±2 wks

Abbreviations for Time and Events Tables:
AE=adverse event; Anti-HBc=antibodies to hepatitis B core antigen; Anti-HBs=antibodies to hepatitis B surface antigen; BMI=body mass index; C=cycle; COPD=chronic obstructive pulmonary disease; CR=complete response; ECOG=Eastern Cooperative Oncology Group; D=day; Dara=daratumumab; DRd=daratumumab with lenalidomide plus low-dose dexamethasone; ECG=electrocardiogram; EOT= End-of-Treatment; ePRO= electronic patient reported outcomes; FEV1= Forced Expiratory Volume (in 1 second); FFPE=formalin-fixed paraffin embedded; FLC=free light chain; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; IAT= indirect antiglobulin test; ICF=informed consent form; IFE=immunofixation; Ig=immunoglobulin; IV= intravenous; MRD=minimal residual disease; MRI=magnetic resonance imaging; MRU=medical resource utilization; OS=overall survival; PBMC= peripheral blood mononuclear cell; PFT=pulmonary function test; PFS2= time from randomization to progression on the next line of therapy or death, whichever comes first; PK=pharmacokinetics; PD= disease progression; PO= per oral; PRO=patient reported outcomes; Q(3)(6)mo=every (3)(6) months; Q16wk=every 16 weeks; SAE=serious adverse event; sCR=stringent complete response; SIPPM= Site Investigational Product Procedures Manual (or equivalent document); SPEP=serum M-protein quantitation by electrophoresis; UPEP=urine M-protein quantitation by electrophoresis; Wk=week

[a]Treatment Arm B – Daratumumab pharmacokinetic and anti-daratumumab antibody sampling at EOT and 8 weeks after the last daratumumab SC dose are required for subjects who switch from daratumumab IV to daratumumab SC treatment. After amendment 8 is implemented, daratumumab pharmacokinetic and anti-daratumumab antibody sampling at EOT and 8 weeks after the last daratumumab IV dose are NOT required for subjects who remain on daratumumab IV treatment.

TIME AND EVENTS SCHEDULE, DOSE ADMINISTRATION

Note: Refer to Attachment 11 for a description of study procedures and data collection during the long-term survival follow-up and Attachment 12 for procedures after final OS analysis.

	Notes	Cycle 1 and Cycle 2				Cycle 3 to Cycle 6		Cycle 7 and after	EOT
		D1	D8	D15	D22	D1	D15	D1	
The start of each cycle may occur ±3 days of the scheduled day in order to accommodate the schedule of the site or subject. The start of each cycle should be scheduled relative to Cycle 1 Day 1 and should not change if visits have shifted within the allowed window. With the implementation of Amendment 8, site visits may be replaced with virtual visits or other local arrangements in exceptional circumstances, with site visits resuming as soon as possible thereafter.									
Hematology	For Cycle 1 Day 1, no need to repeat tests if they have been performed within the past 5 days. Testing may be performed up to 3 days before other administration days. Results of hematology tests must be evaluated before each study drug administration. Perform at additional timepoints, as clinically indicated. To be done by local lab.	X	X	X	X	X	X	X	X
Clinical Chemistry		X				X		X	X
Weight	If a subject's weight changes by more than 10% from baseline, the dose of all study treatments will be re-calculated	X				X		X	
Vital Signs	Vital signs (blood pressure, temperature, pulse/heart rate) measured in sitting position. On Cycle 1 Day 1 before the start of dara administration; at 0.5, 1, 1.5, 2, 3.5 hrs after the start of the administration; at end of administration; and 0.5, and 1 hr after end of administration. For all other doses, vital signs will be measured before administration start and at end of dara administration.	X	X	X	X	X	X	X	
Diary review	Accountability/exposure check	X	X	X	X	X	X	X	X
Pre-dose Medications, Arm B only									
Dexamethasone	Administer approximately 1 hour before dara administration. PO pre-dose medications may be administered within 3 hours before the dose. • Dexamethasone 40 mg weekly IV (preferred) or PO. For subjects older than 75 years or underweight (BMI <18.5), see Section 6.3. Substitutions for dexamethasone allowed, see Attachment 6. • An antihistamine (diphenhydramine 25-50 mg IV or PO, or equivalent) • Acetaminophen (paracetamol) 650-1000 mg IV or PO	X	X	X	X	X	X	X	
Antihistamine		X	X	X	X	X	X	X	
Acetaminophen (paracetamol)		X	X	X	X	X	X	X	

	Notes	Cycle 1 and Cycle 2				Cycle 3 to Cycle 6		Cycle 7 and after	EOT
		D1	D8	D15	D22	D1	D15	D1	
Study Drug Administration, Arm A and Arm B									
Lenalidomide	Dispense on Day 1 for self-administration. In Arm B, on daratumumab administration days, lenalidomide will be administered either prior to or at the same time (preferred) as the pre dose medications.	25 mg daily, Day 1-21 of each cycle (until PD or unacceptable toxicity)							
Dexamethasone	Dispense on Day 1 for self-administration.	40mg weekly PO; Day 1, 8, 15, 22 of each cycle. (until PD or unacceptable toxicity) Not required in Arm B on daratumumab administration days.							
Study Drug Administration, Arm B Only									
Daratumumab (IV or SC)	Refer to SIPPM and IPPI for recommendations on daratumumab IV infusion rate and daratumumab SC dosing. For windows see Table 3.	X	X	X	X	X	X	X	

ABBREVIATIONS

ADCC	antibody-dependent cell-mediated cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
ALT	alanine aminotransferase
Anti-HBc	antibodies to hepatitis B core antigen
Anti-HBs	antibodies to hepatitis B surface antigen
ASCT	autologous stem cell transplantation
AST	aspartate aminotransferase
BMI	body mass index
BUN	blood urea nitrogen
CDC	complement-dependent cytotoxicity
CL	total systemic clearance
Cmax	maximum observed concentration
Cmin	minimum observed concentration
COPD	chronic obstructive pulmonary disease
CR	complete response
CRAB	calcium elevation, renal insufficiency, anemia and bone abnormalities
CrCl	creatinine clearance
CT	computed tomography
DLT	dose limiting toxicity
DMC	Data Monitoring Committee
DRd	daratumumab with lenalidomide plus low-dose dexamethasone
DTT	Dithiothreitol
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
eDC	electronic data capture
EOT	end of treatment
ePRO	electronic patient-reported outcome(s)
EU	European Union
FCBP	females of childbearing potential
FEV	forced expiratory volume
FFPE	formalin fixed paraffin embedded
FISH	fluorescence in situ hybridization
FLC	free light chain
FOIA	Freedom of Information Act
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HIV	human immunodeficiency virus
HR	hazard ratio
IAT	indirect antiglobulin testing
ICF	informed consent form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFE	Immunofixation
Ig	Immunoglobulin
IHC	immunohistochemistry
IMiD	immunomodulatory agent
IMWG	International Myeloma Working Group
INR	international normalized ratio
IPPI	Investigational Product Preparation Instructions
IRB	Institutional Review Board
IRR	infusion-related reaction

ISR	injection-site reaction
ITT	intent-to-treat
IUD	intrauterine device
IV	Intravenous
IWRS	interactive web response system
LDH	lactic acid dehydrogenase
LMWH	low molecular weight heparin
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MP	melphalan-prednisone
MPT	melphalan-prednisone-thalidomide
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
NGS	next generation sequencing
NK	natural killer
OR	overall response
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PC	plasma cell
PCP	pneumocystis carinii pneumonia
PD	disease progression
PFS	progression free survival
PFS2	time from randomization to progression on the next line of therapy or death, whichever comes first
PI	proteasome inhibitor
PK	Pharmacokinetics
PO	per oral
POEMS	polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes syndrome
PQC	Product Quality Complaint
PR	partial response
PRO	patient-reported outcome(s)
QD	once daily
QIg	quantitative immunoglobulins
QTcF	QT corrected according to Fridericia's formula
RBC	red blood cell
Rd	lenalidomide plus low-dose dexamethasone
rHuPH20	recombinant human hyaluronidase PH20
REMS	Risk Evaluation and Mitigation Strategy
SAC	Safety Assessment Committee
SAE	serious adverse event
sCR	stringent complete response
SCT	stem cell transplantation
SIPPM	Site Investigational Product Procedures Manual (or equivalent document)
SLiM	60% Plasmacytosis, Light chains >100, MRI 1 or more focal lesion
SPEP	serum M-protein quantitation by electrophoresis
SUSAR	Suspected Unexpected Serious Adverse Reactions
TTP	time to disease progression
ULN	upper limit of normal
UPEP	urine M-protein quantitation by electrophoresis
US	United States
V	volume of distribution
VD	VELCADE-dexamethasone

VGPR	very good partial response
VMP	VELCADE-melphalan-prednisone
VTD	VELCADE-thalidomide-dexamethasone
VTE	venous thromboembolism
WHO	World Health Organization

1. INTRODUCTION

1.1. Background

1.1.1. Multiple Myeloma

Multiple myeloma is a malignant disorder of the plasma cells, characterized by uncontrolled and progressive proliferation of a plasma cell clone. The disease leads to progressive morbidity and eventual mortality by lowering resistance to infection and causing significant skeletal destruction (with bone pain, pathological fractures, and hypercalcemia), anemia, renal failure, neurological complications and hyperviscosity syndrome.

The majority of patients with multiple myeloma produce a monoclonal protein, also called paraprotein, M-protein or M-component, which is an immunoglobulin (Ig) or a fragment of one that has lost its function (Kyle 2009, Palumbo 2011).[18,26] Normal immunoglobulin levels are compromised, leading to susceptibility of infections. The proliferating multiple myeloma cells displace the normal bone marrow leading to dysfunction in normal hematopoietic tissue and destruction of the normal bone marrow architecture, which is reflected by clinical findings such as anemia, paraprotein in serum or urine, and bone resorption seen as diffuse osteoporosis or lytic lesions shown in radiographs (Kyle 2003).[17] Furthermore, hypercalcemia, renal insufficiency or failure, and neurological complications are frequently seen (Palumbo 2011).[26] A small minority of patients with multiple myeloma are non-secretory.

At the time of diagnosis, multiple myeloma is a heterogeneous disease, with a course that varies on the basis of both disease- and host-related factors (eg, age, renal function, stage, chromosomal abnormalities). Multiple myeloma causes significant morbidity and mortality. It accounts for approximately 1% of all malignancies and 13% of hematologic cancers. Approximately 50,000 patients per year are diagnosed with multiple myeloma in the EU and US, and 30,000 patients per year die due to multiple myeloma (ACS 2013, Ferlay 2010).[1,10]

1.1.2. Treatment Options for Multiple Myeloma

Treatment choices for multiple myeloma vary with age, performance status, comorbidity, the aggressiveness of the disease, and related prognostic factors (Palumbo 2011).[26] Newly diagnosed patients with multiple myeloma are typically categorized into 2 subpopulations usually defined by their age and suitability for the subsequent approach to treatment. Younger patients will typically receive an induction regimen followed by consolidation treatment with high-dose chemotherapy and autologous stem cell transplantation (ASCT). For those not considered suitable for high-dose chemotherapy and ASCT, longer-term treatment with multi-agent combinations including alkylators, high-dose steroids, and novel agents are currently considered as standards of care.

The availability of different efficacious multi-agent regimens has provided clinicians with the opportunity of tailoring treatment for each patient. Selection is based on patients' comorbidities and biologic age, while at the same time, taking into account the expected toxicity profiles of each treatment regimen (Gay 2011).[11]

1.1.3. Transplant-ineligible Population

In general, patients over the age of 65 or with significant comorbidities are usually not considered eligible for more intensive forms of first line therapy, and as a result the treatment approach often favors longer, less-intensive/toxic treatments (Gay 2011).[11] Treatment traditionally consists of systemic chemotherapy, with adjunctive use of radiation or surgery in selected cases associated with extramedullary disease (NCCN 2013, Palumbo 2009, Smith 2005).[23,29,34] For many years, the oral combination melphalan-prednisone (MP) was considered the standard of care for patients with multiple myeloma who were not eligible for ASCT (Gay 2011).[11] The advent of immunomodulatory agents (IMiDs) and proteasome inhibitors (PIs) has led to a multiplicity of new treatment options for newly diagnosed patients not considered suitable for transplant based therapy.

The results of the Frontline Investigation of Revlimid and Dexamethasone versus Standard Thalidomide (FIRST) Study were presented at the American Society of Hematology Meeting in December 2013 (Facon 2013),[9] and most recently published in The New England Journal of Medicine (Benboubker 2014).[2] In this open-label Phase 3 study, non-transplant eligible patients with newly diagnosed myeloma were randomized to either melphalan-prednisone-thalidomide (MPT) or lenalidomide + low-dose dexamethasone (Rd). Patients who received Rd until disease progression had an improved outcome compared to those randomized to MPT, with a 28% reduction in the risk of progressive disease or death (median: 25.5 months, HR 0.72; p 0.00006). Secondary endpoints including duration of response and overall response were superior in the Rd cohorts. The safety profile of Rd was manageable, with reduced hematologic second primary malignancies compared with MPT. In the oral presentation at ASH 2013, the authors indicated that overall survival for patients who received Rd until disease progression was 59.4%, based on a preliminary survival analysis at 4 years (Facon 2013, 2014).[9]

1.2. Daratumumab

Daratumumab is a human IgG1κ monoclonal antibody (mAb) that binds with high affinity to a unique epitope on CD38, a transmembrane glycoprotein. It is a targeted immunotherapy directed towards tumor cells that express high levels of CD38, such as plasma cells from patients with multiple myeloma. This target is distinct from those of other approved agents for multiple myeloma therapy.

For the most comprehensive nonclinical and clinical information as well as Reference Safety Information regarding daratumumab, refer to the latest version of the Investigator's Brochure (Daratumumab IB).[13]

1.2.1. Nonclinical Studies

Based on preclinical data, daratumumab may utilize multiple effector cell functions, resulting in immune mediated killing of tumor cells. In ex vivo experiments utilizing human bone marrow stromal cells co-cultured with primary multiple myeloma cells, complement-dependent cytotoxicity (CDC) occurs rapidly and demonstrates maximal myeloma cell killing by daratumumab within 1 hour of antibody-mediated activation of the complement proteins (de Weers 2011).[6] Daratumumab-induced antibody-dependent cell-mediated cytotoxicity (ADCC)

is slower in its action, with maximal ADCC by daratumumab observed at 4 hours in vitro (de Weers 2011).[6] Daratumumab has also been shown to induce antibody-dependent cellular phagocytosis (ADCP) in the presence of macrophages within 4 hours in vitro (Overdijk 2013).[25] The precise role of some or all of these effector functions in reducing tumor burden in patients is unknown.

In toxicology studies in cynomolgus monkeys and chimpanzees, the major observed toxicities were cytokine release syndrome and thrombocytopenia. A minor decrease in red blood parameters was also observed. Cytokine release was seen only following the first dose and was markedly reduced following implementation of a 10-mg predose of daratumumab. The effect on platelets and red blood cells was reversible.

1.2.2. Clinical Studies

1.2.2.1. Single-Agent Daratumumab Studies (GEN501 and MMY2002)

Two single-agent studies with daratumumab are ongoing (Studies GEN501 and MMY2002), as described in Table 1.

Table 1: Daratumumab Single-Agent Studies GEN501 and MMY2002

<table>
<tr><th>Study Number</th><th>Study Design</th><th colspan="2">Number of subjects Treated/
Treatment Regimen</th></tr>
<tr><td rowspan="4">GEN501</td><td rowspan="4">Open label, Phase 1/2, first in human, single agent study in subjects with multiple myeloma whose disease is relapsed or refractory to at least 2 prior lines of therapies

Population was heavily treated with prior treatment, including ASCT, chemotherapy based regimens, IMiDs, and PIs</td><td colspan="2"><u>Part 1</u>
n 32 total treated with daratumumab weekly

0.005 1 mg/kg (n 17)
2 mg/kg (n 3)
4 mg/kg (n 3)
8 mg/kg (n 3)
16 mg/kg (n 3)
24 mg/kg (n 3)</td></tr>
<tr><td colspan="2"><u>Part 2</u>
n 51 total treated</td></tr>
<tr><td>8 mg/kg (n 30)

Weekly for 8 weeks, followed by q2w for an additional 16 weeks, and monthly thereafter</td><td>16 mg/kg (n 21)

First dose, followed by a 3 week resting period, followed by weekly doses for 7 weeks, then q2w for an additional 14 weeks, and monthly thereafter</td></tr>
<tr><td></td><td></td></tr>
<tr><td rowspan="2">MMY2002</td><td rowspan="2">Open label, multicenter, 2 stage, Phase 2 study of daratumumab for the treatment of 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</td><td colspan="2">n 34 total treated in Stage 1</td></tr>
<tr><td>8 mg/kg (n 18)
q4w</td><td>16 mg/kg (n 16)
qw for 8 weeks, then q2w for another 16 weeks, and then q4w thereafter</td></tr>
<tr><td colspan="3">ASCT autologous stem cell transplantation; IMiD immunomodulatory agent; PI proteasome inhibitor; q2w every 2 weeks; q4w every 4 weeks</td></tr>
</table>

Among the 32 subjects treated in Part 1 of Study GEN501, the maximum tolerated dose (MTD) was not reached following intravenous (IV) infusions up to 24 mg/kg. Two subjects experienced dose-limiting toxicities (DLTs) in the lower dose cohorts (a subject in the 0.1-mg/kg group had Grade 3 anemia and Grade 4 thrombocytopenia, and a subject in the 1.0-mg/kg group had Grade 3 aspartate aminotransferase increased).

Among the 51 subjects treated in Part 2 of Study GEN501, serious adverse events (SAEs) were reported in 37% of subjects (43% of subjects in the 8-mg/kg group and 29% of subjects in the 16 mg/kg-group). The most frequently reported SAEs were pneumonia (6% subjects), and pyrexia (4% of subjects).

Among the 34 subjects treated in Stage 1 of Study MMY2002, SAEs were reported in 27% of subjects (33% of subjects in the 8 mg/kg group, and 19% of subjects in the 16 mg/kg group). The most frequently reported SAE was renal failure acute (6% of subjects).

1.2.2.2. Combination Daratumumab Studies

One study of daratumumab in combination with lenalidomide and dexamethasone (Study GEN503), and one study of daratumumab in combination with various backbone treatment regimens (Study MMY1001) are ongoing (Table 2).

Table 2: Daratumumab Combination Studies GEN503 and MMY1001

Study Number	Study Design	Treatment Regimen	Status/Estimated Start Date Number of subjects Treated/Planned
GEN503	Open label, Phase 1/2 multicenter, dose escalating study investigating the safety of daratumumab in combination with lenalidomide and dexamethasone in subjects with relapsed or refractory multiple myeloma	Phase 1: 2 16 mg/kg daratumumab, in combination with lenalidomide (25 mg daily Days 1 21 of 28 days) and dexamethasone (40 mg weekly)	Part 1: Ongoing (n 13 subjects treated) 2 mg/kg (n 3) 4 mg/kg (n 3) 8 mg/kg (n 4) 16 mg/kg (n 3)
		Phase 2: 16 mg/kg daratumumab, in combination with lenalidomide (25 mg daily Days 1 21 of 28 days) and dexamethasone (40 mg weekly)	Part 2: n 18 subjects treated approximately 30 subjects planned
MMY1001	Open label, non randomized, multicenter, Phase 1b study to evaluate the safety, tolerability, and dose regimen of daratumumab in combination with various backbone treatment regimens for multiple myeloma in either newly diagnosed or those who have received at least 2 prior therapies, depending on backbone treatment regimen	Daratumumab 16 mg/kg (initially, with possibility to de escalate, if necessary) The backbone regimens to be combined with daratumumab include VELCADE dexamethasone (VD), VMP, VTD, and Pom dex	n 18 subjects treated[1] VTD (n 6) VMP (n 5) VD (n 1) Pom dex (n 6) approximately 80 subjects planned

1. As of 21May2014
Pom dex pomalidomide dexamethasone; VD VELCADE dexamethasone; VMP VELCADE melphalan prednisone; VTD VELCADE thalidomide dexamethasone

Based on preliminary efficacy data, 15 of 20 efficacy evaluable subjects in Study GEN503 have achieved a PR or better following treatment with daratumumab in combination with lenalidomide and dexamethasone.

The safety profile observed in Study GEN503 is consistent with historical safety data for lenalidomide and dexamethasone. Doses ranged from 2 mg/kg to 16 mg/kg daratumumab, in combination with the approved doses of lenalidomide (25 mg daily Days 1-21 of 28 days) and dexamethasone (40 mg weekly). No dose-limiting toxicity (DLT) drug-related safety signals have been observed in this heavily pre-treated population of subjects with advanced multiple myeloma. The Part 2 daratumumab dose was determined to be 16 mg/kg. Across all dose cohorts in Part 1 and in the 16 mg/kg expansion cohort for Part 2, the most frequently reported Grade 3 or higher adverse event was neutropenia (6 subjects), which is a known toxicity of lenalidomide. Eight SAEs have been reported. All SAEs were assessed by the investigator as not related to daratumumab. Four subjects experienced infusion-related reactions during the first infusion of daratumumab. These events were determined by the investigator to be related to daratumumab. In all instances, daratumumab was interrupted temporarily and restarted without complication or further incident.

Planned Phase 3 combination studies include a Phase 3 study (MMY3003) comparing daratumumab, lenalidomide, and dexamethasone with Rd and a Phase 3 study (MMY3004) comparing daratumumab, VELCADE, and dexamethasone with VD. Both studies are in patients with relapsed or refractory multiple myeloma and are planned to start in the second half of 2014.

1.2.2.3 Daratumumab Subcutaneous

A new formulation of daratumumab for subcutaneous (SC) administration has been developed to avoid the long infusion time that frequently requires hospitalization with IV administration of daratumumab and to lessen the rate and severity of infusion-related reactions (IRRs) observed with daratumumab IV. A recombinant human hyaluronidase PH20 (rHuPH20) was used to facilitate the SC administration of daratumumab to decrease the volume required for SC administration.

This SC formulation of daratumumab has been evaluated in the Phase 3 Study MMY3012, (COLUMBA), which compared efficacy, pharmacokinetics, and safety of SC vs IV daratumumab in 522 subjects. Adults with relapsed/refractory multiple myeloma were randomized 1:1 to SC (1800 mg; co-formulated with rHuPH20; n 263) or IV (16 mg/kg; n 259) daratumumab. Randomization was stratified by body weight, prior therapy lines, and myeloma subtype. Primary objectives were to demonstrate non-inferiority of SC vs. IV administration in overall response rate (ORR; at least partial response) and maximum trough concentrations (C_{trough}) (Cycle 3, Day 1).

Co-primary endpoints ORR and C_{trough} met predefined non-inferiority criteria, demonstrating that daratumumab SC is non-inferior to IV. ORR was 41% and 37% with SC and IV daratumumab administration, respectively (relative risk, 1.11; 95% CI, 0.89 1.37). Geometric mean ratio for C_{trough} was 107.93% (90% CI, 95.74 121.67). Median duration of injection was 5 minutes (range 1 18) for the first, second, and subsequent SC administrations vs. 7 hours (1 14), 4.3 hours (3-10.5), and 3.4 hour (2 7.7) for corresponding IV infusions. IRRs were reported in 13% of patients receiving daratumumab SC versus 35% receiving daratumumab IV (odds ratio, 0.28; 95% CI, 0.18 0.44, $p<0.0001$) with most occurring during the first administration. Daratumumab SC

offers consistent safety, efficacy and exposure to standard IV administration, with shorter administration times.

1.3. Lenalidomide

Lenalidomide is an immunomodulatory (IMiD) agent that is thought to mediate antimyeloma activity by 3 main mechanisms: 1) direct antitumor effect; 2) inhibition of the microenvironment support for tumor cells; and 3) an immunomodulatory role (Kotla 2009).[15] Direct tumor effect is described both as growth inhibition of myeloma cell lines and induction of apoptosis. The microenvironment support is affected by downregulation of cell adhesion molecules (eg, intercellular adhesion molecule), thus inhibiting stromal cell interaction with tumor cells, and inhibition of growth factors (eg, insulin growth factor 1 and vascular endothelial growth factor) induced by myeloma cell adhesion. Finally, lenalidomide exhibits immunomodulatory activity including inhibition of proinflammatory signaling molecules (cytokines) such as tumor necrosis factor α, IL-1β, and IL-6, the latter of which is a known growth factor for myeloma cells (Vallet 2008).[37]

Importantly, it has also been shown that lenalidomide causes upregulation of natural killer (NK) cells in myeloma (Kotla 2009)[15] and enhances the effector cells of ADCC (Tai 2005, Tai 2008).[36,35]

Lenalidomide is currently approved in the US and EU for the treatment for relapsed/refractory myeloma. However, there is accumulating evidence that lenalidomide is an effective treatment strategy for new diagnosed patients as well. The Eastern Cooperative Oncology Group (ECOG) published a study in which patients with newly diagnosed myeloma were randomized to either high-dose (160 mg/week) or low-dose (40 mg/week) dexamethasone in combination with lenalidomide (Rajkumar 2010).[31] Patients randomized to the low-dose dexamethasone treatment arm had an improved overall survival at one year (96% vs 87%). In terms of response rates, patients in the low-dose cohort had an overall response rate (≥PR) of 68.3%. Median time to progression was 26.1 months in the low dose group.

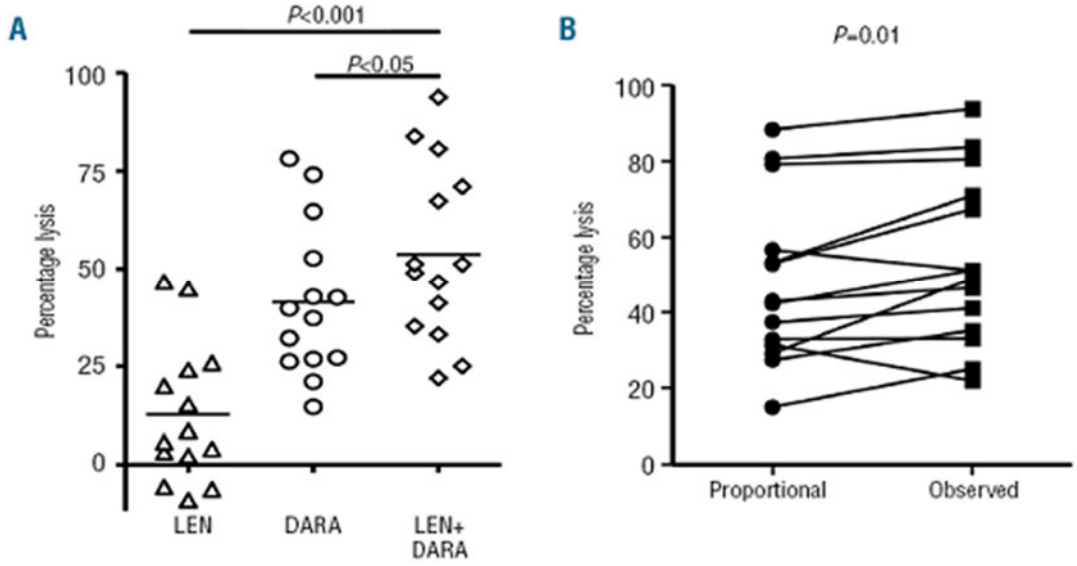
A large, randomized Phase 3 study (FIRST Study) compared Rd given until disease progression (Arm A) or for eighteen 28-day cycles (Arm B) with MPT (Arm C) in subjects newly diagnosed with multiple myeloma (Facon 2013, Benboubker 2014).[9,2] Continuous treatment with Rd (Arm A) significantly improved the primary endpoint of PFS compared with MPT (Arm C). Secondary endpoints (overall response rate [ORR], defined as PR or better, duration of response, and PFS2) consistently showed improvement in favor of Arm A over Arm C. The safety profile of Rd was manageable, with reduced hematologic second primary malignancies compared with MPT.

REVLIMID® (lenalidomide) in combination with dexamethasone was approved by both U.S. Food and Drug Administration and the European Commission for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant, on 18 February 2015 and 20 February 2015, respectively.

1.4. Lenalidomide and Daratumumab

Preclinically, using bone marrow mononuclear cells from patients with multiple myeloma, increased killing of tumor cells was demonstrated when daratumumab was combined with lenalidomide as compared with that of either agent alone as shown in (Figure 1A) (Van der Veer 2011a).[38] Notably, daratumumab and lenalidomide acted in a synergistic fashion to generate an extra effect (Figure 1B).

Figure 1: Improvement of Daratumumab-induced Antibody-dependent Cell-mediated Cytotoxicity by Lenalidomide in Bone Marrow Mononuclear Cells from Patients with Multiple Myeloma



Key: DARA daratumumab; LEN lenalidomide; MM multiple myeloma.

(A) Bone marrow mononuclear cells of 14 patients with multiple myeloma were incubated for 47 hours with the control antibody, with lenalidomide (3 μM), and/or daratumumab (0.1 μg/mL). Surviving multiple myeloma cells were enumerated by Fluorescence activated Cell Sorting analysis of CD138+ cells. The percentages of lysis of multiple myeloma cells treated with lenalidomide, daratumumab, and lenalidomide + daratumumab were calculated by the Tukey's post hoc analysis of repeated measures analysis of variance.

(B) The observed effect (% lysis) of the combination treatment was compared with the expected additive effect (proportional) of the combined treatments. Mixed model analysis supported the conclusion that the combination treatment was synergistic.

Finally, it was demonstrated that peripheral blood mononuclear cells isolated from patients during or just after lenalidomide treatment showed a significantly increased capacity to mediate daratumumab-dependent ADCC against multiple myeloma cells alone (Van der Veer 2011a).[38]

Thus, in this ex vivo clinical setting, daratumumab-mediated multiple myeloma tumor cell killing was demonstrated to be significantly augmented by stimulating effector cells. In conclusion, preclinical data, both from the literature and the sponsor's own ex vivo studies, support the combination of daratumumab with lenalidomide in the treatment of multiple myeloma.

1.5. Overall Rationale for the Study

Multiple myeloma remains incurable with standard chemotherapy, despite the availability of multi agent therapy. Strategies directed at improving and maintaining response for longer periods of time and new treatment options directed at alternative mechanisms are also urgently needed for patients with multiple myeloma.

Recent studies have indicated that multiple drug combinations are superior over single- or double-agent combinations in treating multiple myeloma (Van der Veer 2011b).[39] The addition of new drugs to available regimens can mediate their clinical benefit because of the induction of a higher rate of initial CRs, which then improves relapse-free and overall survival. Contingent on the premise that the combined agents have non-overlapping and synergistic mechanism of actions, the immediate and effective targeting of the tumors with multiple agents appears to be a successful strategy in improving the clinical outcome of multiple myeloma therapy. Such a strategy is in agreement with the emerging concept that the genetic signature of multiple myeloma, and consequently the patient's susceptibility to a specific agent, will be highly heterogeneous, which may lead to drug resistance. Nevertheless, the CR rate of the best chemotherapeutic combinations is currently <50%, and all current combination therapies eventually induce drug resistance.

Based on data from ongoing studies with and the safety information in the label for lenalidomide, the expected safety profile of daratumumab in this combination therapy study is considered manageable. To date, 31 subjects have been treated in Study GEN503, an open-label, Phase 1/2 multicenter, dose-escalating study investigating the safety of daratumumab in combination with lenalidomide and dexamethasone in subjects with relapsed or refractory multiple myeloma. No DLTs have been reported, and the safety profile is consistent with what has been previously reported for lenalidomide monotherapy. Data from several clinical studies support the choice of 16 mg/kg as the daratumumab dose to be administered in this study. Based upon the pre-clinical synergy observed, and the promising clinical data in the relapsed/refractory setting, this is a rational combination to investigate in newly diagnosed patients.

2. OBJECTIVES AND HYPOTHESIS

2.1. Objectives

Primary Objective

The primary objective is to compare the efficacy of daratumumab when combined with lenalidomide and dexamethasone (DRd) to that of lenalidomide and dexamethasone (Rd), in terms of progression-free survival (PFS) in subjects with newly diagnosed myeloma who are not candidates for high dose chemotherapy and autologous stem cell transplant.

Secondary Objectives

The secondary objectives are:

- To evaluate clinical outcomes including:
  - Time to disease progression (TTP)
  - CR rate
  - MRD negativity rate
  - PFS2 (defined as time from randomization to progression on the next line of therapy or death, whichever comes first)
  - Overall survival
  - Time to next treatment
  - Stringent CR (sCR) rate
  - Overall response rate (partial response [PR] rate or better)
  - Proportion of subjects who achieve very good partial response (VGPR) or better
  - Time to response
  - Duration of response
- To evaluate the clinical efficacy of daratumumab combination with Rd in high-risk molecular subgroups
- To evaluate treatment effects on patient reported outcomes and heath economic/resource utilization
- To assess the safety and tolerability of daratumumab when administered in combination with Rd.
- To assess the pharmacokinetics of daratumumab in combination with Rd.
- To assess the immunogenicity of daratumumab in Arm B subjects and the immunogenicity of rHuPH20 in subjects receiving daratumumab SC.

Exploratory Objective

- To explore biomarkers predictive of response or resistance to therapy
- To assess durability of MRD negativity

2.2. Hypothesis

The primary hypothesis of this study is that daratumumab in combination with Rd will prolong PFS as compared with Rd alone in subjects with newly diagnosed multiple myeloma who are ineligible for high dose chemotherapy and autologous stem cell transplant.

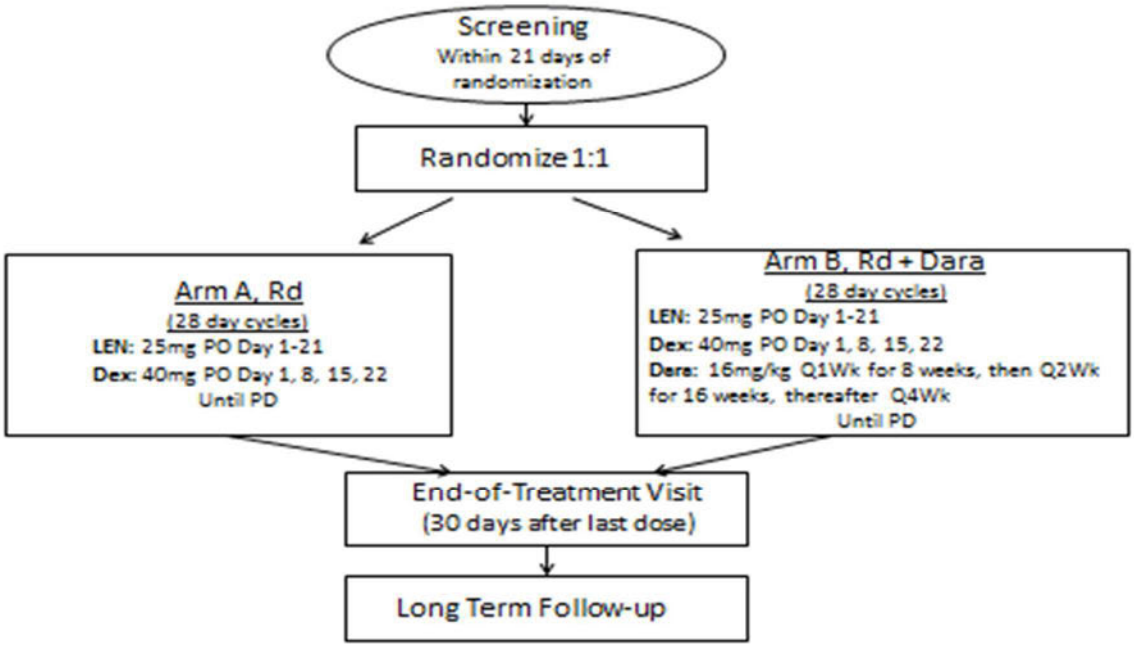
3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a randomized, open-label, active controlled, parallel-group, multicenter study in subjects at least 18 years of age with newly diagnosed multiple myeloma who are not candidates for high dose chemotherapy and ASCT. Approximately 730 subjects will be enrolled in this study with 365 subjects planned per treatment arm.

A diagram of the study design is provided in Figure 2.

Figure 2: Schematic Overview of the Study



NOTE: After Study MMY3008 transitions to long-term survival follow-up, an end-of-treatment visit is no longer required.

Subject participation will include a Screening Phase, a Treatment Phase, and a Follow-up Phase. The Screening Phase will be up to 21 days before Cycle 1, Day 1. The Treatment Phase will extend from Day 1 of Cycle 1 until discontinuation of all study treatment. For subjects assigned to DRd, daratumumab will be administered weekly for the first 8 weeks (Cycles 1-2) of treatment and then every other week for 16 weeks (Cycles 3-6), then every 4 weeks (from Cycle 7 and beyond) until disease progression or unacceptable toxicity. This will equate to 9 consecutive weeks of dosing at the start of the study and a total of 23 doses in the first year. Lenalidomide will be administered at a dose of 25 mg orally (PO) on Days 1 through 21 of each 28-day cycle, and dexamethasone will be administered at a dose of 40 mg once a week in both treatment arms. Subjects in both treatment

arms will continue lenalidomide and dexamethasone until disease progression or unacceptable toxicity. In the DRd arm, subjects will continue on daratumumab until disease progression or unacceptable toxicity. Randomization will be stratified by International Staging System (I vs II vs III), region (North America vs Other), and age (<75 vs ≥75), using an equal allocation ratio of 1:1.

Measures to prevent infusion-related reactions will include medication with dexamethasone, acetaminophen (paracetamol), and an antihistamine before each daratumumab administration.

All subjects randomized to Treatment Arm B in this study initially received daratumumab IV formulation; however, following implementation of protocol amendment 8, subjects still receiving treatment with daratumumab IV will have the option to switch to daratumumab SC on Day 1 of any cycle, at the discretion of the investigator. Subjects with a known allergy/intolerance to sorbitol will not be eligible to switch to daratumumab SC. Note: throughout this document, text has been added to highlight any differences between daratumumab IV and daratumumab SC dosing, and where there is no clarification, it is implied that the descriptions are the same for daratumumab IV and daratumumab SC.

The Follow-up Phase will begin once a subject discontinues all study treatments. Subjects who discontinue study treatment for reasons other than disease progression must continue to have disease evaluations according to the Time and Events Schedule until confirmed disease progression (PD) (see Section 8.4, Subsequent Therapies). After PD is documented, follow-up will be obtained at least every 16 weeks. Subsequent anti-myeloma therapy, PFS2 (per investigator judgment), second primary malignancies, and survival will be recorded. The Follow-up Phase will continue until death, lost to follow up, consent withdrawal, or study end, whichever occurs first.

Two interim analyses are planned. The first interim analysis, with a purpose to evaluate safety, will be performed after a total of approximately 100 subjects have been treated for at least 8 weeks or discontinued the study treatment. The second interim analysis will be performed when 234 PFS events, which is 60% of the total planned events, have been accumulated. The purpose of this interim analysis is to evaluate cumulative interim safety and efficacy data. The significance level at this interim analysis to establish the superiority of DRd over Rd with regard to PFS will be determined 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. If the experimental arm (DRd) is numerically worse than the control arm in terms of PFS (observed hazard ratio >1 favoring the control arm), then the study may be terminated for futility.

As the superiority of DRd over Rd alone with respect to PFS was established at the second interim analysis, the interim PFS analysis will serve as the primary PFS analysis, which otherwise was to occur when approximately 390 PFS events had been observed. The first interim OS analysis was performed at the interim PFS analysis. The second interim OS analysis occurred when 273 deaths had occurred and demonstrated superiority of DRd over Rd alone for OS. The median OS was not reached.

The date established for the primary PFS analysis (24 September 2018) will serve as the clinical cut-off date, after which subject monitoring in the study will be conducted as per Section 9.1.5.

After the second interim OS analysis (19 February 2021), subject monitoring will be conducted according to Section 9.1.7.

Following the positive second interim OS analysis that established the superiority of DRd over Rd alone for OS, the final CSR analysis will be performed approximately 5 years after the last subject was randomized. The final CSR analysis will provide updates to the primary CSR analysis for both efficacy and safety. The sponsor will communicate the clinical cut-off for the final CSR analysis to sites. At the time of this clinical cut-off, the study will transition to long-term survival follow-up (see Section 9.1.8 and Attachment 11).

The clinical cut-off of the final OS analysis will occur when approximately 390 deaths have occurred. No additional eCRF data will be collected after the final OS analysis. Data collected up to this timepoint will be included in the final OS analysis and reported in a separate addendum to the clinical study report.

The sponsor will ensure that subjects who are benefitting from treatment with daratumumab can continue to receive daratumumab after the final OS analysis through end of study (see Section 17.9.1). For these subjects, treatment with daratumumab will be available through continued access within the current study until it is available through another source such as commercial availability, continued access through a long-term extension study, a patient access program, or until 31 January 2026, whichever occurs first.

An Independent Data Monitoring Committee (IDMC) will be commissioned for this study to review efficacy and safety results at the planned interim analyses. After the interim review, they will make recommendations regarding the continuation of the study. In addition, the IDMC may also review cumulative safety data every 6 months besides the 2 interim analyses. The IDMC will no longer review study data after the interim PFS analysis has been completed.

Assessment of tumor response and disease progression will be conducted in accordance with the International Myeloma Working Group (IMWG) response criteria. An assessment of MRD will be conducted on bone marrow samples. Safety evaluations will include adverse event monitoring, physical examinations, electrocardiogram (ECG) monitoring, clinical laboratory parameters (hematology and chemistry), vital sign measurements, and ECOG performance status. Blood samples will be drawn for assessment of pharmacokinetic parameters and immunogenicity.

Following the positive second interim analysis that established the superiority of DRd over Rd alone with respect to the primary endpoint (PFS), the sponsor will provide access to daratumumab for subjects randomized to Arm A (Rd) who have sponsor-confirmed disease progression (see Section 8.4, Subsequent Therapies), if recommended by the investigator. After the cut-off for the final CSR, sponsor confirmation of PD is no longer required and will be based on investigator assessment of PD.

3.2. Study Design Rationale

Rationale for Duration of Lenalidomide Administration

Lenalidomide and dexamethasone are commonly given in the front-line setting in the US. Based upon the FIRST Study (Facon 2013, Benboubker 2014),[9,2] the front-line treatment paradigm in the EU will likely evolve to include Rd in the future. The Facon study showed that treatment until progression conferred clinical benefit over treatment for a fixed duration of time. A retrospective analysis of 2 Phase 3 studies, one administering a lenalidomide based regimen and one administering a VELCADE based regimen, also showed that PFS1, PFS2, and overall survival (OS) were all significantly longer following continuous treatment to progression (Palumbo 2014).[27] This was observed regardless of the particular chemotherapy backbone. Taken together, these data support the principle of treatment until progression.

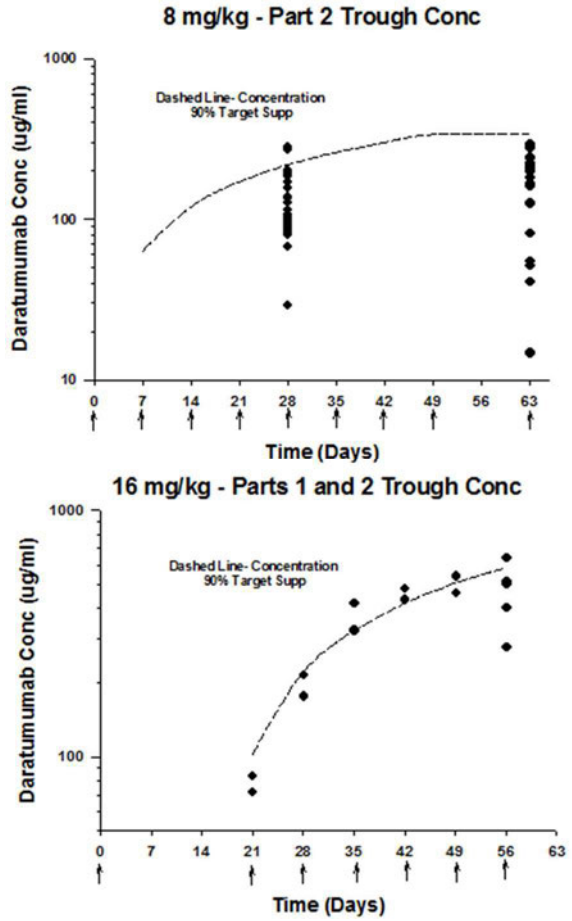
In the current study, treatment with Rd will continue until disease progression or unacceptable toxicity in the control arm (Arm A). This treatment duration is consistent with best current clinical practice based on the above published results.

In the experimental arm (Arm B), treatment with DRd will continue until disease progression or unacceptable toxicity. The protocol was initially designed to discontinue Rd after 24 months to isolate the efficacy and safety of daratumumab from continued exposure to Rd. Based on the data from the FIRST study, lenalidomide treatment until disease progression is emerging as the standard of care and is also consistent with the approved lenalidomide package insert (Hulin 2016; Revlimid USPI 2017).[14,33] Continuous Rd is currently being used as the backbone therapy in many Phase 3 studies evaluating active compounds in patients with myeloma (eg, bortezomib [Durie 2017],[8] carfilzomib, ixazomib, and elotuzumab [ongoing]). Results from the SWOG S0777 study evaluating a combined patient population of transplant eligible and ineligible subjects demonstrated improved median PFS with the addition of 6 months of bortezomib treatment to continuous Rd (43 months vs 30 months) with an acceptable safety profile despite the addition of a third agent to continuous Rd (Durie 2017).[8] Based on these developments, this amendment will allow for treatment to be consistent with the current standard of care.

Rationale for Daratumumab IV Dose

CD38, the target for daratumumab, is expressed on NK cells and clinical data has shown NK cell suppression to be a marker of on target drug activity. Clinical pharmacokinetic data have shown the 16 mg/kg dose to be the lowest dose that results in complete target suppression at all timepoints. This dose and schedule continuously suppressed NK cells throughout dosing. Daratumumab maximal target suppression is presented in Figure 3.

Figure 3: Daratumumab Maximal Target Suppression



8 mg/kg: Observed trough concentration values below predicted 90% suppression throughout dosing

16 mg/kg: Observed trough concentration values at 90% suppression throughout dosing

The ORR appeared higher for the 16 mg/kg dose compared with the 8 mg/kg dose, based on early preliminary data from Part 2 of Study GEN501 and from Study MMY2002 (both ongoing studies) as of a cut-off date of 24 January 2014. In Study GEN501, the ORRs (ie, PR or greater) were 11% and 40% for the 8 mg/kg (n 28) and 16 mg/kg (n 15) dose regimens, respectively. For Study MMY2002, the unconfirmed ORRs for the 8 mg/kg and 16 mg/kg dose regimens were similar to those observed in GEN501. In addition, VGPRs were observed for 7 of 30 subjects treated with the 16 mg/kg dose in the 2 studies. VGPR had not been observed at lower dose levels. These preliminary data support that full target saturation at the 16 mg/kg dose is needed to achieve higher and deeper response rates.

Rationale for Daratumumab SC Dose Regimen

The clinical pharmacology assessment of daratumumab SC monotherapy data are available from daratumumab SC-dosed subjects in a Phase 1/1b study (MMY1004 [Part 2]), a Phase 3 study (MMY3012), and population pharmacokinetics and exposure-response analyses.

In MMY1004, the 1800 mg dose achieved maximum C_{trough} (Cycle 3 Day 1 predose) values that were similar or greater than the maximum C_{trough} observed for the approved 16 mg/kg IV dose following the same dose schedule. The PK data from Part 2 supported the daratumumab SC 1800 mg dose selection for the Phase 3 study. The PK data from MMY3012 study demonstrated that daratumumab SC 1800 mg is non-inferior to daratumumab IV 16 mg/kg in terms of maximum C_{trough} (Cycle 3 Day 1 predose), with the lower bound of the 90% CI for the geometric means ratio for daratumumab SC versus daratumumab IV for maximum C_{trough} (Cycle 3 Day 1 predose) exceeding 80%, thereby meeting the predefined non-inferiority criterion.

Additionally, daratumumab SC 1800 mg monotherapy consistently produced lower peak-to-trough fluctuations, similar or slightly higher trough levels over time, and lower peak concentrations compared with daratumumab IV 16 mg/kg monotherapy. Overall, consistent daratumumab concentrations were observed across the body weight ranges. As expected, slightly higher concentrations were observed for subjects with lower body weights.

There was no apparent relationship between exposure and safety endpoints (SAEs, Grade 3 or higher treatment-emergent adverse events and neutropenia).

Overall, daratumumab SC was well-tolerated with manageable side effects and a significantly reduced incidence of IRRs relative to daratumumab IV. The safety profile of daratumumab administered subcutaneously at a flat dose of 1800 mg continued to be generally comparable to that of the 16 mg/kg IV formulation.

Rationale for DNA and Biomarker Collection

Biomarker samples will be collected to evaluate the depth of clinical response to daratumumab through evaluation of MRD, using DNA sequencing of immunoglobulin genes, and to determine response rates in specific molecular subgroups of multiple myeloma, using DNA/RNA sequencing of multiple myeloma cells to allow for assessment of high risk genomics such as deletion 17p, t(4;14), t(14;20), t(14;16), deletion13, GEP signatures such as UAMS-70, and mutations in p53, BRAF, FGFR, IGH, PI3K, or other molecular subtypes associated with disease progression. Other biomarker goals include evaluation of potential mechanisms of resistance, inter-individual variability in clinical outcomes or identification of population subgroups that respond differently to treatment.

4. SUBJECT POPULATION

Screening for eligible subjects will be performed within 21 days before randomization.

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the investigator should consult with the appropriate sponsor representative before enrolling a subject in the study.

For a discussion of the statistical considerations of subject selection, refer to Section 11.2, Sample Size Determination.

4.1. Inclusion Criteria

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

1. Subject must be at least 18 years of age (or the legal age of consent in the jurisdiction in which the study is taking place).

2. Criterion modified as per Amendment INT-2

   2.1 Subject must have documented multiple myeloma satisfying the CRAB (calcium elevation, renal insufficiency, anemia and bone abnormalities) criteria (see Attachment 1), monoclonal plasma cells in the bone marrow ≥10% or presence of a biopsy proven plasmacytoma, and measurable disease.

   - Measurable disease, as assessed by central laboratory, defined by any of the following:

     IgG 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 serum or urine: Serum immunoglobulin free light chain ≥10 mg/dL and abnormal serum immunoglobulin kappa lambda free light chain ratio.

3. Newly diagnosed and not considered candidate for high-dose chemotherapy with SCT due to:

   - Being age ≥65 years, OR
   - In subjects <65 years: presence of important comorbid condition(s) likely to have a negative impact on tolerability of high dose chemotherapy with stem cell transplantation. Sponsor review and approval of subjects under 65 years of age is required before randomization.

4. Subject must have an ECOG performance status score of 0, 1, or 2 (refer to Attachment 2).

5. Subject must have pretreatment clinical laboratory values meeting the following criteria during the Screening Phase:

   a) hemoglobin ≥7.5 g/dL (≥5 mM/L; prior red blood cell [RBC] transfusion or recombinant human erythropoietin use is permitted);

   b) absolute neutrophil count ≥1.0 x 10^9/L (granulocyte colony stimulating factor [GCSF] use is permitted);

   c) platelet count ≥70 x 10^9/L for subjects in whom <50% of bone marrow nucleated cells are plasma cells; otherwise platelet count >50 × 10^9/L (transfusions are not permitted to achieve this minimum platelet count);

d) aspartate aminotransferase (AST) ≤2.5 x upper limit of normal (ULN);

e) alanine aminotransferase (ALT) ≤2.5 x ULN;

f) total bilirubin ≤2.0 x ULN, except in subjects with congenital bilirubinemia, such as Gilbert syndrome (direct bilirubin ≤2.0 x ULN);

g) Criterion modified per Amendment INT-2

g1) Creatinine clearance ≥30 mL/min (for lenalidomide dose adjustment for subjects with creatinine clearance 30-50 mL/min, refer to Section 6.2). Creatinine clearance can be calculated using the Cockcroft-Gault formula provided in Attachment 3; or for subjects with over- or underweight, creatinine clearance may be measured from a 24-hours urine collection using the formula provided in Attachment 3;

h) Criterion modified per Amendment INT-2

h1) corrected serum calcium ≤14 mg/dL (≤3.5 mM/L); or free ionized calcium ≤6.5 mg/dL (≤1.6 mM/L) (Attachment 4)

6. Criterion modified per Amendment INT-3

6.1 Criterion modified per Amendment INT-2

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

Women of childbearing potential must commit to either abstain continuously from heterosexual sexual intercourse or to use 2 methods of reliable birth control simultaneously. This includes one highly effective form of contraception (tubal ligation, intrauterine device [IUD], hormonal [progesterone-only birth control pills or injections or partner's vasectomy) and one additional effective contraceptive method (male latex or synthetic condom, diaphragm, or cervical cap). Contraception must begin 4 weeks prior to dosing and must continue for 3 months after the last dose of daratumumab. Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy or bilateral oophorectomy. (Also see Attachment 5: Lenalidomide Global Pregnancy Prevention Plan).

7. A man who is sexually active with a woman of childbearing potential must agree to use a latex or synthetic condom, even if he had a successful vasectomy. All men must also not donate sperm during the study, for 4 weeks after the last dose of lenalidomide, and for 3 months after the last dose of daratumumab.

8. A woman of childbearing potential must have 2 negative serum or urine pregnancy tests at Screening, first within 10 to 14 days prior to dosing and the second within 24 hours prior to dosing. For requirements during the Treatment Phase, please see Section 4.3.

9. Each subject (or their legally acceptable representative) must sign an informed consent form (ICF) indicating that he or she understands the purpose of and procedures required for the study and are willing to participate in the study. Subject must be willing and able to adhere to the prohibitions and restrictions specified in this protocol, as referenced in the ICF.

4.2. Exclusion Criteria

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

1. Subject has a diagnosis of primary amyloidosis, monoclonal gammopathy of undetermined significance, or smoldering multiple myeloma. Monoclonal gammopathy of undetermined significance is defined by presence of serum M-protein <3 g/dL; absence of lytic bone lesions, anemia, hypercalcemia, and renal insufficiency related to the M-protein; and (if determined) proportion of plasma cells in the bone marrow of 10% or less (Kyle 2003).[17] Smoldering multiple myeloma is defined as asymptomatic multiple myeloma with absence of related organ or tissue impairment end organ damage (Kyle 2003, Kyle 2007).[17,19]

2. Subject has a diagnosis of Waldenström's disease, or other conditions in which IgM M-protein is present in the absence of a clonal plasma cell infiltration with lytic bone lesions.

3. Subject has prior or current systemic therapy or SCT for multiple myeloma, with the exception of an emergency use of a short course (equivalent of dexamethasone 40 mg/day for 4 days) of corticosteroids before treatment.

4. Subject has a history of malignancy (other than multiple myeloma) within 5 years before the date of randomization (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 5 years).

5. Subject has had radiation therapy within 14 days of randomization.

6. Subject has had plasmapheresis within 28 days of randomization.

7. Subject is exhibiting clinical signs of meningeal involvement of multiple myeloma.

8. Criterion modified as per Amendment INT-2

   8.1a) Subject has 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 <50% of predicted normal.

   8.1b) Subject has had known moderate or severe persistent asthma within the last 2 years (see Attachment 7), or currently has uncontrolled asthma of any classification. (Note that subjects who currently have controlled intermittent asthma or controlled mild persistent asthma are allowed in the study).

9. Criterion modified as per Amendment INT-2

   9.1) Subject is known to be seropositive for human immunodeficiency virus (HIV) or hepatitis B (defined by a positive test for hepatitis B surface antigen [HBsAg] or antibodies to hepatitis B surface and core antigens [Anti-HBs and Anti-HBc, respectively]) or hepatitis C (Anti-HCV antibody positive or HCV-RNA quantitation positive).

10. Subject has any 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.

11. Subject has clinically significant cardiac disease, including:

    - myocardial infarction within 1 year before randomization, or an unstable or uncontrolled disease/condition related to or affecting cardiac function (eg, unstable angina, congestive heart failure, New York Heart Association Class III-IV
    - uncontrolled cardiac arrhythmia (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] Version 4 Grade ≥3) or clinically significant ECG abnormalities
    - screening 12-lead ECG showing a baseline QT interval as corrected by Fridericia's formula (QTcF) >470 msec

12. Subject has known allergies, hypersensitivity, or intolerance to corticosteroids, monoclonal antibodies or human proteins, lenalidomide, or their excipients (refer to respective package inserts or Investigator's Brochure), or known sensitivity to mammalian-derived products.

13. Subject has plasma cell leukemia (according to World Health Organization [WHO] criterion: ≥20% of cells in the peripheral blood with an absolute plasma cell count of more than 2×10^9/L) or POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes).

14. Subject is 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.
15. Subject is a woman who is pregnant, or breast-feeding, or planning to become pregnant while enrolled in this study, within 4 weeks after the last dose of lenalidomide, or within 3 months after the last dose of daratumumab. Or, subject is a man who plans to father a child while enrolled in this study, within 4 weeks after the last dose of lenalidomide, or within 3 months after the last dose of daratumumab.
16. Subject has had major surgery within 2 weeks before randomization or has not fully recovered from surgery, or has surgery planned during the time the subject is expected to participate in the study. Kyphoplasty or vertebroplasty is not considered major surgery.
17. Subject has received an investigational drug (including investigational vaccines) or used an invasive investigational medical device within 4 weeks before randomization or is currently enrolled in an interventional investigational study.
18. Subject has contraindications to required prophylaxis for deep vein thrombosis and pulmonary embolism.
19. Incidence of gastrointestinal disease that may significantly alter the absorption of oral drugs.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's status changes (including laboratory results or receipt of additional medical records) after screening but before the first dose of study treatment is given such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study. Section 17.4, describes the required documentation to support meeting the enrollment criteria. Subjects who fail to meet the inclusion and exclusion criteria (ie, screen failures) may be rescreened once if their condition changes. Rescreening must be discussed with and approved by the sponsor on a case-by-case basis. Subjects who are determined to be eligible for rescreening must sign a new ICF and will then be assigned a new screening number.

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. For restrictions related to concomitant medications, please refer to Section 8.3.

1. For women of childbearing potential, adequate contraception, as specified in Section 4.1, without interruption, must begin 28 days before starting lenalidomide and continue during the Treatment Phase, during any dose interruptions, and for at least 4 weeks after the last dose of lenalidomide, and for 3 months after the last dose of daratumumab. All women must not donate ova during the study, and for at least 4 weeks after the last dose of

lenalidomide, and for 3 months after the last dose of daratumumab. All women must not breastfeed while taking lenalidomide and for at least 28 days after the last dose of lenalidomide.

2. Prior to starting lenalidomide, two negative pregnancy tests are required. The first pregnancy test must be performed within 10 to 14 days prior to the start of lenalidomide and the second pregnancy test must be performed within 24 hours prior to the start of lenalidomide.

3. During the Treatment Phase, pregnancy tests are required weekly during Cycle 1 and then monthly in subsequent cycles in women with regular menstrual cycles or every 2 weeks in women with irregular menstrual cycles. A pregnancy test is also required at the End-of-Treatment Visit and 28 days following the last dose of lenalidomide for women with regular menstrual cycles or 14 and 28 days following the last dose of lenalidomide for women with irregular menstrual cycles. Additional pregnancy tests may be required, as specified in the local lenalidomide Risk Evaluation and Mitigation Strategy (REMS) (where lenalidomide is supplied locally) or the Lenalidomide Global Pregnancy Prevention Plan in Attachment 5 (where lenalidomide is supplied centrally and no local lenalidomide REMS program exists).

4. A man who is sexually active with a pregnant woman or a woman of childbearing potential must always use a latex or synthetic condom during the study and for at least 4 weeks after discontinuing lenalidomide, and for 3 months after discontinuing daratumumab (even if he has undergone a successful vasectomy). All men must not donate semen or sperm during the study, during dose interruptions, for at least 4 weeks after the last dose of lenalidomide, and for 3 months after the last dose of daratumumab.

5. Because of the embryo-fetal risk of lenalidomide, all subjects must adhere to the local lenalidomide REMS program (when lenalidomide is supplied locally), or the lenalidomide Global Pregnancy Prevention Plan provided in Attachment 5 (when lenalidomide is supplied centrally and no local lenalidomide REMS program exists).

6. Subjects must not donate blood during therapy, during dose interruptions, and for at least 4 weeks following discontinuation of lenalidomide.

7. 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

Treatment Allocation

Eligible subjects will be stratified by International Staging System (I vs II vs III see Attachment 8), region (North America vs Other), and age (<75 vs ≥75) and then randomized to treatment in a 1:1 ratio to either Treatment Arm A (Rd alone) or Treatment Arm B (daratumumab+Rd [DRd]). The method of randomization is randomly permuted blocks. An interactive web response system (IWRS) will be used. Each subject will be assigned a unique subject number.

Blinding

As this is an open study, blinding procedures are not applicable.

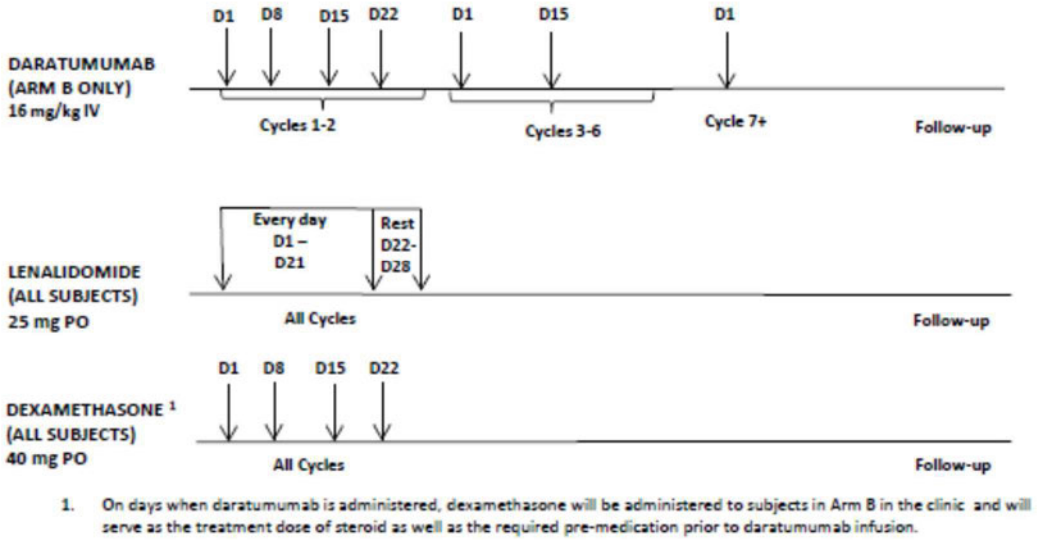
6. DOSAGE AND ADMINISTRATION

In this protocol, the term "study drug" refers to daratumumab only (daratumumab IV or daratumumab SC), and "study treatment" refers to daratumumab, lenalidomide, and dexamethasone. Daratumumab is to be administered as described in the Time and Events Schedule. Each cycle is 28 days. The first visit of a cycle should be 4 weeks after the start of the previous cycle. The start of each cycle may occur ±3 days of the scheduled day in order to accommodate the schedule of the site or subject. Day 1 of subsequent cycles should be adjusted accordingly to maintain the 28-day cycle duration. In Cycles 1 through 6, weekly or bi-weekly daratumumab doses may be given within ±1 day of the scheduled day in order to accommodate the schedule of the site or subject. In all cycles, weekly dexamethasone doses may be given within ±1 day of the scheduled day in order to accommodate the schedule of the site or subject. Changes to within-cycle dosing should not impact Day 1 of the next cycle. Subjects will continue to receive study treatment according to the Time and Events Schedule until disease progression, unacceptable toxicity, or other reasons as listed in Section 10.2.

Subjects whose study treatment is delayed for more than 4 weeks (Cycle 1 to Cycle 6) or more than 6 weeks (Cycle 7 and beyond) should have study treatment discontinued, unless, upon consultation with the sponsor and the review of safety and efficacy, continuation is agreed upon.

A schematic of study treatment administration is provided in Figure 4.

Figure 4: Schematic Overview Study Treatment Administration



1. On days when daratumumab is administered, dexamethasone will be administered to subjects in Arm B in the clinic and will serve as the treatment dose of steroid as well as the required pre-medication prior to daratumumab infusion.

6.1. Daratumumab (Arm B Only)

6.1.1. Daratumumab Preparation

Daratumumab doses will be prepared on the day of the planned administration. Detailed instructions for preparation and administration of daratumumab will be supplied in the Site Investigational Product Procedures Manual (SIPPM) or equivalent document.

6.1.2. Daratumumab IV Administration

Daratumumab (16 mg/kg) will be administered by IV infusion to subjects in Arm B initially once every week for 8 weeks; then once every other week for 16 weeks; thereafter once every 4 weeks until documented progression, unacceptable toxicity, or study end (as defined in Section 17.9.1).

Each subject's dose will be calculated based on the subject's weight rounded to the nearest kilogram. There is no cap on the absolute dose allowed, as long as the dose does not exceed 16 mg/kg. If a subject's weight changes by more than 10% from baseline, the dose of daratumumab will be re-calculated. For recommendations on daratumumab infusion rate, please refer to the SIPPM. All infusions will be performed as outpatient visits. Subjects will receive preinfusion medications and postinfusion medications as outlined in Section 6.1.4.

Every effort should be made to keep subjects on the planned dosing schedule. Time windows for daratumumab administration are outlined in Table 3.

As noted in the Time and Events Schedule, vital signs should be monitored extensively on Cycle 1 Day 1 before, during, and after the first infusion of daratumumab. For all other 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.

6.1.3. Daratumumab SC Administration

Daratumumab SC will be administered by SC injection at a fixed dose of 1800 mg once every 4 weeks until documented progression, unacceptable toxicity, or study end (as defined in Section 17.9.1). Doses will be administered by manual push over 3-5 minutes in the abdominal SC tissue, rotating between the four quadrants. The volume of the SC solution will be 15 mL for the 1800 mg dose. Refer to the Investigational Product Preparation Instructions (IPPI) for additional guidance on SC administration of daratumumab SC.

The dose of daratumumab will remain constant throughout the study. For subjects who initially received daratumumab IV and then switch to daratumumab SC following Amendment 8, it is recommended subjects are observed for a period of time deemed appropriate by the investigator following the first daratumumab SC dose and, if necessary, after subsequent injections. Reasons for continued observation on subsequent daratumumab administrations may include but are not limited to the following: subjects with a higher risk of respiratory complications (eg, subjects with mild asthma or subjects with COPD who have an FEV1 <80% at screening or developed FEV1 <80% during the study without any medical history), subjects with IRR with prior administrations of study drug, subject with a decreased condition on day of dosing compared to prior dosing day.

6.1.4. Prevention of Infusion -Related and Injection-Site Reactions

6.1.4.1. Pre-dose Medication

Pre-dose medications for subjects receiving daratumumab will be administered as described in the Time and Events Dose Administration Schedule. On daratumumab dose (IV or SC) days, subjects will receive the following medications prior to dose:

- Acetaminophen (paracetamol) 650-1000 mg IV or orally (PO) approximately 1 hour or less prior to daratumumab dose
- An antihistamine (diphenhydramine 25-50 mg IV or PO, or equivalent but avoid IV use of promethazine) approximately 1 hour prior to administration (see Attachment 9 for list of antihistamines that may be used); after Cycle 6, if a subject has not developed an infusion-related and injection-site reaction and is intolerant to antihistamines, modifications are acceptable as per investigator discretion.

- Dexamethasone 40 mg IV (preferred) or PO, approximately 1 hour or less prior to daratumumab dose. For subjects older than 75 years or underweight (body mass index [BMI] <18.5), dexamethasone 20 mg may be administered as appropriate (see Section 6.3). An equivalent intermediate-acting or long-acting corticosteroid may substitute (see Attachment 6 for conversion table). On days when subjects receive this dose of dexamethasone in the clinic, dexamethasone will not be self-administered at home. If weekly dexamethasone dosing has been reduced below 10 mg due to adverse events during study, a minimum of dexamethasone 10 mg IV should continue to be administered prior to daratumumab dose.

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

6.1.4.2. Post-dose Medication

For subjects with higher risk of respiratory complications (ie, subjects with mild asthma, or subjects with COPD who have a FEV1 <80%), the following post-dose medications should be considered:

- Antihistamine (diphenhydramine or equivalent)
- Short-acting β_2 adrenergic receptor agonist such as salbutamol aerosol
- Control medications for lung disease (eg, inhaled corticosteroids ± long-acting β_2 adrenergic receptor agonists for subjects with asthma; long-acting bronchodilators such as tiotropium or salmeterol ± inhaled corticosteroids for subjects with COPD)

For subjects previously treated with daratumumab IV who switch to daratumumab SC, post-dose medications may be offered after 1 or more doses of daratumumab SC, per investigator discretion.

In addition, these at-risk subjects may be hospitalized for monitoring for up to 2 nights after a daratumumab administration. If subjects are hospitalized, then their FEV1 should be measured 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 all administrations. 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 infusion-related reactions, then these post-dose medications may be waived after 4 full doses at the investigator's discretion.

6.1.5. Management of Infusion-related Reactions

Infusion-related reactions (IRRs) are systemic reactions related to daratumumab administration (IV or SC). Subjects in Arm B should be carefully observed during daratumumab administrations. Trained study staff at the clinic should be prepared to intervene in case of any infusion reactions 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. Attention to staffing should be considered when multiple subjects will be dosed at the same time.

If an infusion-related reaction develops during daratumumab administration, then the administration should be paused. Subjects who experience adverse events during the daratumumab administration must be treated according to the investigator's judgment and best clinical practice. The following guidelines may apply:

- Subjects should be treated with acetaminophen, antihistamine, or corticosteroids. Intravenous saline may be indicated. For bronchospasm, urticaria, or dyspnea, subjects may require antihistamines, oxygen, corticosteroids, or bronchodilators. For hypotension, subjects may require vasopressors.
- In the event of a life-threatening infusion-related reaction (which may include pulmonary or cardiac events), or anaphylactic reaction, daratumumab should be discontinued and no additional daratumumab should be administered to the subject. Aggressive symptomatic treatment should be applied.

For subjects treated with daratumumab IV, if an infusion is paused, then a longer-than-anticipated infusion time may occur. Overnight stays at the hospital because of slow infusion times should not be reported as a serious adverse event. However, if the underlying cause of the delayed infusion time is an adverse event or serious adverse event, then that should be reported as such.

6.1.5.1. Infusion-Related Events of Grade 1 or Grade 2

If the investigator assesses a Grade 1 or 2 adverse event to be related to daratumumab, then daratumumab administration should be paused. When the subject's condition is stable, the daratumumab administration may be restarted at the investigator's discretion. For subjects treated with daratumumab IV, upon restart, the infusion rate should be half of that used before the interruption. Subsequently, the infusion rate may be increased at the investigator's discretion.

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 the onset, then the subject must be withdrawn from treatment.

6.1.5.2. Infusion-Related Reactions of Grade 3 or Higher

For infusion-related adverse events that are Grade 4, daratumumab should be stopped and treatment with daratumumab will be discontinued for that subject.

For infusion-related adverse events that are Grade 3, the daratumumab administration must be stopped, and the subject must be observed carefully until the resolution of the adverse event or until the intensity of the event decreases to Grade 1, at which point the daratumumab may be restarted at the investigator's discretion. For subjects treated with daratumumab IV, upon restart, the infusion rate should be half of that used before the interruption. Subsequently, the infusion rate may be increased at the investigator's discretion.

If the intensity of the adverse event returns to Grade 3 after restart of daratumumab, then the procedure described in this section may be repeated at the investigator's discretion. Should the intensity of the adverse event increase to Grade 3 for a third time, then treatment with daratumumab will be discontinued for that subject.

6.1.5.3. Injection-Site Reactions

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

6.2. Lenalidomide (Arm A and Arm B)

Lenalidomide will be self-administered at a dose of 25 mg PO each day on Days 1 through 21 of each 28-day cycle for subjects with creatinine clearance >50 mL/min. If creatinine clearance is between 30 and 50 mL/min, the dose of lenalidomide will be 10 mg every 24 hours. Once the creatinine clearance is >50 mL/min during the course of the treatment, lenalidomide can be increased to 25 mg. In both treatment arms, subjects will continue on lenalidomide until progression of disease or unacceptable toxicity. Subjects in Arm B who discontinued treatment with Rd at 24 months may re-start treatment with Rd as per Amendment INT-4.

On daratumumab administration days, it is recommended that lenalidomide should be administered either prior to or at the same time (preferred) as the premedications.

If a daily lenalidomide dose is missed, it may be taken if <12 hours have elapsed since the time that it should have been taken. If the next dose is scheduled to be taken within 12 hours, the missed lenalidomide dose should be skipped.

6.3. Dexamethasone (Arm A and Arm B)

Dexamethasone (or equivalent in accordance with local standards; see Attachment 6 for conversion table) will be administered at a total dose of 40 mg weekly. For subjects older than 75 years or underweight (BMI <18.5), the dexamethasone dose may be administered at a dose of 20 mg weekly. In both treatment arms, dexamethasone will be administered until the subject experiences disease progression or unacceptable toxicity, whichever comes first. Subjects in Arm B who discontinued treatment with Rd at 24 months may re-start treatment with Rd as per Amendment INT-4.

On days when subjects in Arm B receive a dose of daratumumab, dexamethasone will not be self-administered but instead will be administered in the clinic. In this setting, dexamethasone will be utilized as the treatment dose of steroid for that particular day, as well as the required pre-medication prior to daratumumab administration.

If a weekly dexamethasone dose is missed, it may be taken if <4 days have elapsed since the time that it should have been taken. If the next dose is scheduled to be taken within 3 days, the missed dexamethasone dose should be skipped.

6.4. Dose Delays and Dose Modification

Subjects who need to discontinue treatment with any one component of study treatment (lenalidomide, dexamethasone, or daratumumab) may continue to receive treatment with the other components of study treatment, as assigned.

6.4.1. Daratumumab Dose Modification

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

6.4.1.1. Daratumumab-Related Toxicity Management

Refer to Section 6.1.4 for details on management of infusion-related reactions. ONLY if any of the following criteria are met and the event cannot be ascribed to lenalidomide, the daratumumab administration must be held to allow for recovery from toxicity. The criteria for a dose delay are:

- Grade 4 hematologic toxicity
- Grade 3 thrombocytopenia with bleeding
- Febrile neutropenia
- Neutropenia with infection, of any grade
- Grade 3 or higher nonhematologic 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

Other than on Day 1 of a cycle, if a daratumumab dose does not commence within the prespecified window (Table 3) 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.

Table 3: Daratumumab-Related Toxicity Management

Cycles	Frequency	Dose Held	Dosing Re start
1 and 2	Weekly (q1wk)	>3 days	next planned weekly dosing date
3 to 6	Biweekly (q2wks)`	>1 week	next planned biweekly dosing date
7+	Every 4 weeks (Q4W)	>2 weeks	next planned every 4 weeks dosing date

Doses of daratumumab may be delayed up to 4 weeks (Cycle 1 to Cycle 6) or up to 6 weeks (Cycle 7 and beyond). Day 1 of a cycle should not be skipped; however, Day 1 of a cycle may be delayed, and Day 1 of subsequent cycles should be adjusted accordingly to maintain the 28-day cycle duration. However, if a within-cycle dose is delayed, then the dates of the subsequent within-cycle doses should not be adjusted. Any adverse event deemed to be related to daratumumab that requires a dose hold of more than 4 weeks (Cycle 1 to Cycle 6) or more than 6 weeks (Cycle 7 and beyond) will result in permanent discontinuation of daratumumab. If a dose delay occurs, then pharmacokinetic and pharmacodynamic assessments should be performed on the actual administration day of daratumumab, not on the original scheduled administration day.

6.4.1.2. Daratumumab Interruption or Missed Doses

A daratumumab dose that is held for more than the permitted time (Table 3) from the per-protocol administration date for any reason other than toxicities suspected to be related to daratumumab should be brought to the attention of the Sponsor at the earliest possible time. Subjects whose dose was delayed for more than 4 weeks (Cycle 1 to Cycle 6) or more than 6 weeks (Cycle 7 and beyond) should have study treatment discontinued, unless, upon consultation with the sponsor and the review of safety and efficacy, continuation is agreed upon. Infusion-related reactions may occur upon re-initiation of daratumumab after a prolonged delay in treatment and subjects receiving daratumumab SC should have prolonged observation following the first dose post re-initiation.

6.4.2. Lenalidomide Dose Reductions

Dose adjustments of lenalidomide will follow the approved labeling as follows:

- Starting dose: 25 mg
- Dose level 1: 15 mg
- Dose level 2: 10 mg
- Dose level 3: 5 mg

Dose adjustments should be based on the highest grade of toxicity that is ascribed to lenalidomide. After initiation of lenalidomide, subsequent lenalidomide dose adjustment is based on individual subject treatment tolerance. If the investigator determines that an adverse event may be related to lenalidomide, dose adjustment can be done even if not specified in this protocol. In the event of a dose adjustment, lenalidomide doses maybe re-escalated at the investigator's discretion.

6.4.2.1. Thrombocytopenia

If the subject's platelet count decreases, dose adjustments should be made according to the recommendations in Table 4.

Table 4: Lenalidomide Dose Adjustment for Thrombocytopenia

Platelet Count	Recommended Course of Action
• When count first falls to $<30 \times 10^9$/L • When count returns to $\geq 30 \times 10^9$/L	• Interrupt lenalidomide treatment, follow complete blood count weekly • Resume lenalidomide at the next lower dose
• For each subsequent drop in count to $<30 \times 10^9$/L • When count returns to $\geq 30 \times 10^9$/L	• Interrupt lenalidomide treatment • Resume lenalidomide at the next lower dose

6.4.2.2. Neutropenia

If the subject experiences neutropenia, the investigator should consider the use of growth factors in the subject's management. If the subject's neutrophil count decreases further, dose adjustments should be made according to the recommendations in Table 5.

Table 5: Lenalidomide Dose Adjustment for Neutropenia

Neutrophil Count	Recommended Course of Action
• When count first falls to <1.0 × 10^9/L • When count returns to ≥1.0 × 10^9/L and neutropenia is the only observed toxicity	• Interrupt lenalidomide treatment, consider G CSF treatment, follow complete blood count weekly • Resume lenalidomide at 25 mg daily or initial starting dose
• When count returns to ≥1.0 × 10^9/L and dose dependent hematological toxicities other than neutropenia are observed	• Resume lenalidomide at the next lower dose
• For each subsequent drop in count to <1.0 × 10^9/L • When count returns to ≥1.0 × 10^9/L	• Interrupt lenalidomide treatment • Resume lenalidomide at the next lower dose level

6.4.2.3. Renal Impairment

Because lenalidomide is primarily excreted unchanged by the kidney, adjustments to the dose of lenalidomide are recommended to provide appropriate drug exposure in subjects with moderate or severe renal impairment. Lenalidomide dose adjustment should be instituted for subjects with a creatinine clearance of 50 mL/minute or less. The recommended doses for subjects with multiple myeloma and renal impairment are shown in Table 6.

Table 6: Lenalidomide Dose Adjustment for Renal Impairment

Category	Renal Function[a]	Dose
Moderate renal impairment	CrCl 30 50 mL/min	10 mg every 24 hours
Severe renal impairment	CrCl <30 mL/min (not requiring dialysis)	15 mg every 48 hours
End stage renal disease	CrCl <30 mL/min (requiring dialysis)	5 mg once daily. On dialysis days, administer the dose after dialysis

Key: CrCl creatinine clearance.

[a] Estimated by creatinine clearance as calculated by the Cockcroft Gault equation and adjusted for body weight in subjects with a body mass index >30 kg/m^2.

6.4.2.4. Other Adverse Events

For other Grade 3 or 4 non-hematologic and non-renal toxicities judged by the investigator to be related to lenalidomide alone, treatment with lenalidomide should be interrupted and restarted at the next lower dose level once the toxicity has resolved to Grade 2 or less. Treatment with daratumumab and dexamethasone may continue.

Note that the dose modifications above are suggested, but physician discretion and clinical judgment should prevail.

6.4.3. Dexamethasone Dose Modifications

Dexamethasone may be reduced, if necessary, according to Table 7. For other Grade 3 or 4 non-hematologic and non-renal toxicities judged by the investigator to be related to dexamethasone alone, treatment with dexamethasone should be interrupted and restarted at the next lower dose level once the toxicity has resolved to Grade 2 or less. Treatment with daratumumab and lenalidomide may continue. In the event of a dose adjustment, dexamethasone doses maybe re-escalated at the investigator's discretion. For complete details on dexamethasone, refer to the most current local product prescribing information.

Note that Table 7 represents suggested dose modifications of dexamethasone, but physician discretion and clinical judgment should prevail.

If weekly dexamethasone dosing has been reduced below 10 mg due to adverse events during study, a minimum of dexamethasone 10 mg IV should continue to be administered prior to daratumumab doses.

Table 7: Recommended Dose Reduction for Dexamethasone

CTCAE Category	Toxicity	Dose Change
Gastrointestinal	Grade 1 2 Dyspepsia, gastric or duodenal ulcer, gastritis requiring medical management	Treat with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measure, decrease dexamethasone dose by 50%.
	> Grade 3 requiring hospitalization or surgery	Hold dexamethasone until symptoms adequately controlled. Restart at 50% of current dose along with concurrent therapy with H2 blockers, sucralfate or omeprazole. If symptoms persist despite above measure, discontinue dexamethasone and do not resume.
	Acute pancreatitis	Discontinue dexamethasone and do not resume
Cardiovascular	> Grade 3 Edema limiting function and unresponsive to therapy or anasarca	Diuretics as needed and decrease dexamethasone dose by 25%; if edema persists despite above measures, decrease dose to 50% of initial dose; discontinue dexamethasone and do not resume if symptoms persist despite 50% reduction
Neurology/ Psychiatric	> Grade 2 interfering with function but not interfering with activities of daily living	Hold dexamethasone until symptoms adequately controlled. Restart at 50% of current dose. If symptoms persist despite above measure, discontinue dexamethasone and do not resume
Musculoskeletal	> Grade 2 Muscle weakness Symptomatic and interfering with function but not interfering with activities of daily living	Decrease dexamethasone dose by 25%; if weakness persists despite above measures, decrease dose to 50% of initial dose; discontinue dexamethasone and do not resume if symptoms persist despite 50%
Metabolic	> Grade 3 Hyperglycemia	Treatment with insulin or oral hypoglycemic agents as needed. If uncontrolled despite above measure, decrease dose by 25% decrements until levels are satisfactory

7. TREATMENT COMPLIANCE

Study drug (daratumumab) will be administered by qualified site staff, and the details of each administration will be recorded in the electronic case report form (eCRF). Subjects will be provided with a treatment diary which will be used to assess compliance with lenalidomide and dexamethasone treatment. Additional details are provided in the SIPPM or equivalent document.

8. CONCOMITANT THERAPY

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 eCRF and recorded in the source documents beginning with signing of the ICF to 30 days after the last dose of the last study treatment until the long-term survival follow-up starts (defined in Section 9.1.8), or until the start of subsequent anti-myeloma treatment, if earlier: growth factors, transfusions, anti-infectives (antibacterials, antivirals, and antimycotics), steroids, anti-arrhythmics and other

cardiac supportive therapy, anti-epileptics, centrally acting psychiatric medication, anti-histamines and other medications targeting post-dose systemic reactions, bisphosphonates, and any anti-myeloma therapy (including radiation). Concomitant medications to manage adverse events and SAEs will be recorded as per Section 12.3.1.

8.1. Recommended Therapies

8.1.1. Prevention of Deep Vein Thrombosis and Pulmonary Embolism

Lenalidomide has been associated with increased incidence of deep vein thrombosis and pulmonary embolism. Therefore, prophylaxis of venous thromboembolism (VTE) for all subjects is recommended according to IMWG guidelines as well as at the investigator's discretion (Palumbo 2008).[28] Both individual and myeloma-related risks of VTE should be taken into account in determining the type of thromboprophylaxis. In summary:

- If no risk factor, or any one risk factor is present, aspirin 81-325 mg once daily is recommended or dose per institutional standards
- If 2 or more risk factors are present, low molecular weight heparin (LMWH) (equivalent of enoxaparin 40 mg once daily) or full-dose warfarin, international normalized ratio (INR) 2-3, is recommended
- If any myeloma therapy-related risk factor is present, then LMWH (equivalent of 40 mg enoxaparin once daily) or full-dose warfarin (target INR 2-3) is recommended

8.1.2. Bisphosphonate Therapy

Bisphosphonate therapy is recommended to be continued per treatment guidelines (NCCN 2013).[23] 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.

Subjects who are currently using bisphosphonate therapy when they enter the study should continue the same treatment. If clinically indicated, subjects may initiate bisphosphonate therapy as soon as possible during Screening and no later than the end of Cycle 1. After Cycle 1, investigators should not prescribe bisphosphonates to subjects who have not received it before, unless it has been discussed with the sponsor and there is no sign of disease progression.

8.1.3. Therapy for Tumor Lysis Syndrome

Subjects should be monitored for symptoms of tumor lysis syndrome. Management of tumor lysis syndrome, including hydration and monitoring for abnormal laboratory test results such as hyperkalemia, hyperuricemia, and hypocalcemia, are highly recommended. It is also recommended that high-risk subjects, ie, those with a high tumor burden, be treated prophylactically in accordance with local standards (eg, rehydration; diuretics; allopurinol 300 mg daily and medication to increase urate excretion).

8.1.4. Prophylaxis for Pneumocystis carinii

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

8.1.5. Prophylaxis for Herpes Zoster Reactivation

Prophylaxis for herpes zoster reactivation is recommended during the Treatment Phase, as per institutional guidelines.

8.1.6. Prevention of Steroid Induced Gastritis

Dexamethasone and other steroids may induce gastritis. Medications to prevent gastritis are permitted per institutional guidelines, for example proton pump inhibitors (omeprazole or equivalent) or sucralfate, or H2 blockers (ranitidine or equivalent).

8.1.7. Management of Hepatitis B Virus Reactivation

Primary antiviral prophylaxis is permitted as per local standard of care. Per protocol, hepatitis B virus (HBV) DNA testing by polymerase chain reaction (PCR) is required for subjects at risk for HBV reactivation (see Section 9.8).

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

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:

- Colony stimulating factors, erythropoietin, and transfusion of platelets and red blood cells. If erythropoietin is given, then this should be given according to the local lenalidomide label, as there is an increased risk of thrombosis with lenalidomide.
- It is important to prevent constipation (eg, adequate hydration, high-fiber diet, and stool softeners if needed)
- Adequate hydration is recommended for prevention of myeloma-related kidney disease
- Prophylactic antiemetics, with the exception of corticosteroids

- Vaccination is allowed per local guidelines (see Section 8.3 for Prohibited Therapies).

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

8.3. Prohibited Therapies

Concomitant administration of any other antineoplastic therapy for the intention of treating multiple myeloma is prohibited prior to confirmation of disease progression, including medications that target CD38, as well as clarithromycin (Ghosh 2013).[12] For management of second primary malignancies please see Section 10.2. Continuation of the study treatment during or after emergency orthopedic surgery or radiotherapy because of the subject's benefit may occur only in the absence of disease progression and after review by the sponsor. Such 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 radiotherapy is to occur within the first 2 cycles of treatment and the absence of evidence of disease progression is to be reviewed by the sponsor.

Concomitant administration of investigational agents is prohibited. Administration of commercially available agents with activity against or under investigation for multiple myeloma, including systemic corticosteroids (>10 mg prednisone per day or equivalent) should be avoided (other than those given for infusion-related reactions as described in Section 6.1.4.2 or for the treatment of adverse events [if no other treatment options are available]). Nonsteroidal anti-inflammatory agents should be used with caution in order to prevent myeloma-related kidney disease.

Administration of live attenuated and replication-competent viral vector vaccines are prohibited.

Typically, IV contrast is NOT used in computed tomography (CT) scanning of the 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. The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

8.4. Subsequent Therapies

After discontinuation of study therapy subjects should continue disease evaluations per the Time and Events Schedule until confirmed PD or until the cut-off date for the final CSR analysis, whichever is earlier. Subsequent anti-myeloma therapy cannot be started before disease progression is established per the IMWG criteria (Section 9.2.1.1, Response Categories) and confirmed by the sponsor. This sponsor confirmation is no longer required after the cut-off for the final CSR analysis.

After PD (and sponsor confirmation when required), choice of subsequent therapy is at the discretion of the investigator. Subjects randomized to Arm A (Rd) may have the option to receive daratumumab provided by the sponsor (in any subsequent line of therapy) if recommended by the

investigator. Eligibility for and administration of daratumumab including safety management (eg, infusion-related reactions and HBV monitoring) must be in accordance with local prescribing information and local regulations. For these subjects, daratumumab should not be added to an ongoing subsequent therapy regimen until the subject has progressed on that regimen. Subjects in Arm A (Rd) who receive daratumumab after PD through the sponsor will remain in the long-term survival follow-up phase of the study. Serious adverse events must be reported for these subjects until 30 days after daratumumab is discontinued. Second primary malignancies will continue to be reported until end of study.

All subsequent therapy for multiple myeloma (including start and end date, best response, and date of progression to the subsequent therapy) should be documented in the appropriate section of the eCRF, including during long-term survival follow-up.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedule summarizes the frequency and timing of efficacy, pharmacokinetic, immunogenicity, biomarker, patient reported outcomes, and safety measurements applicable to this study. Every effort should be made to keep subjects on the planned study schedule, including subjects who switch from daratumumab IV to daratumumab SC following Amendment 8.

All visit-specific PRO assessments should preferably be conducted/completed before any tests, procedures, or other consultations for that visit to prevent influencing subject perceptions. Refer to Section 9.7 for details.

Blood collections for pharmacokinetic assessments should be kept as close to the specified time as possible. Other measurements may be done earlier than specified timepoints if needed. Actual dates and times of assessments will be recorded in the source documentation.

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.

The blood volume for the study is estimated at approximately 65 mL during screening and 360 mL during the first year (approximately 20-35 mL per cycle for routine testing, plus additional PK and biomarker samples). In the Follow-up Phase, subjects prior to PD will continue to have approximately 20 mL blood drawn per month for serum disease evaluations. This includes laboratory assessments associated with safety, efficacy, and pharmacokinetic evaluations, as well as scientific research samples. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples. After the final CSR analysis, no blood will be collected, only local routine testing will be performed as per local institutional practice to ensure patients' safety for continued treatment.

With the implementation of Amendment 8, site visits may be replaced with virtual visits or other local arrangements in exceptional circumstances, with site visits resuming as soon as possible thereafter.

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 screening assessment is conducted (that was not performed as part of the subject's standard of care). During the Screening Phase, eligibility criteria will be reviewed, and a complete clinical evaluation will be performed as specified in Time and Events Schedule. Screening procedures will be performed within 21 days before randomization; however, results of tests such as skeletal survey, radiologic tests (eg, magnetic resonance imaging [MRI] to document baseline size of known or suspected extramedullary plasmacytomas; ECG; chest x rays [or full chest CT scan]; or bone marrow aspirate or biopsy) performed up to 6 weeks (42 days) before randomization as routine standard of care for the subject's disease can be used. See Attachment 1 for the modified IMWG Diagnostic Criteria.

Subjects <65 years must have known presence of important comorbid condition(s) likely to have a negative effect on the tolerability of high dose chemotherapy with SCT. Documentation of the condition, for example diagnosis of concomitant infectious disease(s), should be provided. Sponsor review and approval of subjects under 65 years of age is required before randomization.

A negative pregnancy test for women of childbearing potential must be documented twice, once within 10-14 days before the first dose and a second time within 24 hours before the first dose of any component of the treatment regimen.

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.

9.1.3. 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 randomization. A window of ±3 days is allowed for Day 1 of each cycle visits to the clinic. Each cycle is 28 days. The first visit of a cycle should be 4 weeks after the start of the previous cycle. The start of each cycle may occur ±3 days of the scheduled day in order to accommodate the schedule of the site or subject. Day 1 of subsequent cycles should be adjusted accordingly to maintain the 28-day cycle duration. In Cycles 1 through 6, weekly or bi-weekly daratumumab infusions may be given within ±1 day of the scheduled day in order to accommodate the schedule of the site or subject. In all cycles, weekly dexamethasone doses may be given within ±1 day of the scheduled day in order to accommodate the schedule of the site or subject. Changes to within-cycle dosing should not impact Day 1 of the next cycle. 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 diagnosed, then the subject will discontinue study treatment, complete the End-of-Treatment Visit, and enter the Follow-up Phase. If disease progression has not occurred at the time of the End-of-Treatment visit, disease evaluations must continue until disease progression is confirmed. Subsequent anti-myeloma treatment will not be started until after disease progression is confirmed by the Sponsor. After the cut-off for the final CSR analysis, confirmation of PD by the sponsor is no longer required.

For those subjects continuing treatment after the final CSR analysis, routine safety monitoring should comply with the local institution practice (Attachments 11 and 12).

End-of-Treatment Visits

Unless a subject withdraws consent for study participation or is lost to follow up, an End-of-Treatment Visit is to occur within 4 weeks after the last dose of all study treatments. 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 that occur up to 30 days after the last dose of study treatment. Additional information on reporting of adverse events is presented in Section 12.

After the final CSR analysis, end of treatment visits are no longer required.

9.1.4. Follow-up Phase

The Follow-up Phase will begin once a subject discontinues all study treatments. Subjects who discontinue study treatment before disease progression must continue to have disease evaluations. Ideally, the timing of disease evaluations should follow the Time and Events Schedule until confirmed PD (see Section 8.4, Subsequent Therapies), death, the start of a new anti-myeloma therapy, withdrawal of consent, lost to follow-up, or the end of the study. After disease progression is documented, subsequent anti-myeloma therapy, PFS2 (per investigator judgment), second primary malignancies and survival status will be obtained at least every 16 weeks ±2 weeks until the start of the long-term survival follow-up. Every 16-week follow-up contacts, as well as Week 8 and Week 16 post-PD ECOG and ePRO assessments, should be scheduled from the date of confirmed progression (ie, the date of the confirmatory laboratory assessment, not the date of confirmation by the sponsor). In subjects for whom disease progression will not be documented (eg, received subsequent anti-myeloma treatment or refused disease evaluations, but agreed to follow-up contacts), the every 16-week follow-up should be scheduled from the date of the End-of-Treatment Visit.

For Follow-up Phase procedures during long-term survival follow-up, please see Attachment 11. If the information is obtained via telephone contact, written documentation of the communication must be available for review in the source documents. If the subject has died, the date and cause of death will be collected and documented in the eCRF.

9.1.5. Assessments Following the Positive Second Interim Analysis of PFS

Following the positive second interim analysis of PFS, subjects remaining in the study will continue to be monitored as follows until the next interim analysis of OS (ie, when 260 deaths have occurred):

Subjects who Have had Disease Progression

For subjects whose disease has already progressed, every-16-week follow-up contacts should be performed to capture:

- Survival
- Subsequent anti-myeloma therapy
- New second primary malignancies

These data may be collected directly from subject or indirectly (eg, from medical correspondence or visits).

Subjects who Have not had Disease Progression

For subjects in the randomized portion of the study who have not experienced disease progression, disease assessments will continue to occur per the Time and Events Schedule until disease progression is confirmed by the sponsor.

ECOG and ePRO will be collected every 6 months (± 14 days) until PD. Also 8 and 16 weeks after PD (see Section 9.1.4).

9.1.6. Assessments Following Implementation of Amendment 8

Following the implementation of Amendment 8, disease evaluations are to be performed locally per the site's standard of care. Quantitative immunoglobulin testing is no longer required. All subjects must still meet IMWG criteria for progression (see Table 8), prior to initiation of subsequent anti-myeloma therapy.

Daratumumab pharmacokinetic, anti-daratumumab antibody, and rHuPH20 immunogenicity sampling at EOT and 8 weeks after the last daratumumab SC dose are required for subjects who switch from daratumumab IV to daratumumab SC treatment. Following Amendment 8, subjects in Arm B who remain on daratumumab IV will no longer have pharmacokinetic and immunogenicity samples collected.

9.1.7. Assessments Following the Interim OS Analysis

Following the interim OS analysis (ie, when 260 deaths have occurred), subjects remaining in the study will continue to be monitored as follows until the cut-off for the final CSR analysis:

- For subjects whose disease has already progressed at the time of the interim OS analysis, only survival, subsequent anti-myeloma therapy, PFS2 and all new second primary malignancy information will be collected, which may be obtained directly from subject or indirectly (eg, from medical correspondence or visits).

- Once the interim OS analysis has occurred and when the median PFS is reached in the DRd arm, the sponsor will notify the investigators that from that point onward, sponsor confirmation of disease progression will no longer be required, with the exception of subjects who progress on the Rd arm and then request subsequent therapy with daratumumab (Section 8.4). All subjects must still meet IMWG criteria for progression (see Table 8), prior to initiation of subsequent anti-myeloma therapy.

9.1.8. Final CSR Analysis and Long-term Survival Follow-up

Sites will be notified by the sponsor of the clinical cut-off date for the final CSR analysis. Following the final CSR analysis, which will provide updates to the primary CSR analysis for both efficacy and safety, all subjects will enter long-term survival follow-up. Attachment 11 describes study procedures to be followed for subjects in the long-term survival follow-up phase. Long-term survival follow-up will continue until the final OS analysis (defined in Section 9.1.9).

9.1.9. Final OS analysis Until End of Study

Sites will be notified by the sponsor of the clinical cut-off date for the final OS analysis, which will occur when approximately 390 deaths have occurred. After the final OS analysis, all eCRF data collection will end. Attachment 12 describes study procedures to be followed for subjects who continue study treatment after the final OS analysis until the end of study (defined in Section 17.9.1).

9.2. Efficacy

9.2.1. Evaluations

Disease response and progression will be based on assessments from IMWG Guidelines as defined in Section 9.2.1.1. Previous studies have demonstrated potential interference of therapeutic monoclonal antibodies with detection of endogenous myeloma M-protein on serum immunofixation (IFE) (McCudden 2010).[22] Daratumumab detection on serum immunofixation has been demonstrated in subjects treated with 16 mg/kg, and may interfere with the traditional IMWG criteria of negative serum IFE for complete response or stringent complete response. To mitigate this interference, the sponsor has developed a reflex assay that utilizes anti-idiotype antibody to bind daratumumab and confirm its interference on IFE (see laboratory manual). For all subjects with VGPR, and a negative endogenous M-protein by serum M-protein quantitation by electrophoresis (SPEP), reflex IFE testing will be performed to confirm the presence of daratumumab on IFE.

9.2.1.1. Response Categories

Disease evaluations must be performed every 28 days for the first 2 years and then every 8 weeks until disease progression (or other reasons as per Section 10). A window of ±7 days is allowed. If treatment has been delayed for any reason, the disease evaluations must be performed according to schedule, regardless of any changes to the dosing regimen.

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, Rajkumar 2011)[7,32] presented in Table 8. For quantitative immunoglobulin, M-protein, and immunofixation measurements in serum and 24-hour urine, the investigator will use results provided by the central laboratory. Subjects with positive serum IFE and confirmed daratumumab IFE interference, that meet all other clinical criteria for complete response or stringent complete response, will be considered CR/sCR.

Disease progression must be consistently documented across clinical study sites using the criteria in Table 8. For patients with measurable disease by SPEP or UPEP at baseline, increases in serum free light chains (FLC) or the FLC ratio alone do not meet criteria for progressive disease.

Table 8: International Uniform Response Criteria Consensus Recommendations

Response	Response Criteria
Stringent complete Response (sCR)	• CR as defined below, *plus* • Normal FLC ratio, *and* • 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 • In addition to the above criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required.
Stable disease (SD)	• Not meeting criteria for CR, VGPR, PR, or progressive disease
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) • 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 the IMWG criteria (Durie 2006, Rajkumar 2011).[7,32] In the 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; >2.875mM/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.

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 the IMWG criteria. For CR/sCR, the IMWG criteria require subjects to have a negative SPEP and serum IFE. As an immunoglobulin, daratumumab can be picked up by SPEP and serum IFE and may cause false positive SPEP and IFE results. A reflex assay has been developed by the sponsor to confirm daratumumab interference on these assays.

Serum free light chain assay test results will be analyzed by the central laboratory for the assessment of stringent complete response (sCR), according to the most recently published IMWG criteria (Durie 2006).[7] 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 (see Section 8.4, Subsequent Therapies), death, the start of a new treatment for multiple myeloma, withdrawal of consent for study participation, lost to follow-up, or until the final CSR analysis, whichever occurs first. Disease evaluations scheduled for treatment days should be collected before study treatment is administered.

During the long-term survival follow-up until final OS analysis (defined in Section 9.1.9), subjects still receiving study treatment will have efficacy evaluations performed as detailed in Attachment 11.

After the final OS analysis until the end of study (defined in Section 17.9.1) subjects still receiving study treatment will have efficacy evaluations performed as detailed in Attachment 12.

9.2.1.2. Myeloma Protein Measurements in Serum and Urine

Blood and 24-hour urine 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. If the 24-h urine collection (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.

- Serum quantitative immunoglobulins (QIgs)

All subjects will be evaluated for IgG, IgA, IgM, IgE, and IgD at Screening. Every 16 weeks during treatment and at the EOT visit, subjects with IgD or IgE disease will be evaluated for IgG, IgA, IgM, IgE, and IgD and subjects with IgG, IgA, or IgM disease will be evaluated for IgG, IgA, and IgM.

- Serum M-protein quantitation by electrophoresis (SPEP)
- Serum immunofixation at Screening and thereafter when a CR is suspected or maintained. If daratumumab interference is suspected based on SPEP and IFE results, additional reflex IFE testing may be performed.
- Serum free light chain assay (monthly for subjects with free light chain (FLC) disease, all others per Time and Events Schedule)
- 24-hour urine M-protein quantitation by electrophoresis (UPEP)
- Urine immunofixation at Screening and thereafter when a CR is suspected or maintained.

Blood and 24-hour urine samples will be collected as specified in the Time and Events Schedule until the development of confirmed disease progression. After subjects have completed 24 months of study treatment, the timing of collection for SPEP and UPEP (and the timing of collection of FLC for subjects with light chain multiple myeloma) will change from every 4 weeks to every 8 weeks. Disease progression based on 1 of the laboratory tests alone must be confirmed by at least 1 repeat investigation performed at least 1 day later. Disease evaluations will continue beyond relapse from CR until disease progression is confirmed. 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) or maintained. However, for subjects with light chain multiple myeloma, serum free light chain assay will be performed routinely. Serum immunofixation (IFE) assay samples will be split into 2 aliquots, with 1 reserved for potential follow-on testing if daratumumab interference with IFE is suspected. As daratumumab is a monoclonal IgG antibody, additional serum samples may be utilized to monitor for potential daratumumab interference with the IFE.

9.2.1.3. Serum Calcium Corrected for Albumin

Blood samples for calculating serum calcium corrected for albumin will be collected and analyzed centrally (as specified in the Time and Events Schedules) until the development of confirmed disease progression. Development of hypercalcemia (corrected serum calcium >11.5 mg/dL or 2.8 mM/L) can indicate disease progression or relapse if it is not attributable to any other cause (see disease response criteria). 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.

Measurement of free ionized calcium is an acceptable alternative to corrected serum calcium for determining hypercalcemia. Free ionized calcium levels greater than the ULN (local laboratory reference ranges) are considered to be hypercalcemic for this study.

9.2.1.4. β_2-microglobulin and Albumin

Blood samples for β_2 microglobulin and albumin are to be collected at Screening, and will be analyzed by the central laboratory.

9.2.1.5. Bone Marrow Examination

Bone marrow aspirate or biopsy will be performed at Screening for clinical characterization (morphology, IHC or immunofluorescence or 2- to 4- color flow cytometry, and cytogenetics), to establish baseline multiple myeloma clonality to monitor for MRD and to perform molecular subtyping to monitor daratumumab activity in high-risk molecular subgroups. Good quality slides are required for morphological examination to determine plasma cell percentage in the bone marrow. Assessment by flow cytometry alone is not sufficient. Bone marrow examination for disease assessment will be performed locally; however, a portion of the bone marrow aspirate must be sent to the central laboratory for analysis of MRD and molecular subtyping. A fresh bone marrow aspirate at screening is required if at all possible, by exception non-decalcified diagnostic tissue (bone marrow aspirate slides or FFPE tissue) may be supplied for MRD assessment instead. Additional bone marrow aspirates will be performed to confirm sCR and CR (only one analysis is required, with either IHC or immunofluorescence or 2- to 4- color flow cytometry included in the analysis) and to monitor for MRD at time points detailed in Table 9. If feasible, a bone marrow aspirate may be collected from subjects at disease progression to evaluate mechanisms of daratumumab resistance.

Bone marrow assessments to be performed locally and centrally are summarized in Table 9.

Table 9: Bone Marrow Testing

	Local Testing	Central Testing
Screening	Disease characterization (morphology, and either immunohistochemistry, immunofluorescence, or flow cytometry). Cytogenetic analysis by conventional karyotype or FISH.	MRD and molecular subtyping: a portion of bone marrow aspirates collected at screening will be sent to a central laboratory. If a fresh bone marrow aspirate will not be performed at screening because the procedure has already been done within 42 days prior to randomization, then the unstained or stained, non decalcified diagnostic tissue (3 5 bone marrow aspirate smears, or 3 5 touch prep slides from biopsy, or 3 5 bone marrow clot slides) should be collected for MRD assessment at baseline.
During Treatment	At time of suspected CR/sCR: Evaluate Plasma cell percentage in the bone marrow to confirm CR Evaluate clonality of plasma cells (by flow cytometry, IHC or IF**) in the bone marrow to confirm sCR *(If sCR criteria are not met, repeat local testing for sCR with subsequent bone marrow testing.)*	A portion of bone marrow aspirates collected at time of suspected CR/sCR, and 12, 18, 24, 30, 36, 48, and 60 (+/ 1) months post C1D1, will be analyzed for MRD*.
Disease Progression	Not applicable.	If feasible, a bone marrow aspirate is requested to be collected from subjects at disease progression and sent to central laboratory to evaluate mechanisms of daratumumab resistance.

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

* If one of these time points occurs within 1 month of suspected CR/sCR, a repeat bone marrow will not be requested. These bone marrow tests will only be required if patient's response is near CR or better by blood and urine evaluations.

** Immunohistochemistry or immunofluorescence (both require kappa/lambda ratio from analysis of ≥100 plasma cells) or 2 to 4 color flow cytometry are acceptable methods to evaluate plasma cell clonality.

9.2.1.6. Minimal Residual Disease Assessment

Minimal Residual Disease (MRD) assessment by next-generation sequencing (NGS) is a relatively new and effective tool in the assessment of patients with multiple myeloma (Ladetto 2014).[20] Several studies have demonstrated that MRD status is correlated with PFS and OS (Martinez-Lopez 2014).[21] In this study, bone marrow samples will be collected when a bone marrow aspirate is performed at Screening and at the subsequent timepoints outlined in Table 9 and Time and Events Schedule.

9.2.1.7. Assessment of Lytic 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 locally by X-ray or low-dose CT during the Screening Phase. Please note that 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, imaging should be performed whenever clinically indicated based on symptoms, to document response or progression. Magnetic resonance imaging (MRI) may be included as an additional assessment at the discretion of the investigator; however, focal lesions identified by MRI alone cannot be counted as lytic disease. 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.

Sometimes subjects present with disease progression manifested by symptoms of pain due to bone changes. Therefore, disease progression may be documented, in these cases, 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 no repeat confirmatory imaging is necessary. In instances where changes may be more subtle, repeat imaging may be performed in 1 to 3 weeks per investigator discretion.

9.2.1.8. 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 scan evaluations are an acceptable alternative if there is no contraindication to the use of intravenous contrast. Positron emission tomography scan or ultrasound tests are not acceptable to document the size of extramedullary plasmacytomas.

Extramedullary plasmacytomas should be assessed for all subjects with a history of plasmacytomas or if clinically indicated at Screening, by clinical examination or radiologic imaging. Assessment of measurable sites of extramedullary disease will be performed and evaluated locally every 4 weeks (by physical examination) for subjects with a history of plasmacytomas or as clinically indicated during treatment for other subjects until development of confirmed CR or confirmed disease progression. If assessment can only be performed radiologically, then evaluation of extramedullary plasmacytomas may be done every 12 weeks. For every subject, the methodology used for evaluation of each disease site should be consistent across all visits. Irradiated or excised lesions will be considered not measurable, and will be monitored only for disease progression.

To qualify for PR, 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 8). 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.

9.2.2. Endpoints

Primary Endpoints

The primary endpoint is PFS, which is defined as the duration from the date of randomization to either progressive disease, or death, whichever occurs first. Disease progression will be determined according to the IMWG criteria (Durie 2006, Rajkumar 2011).[7,32] For subjects who have not progressed and are alive, data will be censored at the last disease evaluation before the start of any

subsequent anti-myeloma therapy. Relapse from CR by positive immunofixation or trace amount of M-protein is not considered to be progressive disease and is not included in the PFS calculation.

As the superiority of DRd over Rd alone with respect to PFS was established at the second interim analysis, the interim PFS analysis will serve as the primary PFS analysis, which otherwise was to occur when approximately 390 PFS events had been observed.

Secondary Endpoints

The secondary efficacy endpoints include:

- Time to disease progression (TTP) is defined as the time from the date of randomization to the date of first documented evidence of PD, as defined in the IMWG criteria. For subjects who have not progressed, data will be censored at the date of the disease evaluation before the start of any subsequent anti-myeloma therapy.
- CR rate, defined as the percentage of subjects achieving CR, as defined:

  Negative immunofixation of serum and urine, and

  Disappearance of any soft tissue plasmacytomas, and

  <5% plasma cells (PCs) in bone marrow

  For those subjects with negative SPEP and suspected daratumumab interference on immunofixation, a reflex assay using anti-idiotype antibody will be utilized to confirm daratumumab interference and rule out false positive immunofixation. Subjects who have confirmed daratumumab interference, but meet all other clinical criteria for CR or sCR, will be considered CR/sCR.
- MRD negativity rate, defined as the proportion of subjects assessed as MRD negative, at any timepoint after the date of randomization.
- Progression-free Survival on Next line of Therapy (PFS2), defined as the time from randomization to progression on the next line of treatment or death, whichever comes first. Disease progression will be based on investigator judgment. For those subjects who are still alive and not yet progressed on the next line of treatment, they will be censored on the last date of follow-up.
- OS, measured from the date of randomization to the date of the subject's death. If the subject is alive or the vital status is unknown, then the subject's data will be censored at the date the subject was last known to be alive.
- sCR rate, defined as the percentage of subjects achieving CR in addition to having a normal FLC ratio and an absence of clonal cells in bone marrow by immunohistochemistry, immunofluorescence, 2-4 color flow cytometry.
- Time to next treatment, defined as the time from randomization to the start of the next-line treatment.
- Overall response rate (ORR), defined as the proportion of subjects who achieve PR or better, according to the IMWG criteria, during or after the study treatment.

- Proportion of subjects who achieve VGPR or better, defined as the proportion of subjects achieving VGPR and CR (including sCR) according to the IMWG criteria during or after the study treatment at the time of data cut-off.
- Time to response, defined as the time between the randomization and the first efficacy evaluation that the subject has met all criteria for CR or PR. For subjects without response (CR/PR), data will be censored either at the date of progressive disease or, in the absence of progressive disease, at the last disease evaluation before the start of subsequent anti-myeloma therapy.
- Duration of response, calculated from the date of initial documentation of a response (PR or better) to the date of first documented evidence of progressive disease, as defined in the IMWG criteria. For subjects who have not progressed, data will be censored at the last disease evaluation before the start of any subsequent anti-myeloma therapy.
- To evaluate clinical efficacy of DRd in high risk molecular subgroups compared to Rd alone.
- To evaluate the impact of DRd compared to Rd on patient-reported perception of global health.

Exploratory Endpoints

- Biomarkers predictive of response or resistance to daratumumab.
- Durability of MRD negativity.

9.3. Pharmacokinetics and Immunogenicity

9.3.1. Evaluations

For subjects in Arm B, pharmacokinetic samples to determine the serum concentration of daratumumab and immunogenicity samples to determine the generation of antibodies to daratumumab will be obtained according to the Time and Events Schedule. In the Follow-up Phase, for all subjects in Arm B (DRd), samples are to be collected for PK and immunogenicity assessments 8 weeks after the last dose of daratumumab, regardless of whether there has been confirmed disease progression. Daratumumab pharmacokinetic and anti-daratumumab antibody sampling at EOT and 8 weeks after the last daratumumab SC dose are required for subjects who switch from daratumumab IV to daratumumab SC treatment. Following Amendment 8, subjects in Arm B who remain on daratumumab IV will no longer have pharmacokinetic and immunogenicity samples collected.

Venous blood samples (5 mL per sample) will be collected to determine serum concentration of daratumumab and the serum will be divided into 3 aliquots (1 aliquot for pharmacokinetic analysis, 1 aliquot for antibodies to daratumumab analysis [when appropriate], and 1 aliquot as a backup). Samples collected for determining serum concentrations of daratumumab in this study may be retained to address questions about drug characteristics that may arise at a later time point.

Samples will also be collected from all subjects receiving daratumumab SC to evaluate the immunogenicity of rHuPH20 according to the Time and Events Schedule. At specified time point, venous blood samples (5 mL per sample) will be collected and the plasma will be divided into 5 aliquots to accommodate immunogenicity screening, confirmatory, and titer assays and neutralizing antibody analysis (when appropriate) as well as volume for backup. The exact dates and times of blood sampling must be recorded. Refer to the Laboratory Manual or equivalent document for sample collection requirements. Collected samples must be stored under the specified and controlled conditions for the temperatures indicated in the laboratory manual.

9.3.2. Analytical Procedures

Serum samples will be analyzed to determine concentrations of daratumumab or generation of antibodies to daratumumab using validated immunoassay methods by or under the supervision of the sponsor's bioanalytical facility.

For the rHuPH20 immunogenicity assessments, plasma samples will be screened for antibodies binding to rHuPH20 and will be assessed in confirmatory and titer assays as necessary. Neutralizing antibody assessments may also be performed to further characterize immune responses that are generated.

9.3.3. Pharmacokinetic Parameters

The pharmacokinetic parameters are defined as:

CL	Total systemic clearance of drug after IV administration
C_{max}	Maximum observed concentration
C_{min}	Minimum observed concentration
V	Volume of distribution

Pharmacokinetic samples to determine serum concentration of daratumumab will be obtained from all subjects. Pharmacokinetic endpoints include:

- Minimum observed concentration (C_{min})
- Maximum observed concentration (C_{max})

If sufficient data are available, then other pharmacokinetic parameters may be calculated, including but not limited to total systemic clearance of drug after IV administration (CL) and volume of distribution (V).

9.3.4. Immunogenicity Assessments (Antibodies to daratumumab and rHuPH20)

Venous blood samples drawn from subjects in the DRd arm will be assessed for the generation of antibodies to daratumumab (immunogenicity), according to the Time and Events Schedule. Plasma samples will be collected from subjects treated with daratumumab SC according to the Time and Events Schedule for the assessment of the generation of antibodies to rHuPH20. In the Follow-up Phase, for subjects in Arm B (DRd), samples are to be collected for immunogenicity assessments 8 weeks after the last dose of daratumumab, regardless of whether there has been confirmed disease

progression. Following Amendment 8, subjects in Arm B who remain on daratumumab IV will no longer have immunogenicity samples collected.

All samples collected for immunogenicity analysis of daratumumab will also be evaluated for daratumumab serum concentration to ensure appropriate interpretation of immunogenicity data. At each time point, immunogenicity and serum daratumumab concentration analyses will be performed on aliquots from the same blood draw and no additional sampling is required. Procedures for sample collection, preparation, identification, storage, and shipment will be provided in the Laboratory Manual or equivalent document.

Serum samples will be screened for antibodies binding to daratumumab and serum titer will also be determined from confirmed positive samples using validated assay methods by or under the supervision of the sponsor. Other immunogenicity analyses (eg, assessment of neutralizing capabilities) may be performed to further characterize the immune responses that are generated.

A blood sample should be drawn, if possible, for determination of antibodies to daratumumab (IV or SC treatment) any time an infusion reaction is observed or reported during the study. Daratumumab serum concentration will also be determined from the same infusion reaction sample for the purpose of interpreting immunogenicity data. In the subjects receiving daratumumab SC, a plasma sample should also be obtained for determination of antibodies to rHuPH20. These samples will be stored and evaluated if deemed necessary. If the infusion reaction results in treatment discontinuation, then subjects should undergo all scheduled safety and efficacy evaluations. Samples collected for the analysis of daratumumab immunogenicity/serum concentration or rHuPH20 immunogenicity may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period or for the evaluation of relevant biomarkers by the sponsor or sponsor's designee.

9.4. Pharmacokinetic/Pharmacodynamic Evaluations

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

9.5. Biomarkers

Biomarker assessments will focus on 2 main objectives including evaluating the ability of daratumumab + Rd to reduce MRD in subjects who achieve a complete response (compared to Rd alone) and to determine the clinical benefit (ORR, PFS, and OS) of daratumumab + Rd in high-risk molecular subtypes (del17p, t(4;14), t(14;16), specific gene signatures, specific mutations). Bone marrow aspirates will be collected at screening and following treatment as outlined in the Time and Events Schedule. Baseline bone marrow aspirate samples will be subjected to DNA and RNA sequencing in order to classify subjects into high-risk molecular subgroups and to establish the myeloma clone for MRD monitoring. A fresh bone marrow aspirate at Screening is required if at all possible, by exception non-decalcified diagnostic tissue (please see Table 9 Bone Marrow Testing for further information) may be supplied for MRD assessment instead. For subjects who

achieve a CR or sCR, bone marrow aspirates will be utilized for assessment of MRD by next-generation sequencing (NGS) of immunoglobulin heavy and light chains (Vij 2013).[40] If this methodology is unavailable, or determined to be scientifically inferior, then alternative methods for MRD assessment may be utilized. In cases where daratumumab is suspected of interfering with serum IFE and preventing clinical CR response calls, subjects with VGPR will also be evaluated for MRD by NGS.

In addition to planned bone marrow aspirate assessments, a whole blood sample will be collected from subjects as outlined in the Time and Events Schedule for processing to plasma and PBMCs. These samples may be used to evaluate specific subsets of immune cells such as cytotoxic T cells, regulatory T cells, MDSCs, and activated NK cells. Cells may also be used for additional phenotypic and functional profiling. Proteomic analysis may also be used to evaluate changes in cytokines, complement proteins, soluble CD38, soluble CD59, IFNγ, granzyme, perforin, and other proteins associated with ADCC/CDC/ADCP to evaluate potential biomarkers of response and resistance.

Potential mechanisms of tumor resistance, such as changes in antigen (CD38) expression or increased expression in complement inhibitory proteins (CD46, CD55, and CD59) in multiple myeloma cells, may be monitored in subjects if a bone marrow aspirate sample is deemed feasible for collection at progressive disease. In addition, changes in expression patterns of genes associated with ADCC, CDC, or other mechanisms of action of daratumumab may be evaluated.

Biomarker analyses are dependent upon the availability of appropriate biomarker assays and may be deferred or not performed if during or at the end of the study it becomes clear that the analysis will have no scientific value, or if there are not enough samples or not enough 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. Samples for biomarker evaluations will be collected as specified in the Time and Events Schedule and may be used for additional biomarker testing that may arise at a later time point (see Section 16.2.5).

9.6. Medical Resource Utilization

Medical resource utilization (MRU) data, including primary non-protocol driven hospitalizations, outpatient visits, and emergency room visits, should be collected in the eCRF (Hospitalization/Outpatient Visits CRF) by the Investigator and study-site personnel for all subjects throughout the study. Please see CRF completion guidelines.

9.7. Patient Reported Outcomes

It is anticipated that the addition of daratumumab will provide benefits in terms of symptom reduction, improved functioning, and improved utilities. To measure functional status, well-being, and symptoms, the EORTC QLQ-C30 and the EQ-5D-5L instruments will be used. Both questionnaires will be completed at the timepoints outlined in the Time and Events Schedule. All visit-specific PRO assessments should be conducted before any tests, procedures, or other

consultations for that visit to prevent influencing subject perceptions. All PRO measures will be completed using an electronic device (ePRO). For more details refer to the ePRO user manual.

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). The recall period is 1 week (the past week). The EORTC QLQ-C30 has been widely used among cancer patients. Scores are transformed to a 0 to 100 scale. Administration time is approximately 11 minutes. Reliability, validity, and clinically meaningful change have been demonstrated in multiple myeloma patients (Wisloff 1996, Wisloff 1997).[41,42] 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. For purposes of this study, the EQ-5D-5L will be used to generate utility scores for use in cost effective 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" with anchors ranging from 0 (worst imaginable health state) to 100 (best imaginable health state) (Herdman 2011).[13] The scores for the 5 separate questions are categorical and cannot be analyzed as cardinal numbers. However, the scores for the 5 dimensions are used to compute a single utility score ranging from zero (0.0) to 1 (1.0) representing the general health status of the individual.

9.8. Safety Evaluations

Safety will be measured by adverse events, laboratory test results, ECGs, vital sign measurements, physical examination findings, and assessment of ECOG performance status score. Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the eCRF. Any clinically significant abnormalities persisting at the final CSR analysis (defined in Section 9.1.8)/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. As a biologic agent, 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 (with the exception of progression of multiple myeloma) 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.

For subjects who continue to receive study treatment after the final CSR analysis, only serious adverse events will be collected until end of study (defined in Section 17.9.1), as described in Attachment 11 and Attachment 12.

Clinical Laboratory Tests

Blood samples for serum chemistry and hematology will be collected. The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the eCRF. The laboratory reports must be filed with the source documents.

The tests below will be performed by the local laboratory unless otherwise noted.

- Hematology Panel

  -hemoglobin
  -white blood cell (WBC) count with absolute neutrophils and lymphocytes
  -platelet count

- Serum Chemistry Panel

  -blood urea nitrogen (BUN) or urea
  -creatinine
  -glucose
  -aspartate aminotransferase (AST)
  -alanine aminotransferase (ALT)
  -creatinine clearance (calculated or measured)
  -alkaline phosphatase
  -lactic acid dehydrogenase (LDH)
  -uric acid
  -total; direct bilirubin (not required except in case of congenital bilirubinemia, such as Gilbert disease)
  -total protein
  -sodium*
  -potassium*

  *Sodium and potassium assessment was added in Protocol Amendment 2, however collection of sodium and potassium results will be done retrospectively from the date of subject consent for the duration of the study, if collected as part of routine care.

Serum or Urine Pregnancy Testing

For women of childbearing potential only: lenalidomide is a thalidomide analogue and is contraindicated for use during pregnancy. Birth defects have been observed in preclinical studies of lenalidomide similar to thalidomide in humans. Therefore, strict monitoring for pregnancy must be conducted during Screening and throughout the Treatment Phase, as specified in the Time and Events Schedule. Where lenalidomide is supplied locally, subjects must adhere to the local lenalidomide REMS program. Where lenalidomide is supplied centrally and no local lenalidomide REMS program exists, then subjects must adhere to the lenalidomide Global Pregnancy Prevention Plan in Attachment 5.

If pregnancy or a positive pregnancy test does occur, then study treatment should be discontinued immediately, and the subject should be referred to an obstetrician experienced in reproductive toxicity for further evaluation and counseling.

Calcium and Albumin Adjusted Calcium:

These parameters will be part of the efficacy evaluations as specified in Section 9.2.1.3, and will be analyzed by the central laboratory. Measurement of calcium and albumin should follow the schedule for disease assessments. Measurement of free ionized calcium is an acceptable alternative to corrected serum calcium for determining hypercalcemia.

Daratumumab Interference with Indirect Antiglobulin Test (IAT) results:

Daratumumab interferes with the Indirect Antiglobulin Test (IAT), which is a routine pre-transfusion test performed to identify a patient'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) 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 IAT interference by treating reagent RBCs with dithiothreitol (DTT) (Chapuy 2015[4], Chapuy 2016).[5]

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

- Providing ABO/RhD compatible, phenotypically or genotypically matched units
- Providing ABO/RhD compatible, K-negative units after ruling out or identifying alloantibodies using dithiothreitol (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 IB.

Pulmonary Function Test

Subjects with known or suspected COPD must have a FEV1 test during screening. Refer to Section 6.1.4.2 for details on subjects with higher risk of respiratory complications.

Electrocardiogram (ECG)

ECGs will be performed as specified in the Time and Events Schedule. 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 time point as ECG recording, then the procedures should be performed in the following order: ECG(s), vital signs, blood draw.

Vital Signs

Vital signs (pulse/heart rate, temperature, and blood pressure) will be performed as specified in the Time and Events Schedule. It is recommended that blood pressure (sitting) and pulse measurements be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones). Only vital signs associated with an adverse event will be entered in the eCRF; all measurements will be recorded in the source documents.

Physical Examination and ECOG Performance Status

A complete physical examination (including neurological examination) should be performed during the Screening Phase. Thereafter, only a symptom and disease directed physical examination is required. Height will be measured at screening only; weight will be measured regularly as specified in the Time and Events Schedule. Abnormalities will be recorded in the appropriate sections of the eCRF. ECOG Performance Status (Attachment 2) will be used to evaluate the impact of the disease status on the activities of daily living. When scheduled, ECOG assessments along with PRO questionnaires should be obtained prior to any other study procedures planned for the same day.

HBV Serology and DNA Testing

Closely monitor subjects with a known history of hepatitis B infection or positive hepatitis B serologies (HBsAg, Anti-HBc and/or Anti-HBs with exception of serologic findings suggestive of HBV vaccination [Anti-HBs positivity as the only serologic marker] and a known history of prior HBV vaccination) who are enrolled in Arm B for clinical signs of active HBV infection and obtain serial testing for HBV DNA every 3 months during treatment and for 6 months following the last dose of daratumumab. If the hepatitis B serologic status of a subject in the DRd arm is unknown, HBsAg, Anti-HBs, and Anti-HBc testing is recommended if the subject is still receiving daratumumab (or is within 6 months after the last dose).

After the final CSR analysis until end of study (defined in Section 17.9.1), subjects still receiving will have HBV DNA testing performed as detailed in Attachment 11 and Attachment 12.

9.9. Sample Collection and Handling

If blood samples are collected via an indwelling cannula, an appropriate amount (1 mL) of serosanguineous fluid slightly greater than the dead space volume of the lock will be removed from the cannula and discarded before each blood sample is taken. After blood sample collection, the cannula will be flushed with 0.9% sodium chloride, United States Pharmacopeia (or equivalent)/sodium heparin of 10 U/mL and charged with a volume equal to the dead space volume of the lock. If a mandarin (obturator) is used, blood loss due to discard is not expected. Refer to the Time and Events Schedule for the timing and frequency of all sample collections.

For samples collected from the central laboratory, sample dates and times must be recorded on the laboratory requisition form. Further instructions for the collection, handling, storage, and shipment

of samples are found in the laboratory manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual.

Subjects still receiving study treatment after the final CSR analysis will have safety and efficacy assessments performed as per local institution practice (see Attachments 11 and 12).

10. SUBJECT COMPLETION/WITHDRAWAL

10.1. Completion

A subject will be considered to have completed the study if he or she has finished all protocol-specified procedures, has not been lost to follow up, or has not withdrawn consent for study participation before the final OS analysis.

10.2. Discontinuation of Study Treatment

If a subject's study treatment must be discontinued before the end of the treatment regimen, this will not result in automatic withdrawal of the subject from the study. After treatment discontinuation, the subject will move into the Follow-up Phase. The End-of-Treatment Visit and Follow-up visit assessments should continue as specified in the Time and Events Schedule. If study treatment is discontinued for a reason other than disease progression, then disease evaluations will continue to be performed as specified in the Time and Events Schedule.

Subjects who need to discontinue treatment with any one component of study treatment (lenalidomide, dexamethasone, or daratumumab) may continue to receive treatment with the other components of study treatment, as assigned.

A subject's study treatment will be discontinued if:

- The investigator believes that for safety reasons (eg, adverse event) it is in the best interest of the subject to discontinue study treatment
- The subject becomes pregnant or a positive pregnancy test does occur
- The subject (or the subject’s legally acceptable representative) withdraws consent for administration of study treatment
- The subject initiates treatment with a prohibited medication
- The subject received concurrent (non-protocol) treatment for multiple myeloma
- The subject experiences unacceptable toxicity, including infusion-related reactions described in Section 6.1.5
- The subject’s dose of daratumumab is held for more than 4 weeks in Cycles 1- 6 or for more than 6 weeks in Cycle 7 and beyond (unless Sponsor approves continuation)

- The subject experiences disease progression (please see below). Relapse from CR is not considered as disease progression

A subject who experiences a second primary malignancy that can be treated by surgery may continue to receive the assigned study treatment and the subject should continue to be followed for subsequent progression of multiple myeloma. Subjects who require radiation therapy for treatment of second primary malignancy must have study treatment discontinued unless, upon consultation with the Sponsor and review of data, continuation is agreed upon. Subjects who require systemic treatment of a new malignancy must end study treatment but should continue to be followed for PFS2 and OS.

Before subjects discontinue study treatment due to disease progression, sites will document disease progression (for example by completing a disease progression form or by contacting the IWRS) as soon as possible and within 48 hours. The medical monitor will confirm that treatment should be discontinued. After confirmation from the sponsor, study treatment may be discontinued and the subject entered into Follow-up.

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

10.3. 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 for study participation
- Death
- The study investigator or Sponsor, for any reason, stops the study or stops the subject's participation in the study

Before a subject is considered 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 from the study, the reason for withdrawal is to be documented in the eCRF and in the source document. Study treatment assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw will not be replaced. If a subject withdraws from the study, assessments outlined in the End-of-Treatment Visit should be obtained.

Withdrawal From the Use of Samples in Future Research

The subject may withdraw consent for use of samples for future research (refer to Section 16.2.5). 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.

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

The primary analysis population will be the intent-to-treat (ITT) population, which will include all randomized subjects. Safety will be evaluated for the population of all treated subjects. The pharmacokinetic analyses will be performed on the pharmacokinetic evaluable population. Continuous variables will be summarized using descriptive statistics such as mean, standard deviation, and range. Categorical variables will be summarized using frequency tables. For time-to-event variables, the Kaplan-Meier method will be used for descriptive summaries.

11.2. Sample Size Determination

The sample size calculation is performed on the basis of the following assumption. Based on the published data, the median PFS for Rd arm is assumed to be approximately 24 months. Assuming that DRd can reduce the risk of the disease progression or death by 25%, ie, assuming the hazard ratio (DRd vs Rd) of 0.75, a total of 390 PFS events is needed to achieve a power of 80% to detect this hazard ratio with a log-rank test (two-sided alpha is 0.05). With a 21-month accrual period and an additional 24-month follow-up, the total sample size needed for the study is approximately 730 (365/arm) subjects. The sample size calculation has taken into consideration an annual dropout rate of 5%.

Long-term survival follow-up was originally planned to continue until 330 deaths had been observed or 7 years after the last subject was randomized. Therefore, this study would achieve approximately 80% power to detect a 27% reduction in the risk of death (hazard ratio 0.73) with a log-rank test (two-sided alpha 0.05). However, after reaching statistical significance at the second interim OS, the long-term survival follow-up will be extended to approximately 390 deaths when the median survival for the DRd group has likely been reached.

11.3. Efficacy Analyses

Response to study treatment and progressive disease will be evaluated by a validated computer algorithm.

Primary Endpoint

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 arms. 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.

Secondary Endpoints

Other time-to-event efficacy endpoints, including TTP, PFS2, OS, and time to subsequent anti myeloma treatment, will be analyzed using the same method as for PFS. For overall survival, the final analysis will occur after approximately 390 deaths have been observed. Earlier analyses, in which overall survival is analyzed, will be considered as interim analyses. Even though the significance of PFS has already been established at the second interim analysis, testing of OS will continue as planned until a definitive conclusion on OS is reached. The details about testing of OS over time are specified in Section 11.10. The analysis of OS may be confounded by subjects from Arm A receiving daratumumab after disease progression. Exploratory analysis may be performed to adjust for the effect daratumumab exposure may have on OS for the subjects who were randomized to Arm A (Rd).

Comparison between the 2 treatment arms of overall response rates, VGPR or better rate, CR or better rate, 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, and will be provided as the measure of treatment effect. Duration of response will be provided descriptively without formal statistical comparison.

Strong control of familywise Type I error rate will be controlled at a two-sided significance level of 0.05 for the following major secondary endpoints: TTP, CR rate, MRD negativity rate, PFS2 and OS. A sequential hierarchical testing procedure will be used. Details about this hierarchical procedure will be specified in the statistical analysis plan for this study prior to any efficacy analysis.

11.4. Pharmacokinetic Analyses

Pharmacokinetic analyses will be performed on the pharmacokinetic-evaluable population, defined as subjects who have received one dose of daratumumab and at least one post-dose sample. All serum concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration data presentation. Concentrations below the lowest quantifiable concentration will be treated as zero in the summary statistics. All subjects and samples excluded from the analysis will be clearly documented in the study report.

Descriptive statistics will be used to summarize daratumumab serum concentrations at each sampling time point and pharmacokinetic parameters of daratumumab such as Cmin and Cmax. If sufficient data are available, then other pharmacokinetic parameters may be calculated, including but not limited to CL and V.

If sufficient data are available, then population pharmacokinetic analysis of serum concentration time data of daratumumab, will be performed using nonlinear mixed-effects modeling. The potential population PK analysis may also include PK data from other studies. If the population pharmacokinetic analysis is conducted, then details will be given in a population pharmacokinetic analysis plan and the results of the analysis will be presented in a separate report.

11.5. Immunogenicity Analyses

The incidence of antibodies to daratumumab will be summarized for all subjects who receive a dose of daratumumab and have appropriate samples for detection of antibodies to daratumumab. The incidence of antibodies to rHuPH20 will be summarized for all subjects who receive a dose of daratumumab SC and have appropriate samples for detection of antibodies.

11.6. Pharmacokinetic/Pharmacodynamic Analyses

If sufficient data are available, then population pharmacokinetic analysis serum concentrations of serum concentration-time data of daratumumab will be performed using nonlinear mixed-effects modeling. If the population pharmacokinetic analysis is conducted, then details will be given in a population pharmacokinetic analysis plan and results of the analysis will be presented in a separate report.

11.7. Biomarker Analyses

Biomarker studies are designed to identify markers predictive of response (or resistance) to daratumumab. Analyses will be performed and 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 or time-to-event endpoints will identify responsive (or resistant) subgroups in addition to genes and pathways attenuated following treatment with daratumumab. In order to remove any confounding influence of prognostic factors, any predictive biomarker identified in this study could be verified in a prospective clinical study with a control treatment arm.

Any biomarker measures will be listed, tabulated, and where appropriate, plotted. Subjects will be grouped by prescribed dose. Complete responders will be utilized to investigate the prognostic effect of MRD on PFS. MRD analysis will include evaluation of data from other studies to determine if decreased MRD is seen with daratumumab + Rd based chemotherapy regimen compared with the Rd based chemotherapy alone.

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.

In addition, due to the small sample sizes of high-risk subgroups within the multiple myeloma subject population, a meta-analyses may be performed across daratumumab Phase 3 studies to evaluate clinical efficacy of daratumumab with standard of care agents in pre-specified subgroups of multiple myeloma subjects. The meta-analysis protocol will pre-specify the objective of the meta-analysis, the criteria for inclusion and exclusion of studies, the hypotheses and endpoints, and statistical methods including a method for investigation of heterogeneity. This meta-analytic approach, supported by high-quality data from the individual studies, should be able to provide definitive evidence on the effectiveness of daratumumab in the subpopulation of multiple myeloma subjects with high-risk molecular abnormalities. In a similar fashion, a meta-analysis examining

MRD negativity in daratumumab treated subjects in frontline, newly diagnosed multiple myeloma (MMY3006, MMY3007, MMY3008) may also be performed.

11.8. Patient Reported Outcomes

EORTC-QLQ-C30 scores will be evaluated for all domains except "financial problems" among subjects with at least one post-baseline assessment and 50% completion of the relevant items for a domain. Descriptive analyses followed by mixed model repeated measures will be used to analyze each domain score. No adjustment for multiple comparisons will be made.

EQ-5D-5L scores will be summarized at each time point.

11.9. Safety Analyses

Adverse Events

The verbatim terms used in the eCRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The severity assessment for an adverse event or serious adverse event should be completed using the NCI CTCAE Version 4. All reported adverse events with onset during the treatment phase (ie, treatment-emergent adverse events, and adverse events that have worsened since baseline) 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 arm.

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 time point. Changes from baseline results will be presented in pre- versus post treatment cross-tabulations (with classes for below, within, and above normal ranges). Frequency tabulations of the abnormalities will be made. 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 toxicity grade experienced by the subject during the study will be provided as shift tables. Worst toxicity grade during treatment will be presented, according to NCI CTCAE (version 4). Clinically relevant changes (i.e. causing a treatment intervention and/or need for concomitant therapy) will be also recorded on the adverse event eCRF. All other lab abnormalities need not be recorded as adverse events.

Electrocardiogram (ECG)

Electrocardiogram data will be summarized and listed.

Vital Signs

Descriptive statistics of baseline temperature, pulse/heart rate, and blood pressure (systolic and diastolic) values will be summarized.

11.10. Interim Analysis

Two interim analyses are planned. The first interim analysis, with a purpose to evaluate safety, will be performed after a total of approximately 100 subjects have been treated for at least 8 weeks or discontinued the study treatment. The second interim analysis will be performed when 234 PFS events, which is 60% of the total planned events, have been accumulated. The purpose of this interim analysis is to evaluate cumulative interim safety and efficacy data. The significance level at this interim analysis to establish the superiority of DRd over Rd with regard to PFS will be determined 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. If the experimental arm (DRd) is numerically worse than the control arm in terms of PFS (observed hazard ratio >1 favoring the control arm), then the study may be terminated for futility, with a conditional power of less than 20% under the alternative hypothesis given the observed interim data.

As the superiority of DRd over Rd alone with respect to PFS was established at the second interim analysis, the interim PFS analysis will serve as the primary PFS analysis, which otherwise was to occur when approximately 390 PFS events had been observed. The first interim OS analysis was performed at the interim PFS analysis. The second interim OS analysis will now occur when approximately 260 deaths have occurred which will be about the same time the primary PFS analysis would have taken place. All applicable available data prior to that time will be included in each of the respective analyses.

11.11. Data Monitoring Committee

An IDMC, consisting of 2 clinicians and 1 statistician who are independent experts not otherwise participating in the study, will be established to review efficacy and safety results at the planned interim analyses. After the interim review, they will make recommendations regarding the continuation of the study. In addition, the IDMC may also review cumulative safety data every 6 months besides the 2 interim analyses. The IDMC will no longer review study data after the interim PFS analysis has been completed. The details will be provided in a separate IDMC charter.

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.

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 Conference on Harmonisation [ICH])

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

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 including any second primary malignancy 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.

Suspected Unexpected Serious Adverse Reactions (SUSARs)

If a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the study treatment 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). Refer to Section 12.3.3 for SUSAR Reporting Requirements.

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 daratumumab, the expectedness of an adverse event will be determined by whether or not it is listed within the Reference Safety Information included in the Investigator's Brochure.

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.

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 this document will be graded according to investigator clinical judgment by using the standard grading outlined in the NCI-CTCAE Version 4.03.

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 and/or safety evaluation include, but are not limited to:

- Overdose of a sponsor study drug. No MTD has been reached for daratumumab. However, if the dose exceeds the maximum tested dose of 24 mg/kg, then it will be considered as overdose in this study.
- Suspected abuse/misuse of a sponsor study drug
- Inadvertent or accidental exposure to a sponsor study drug
- Medication error involving a sponsor product (with or without subject exposure to the sponsor study drug, eg, name confusion)

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

12.3. Procedures

12.3.1. All Adverse Events

All adverse events and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until 30 days after the last dose of study treatment until the start of the long-term survival follow-up, unless the subject withdraws consent for study participation, or starts subsequent anti-myeloma therapy. For subjects still receiving study treatment after the final CSR analysis and until the end of study, serious adverse events will continue to be reported as detailed in Attachments 11 and 12. 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 daratumumab need to be reported. Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study treatment, must be reported using the Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Expected progression of disease should not be considered an AE (or SAE). However, if determined by the investigator to be more likely related to the study treatment than the underlying disease, the clinical signs or symptoms of progression and the possibility that the study treatment is enhancing

disease progression, should be reported per the usual reporting requirements (see Section 12.1). 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 10. Anticipated events will be no longer be reported after the final CSR analysis.

All adverse events, regardless of seriousness, severity, or presumed relationship to study treatment, must be recorded using medical terminology in the source document and the eCRF. 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 eCRF 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 investigational institute where required). The investigator (or sponsor where required) must report these events 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 and for at least 6 months (Arm B) after treatment ends 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 testing as described in Section 9.8 for subjects in Arm B)

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 administration of daratumumab, then the hospitalization should not 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 eCRF). 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.

For subjects still receiving study treatment during the long-term survival follow-up until end of study, serious adverse events will continue to be reported as detailed in Attachment 11 and Attachment 12.

12.3.3. Suspected Unexpected Serious Adverse Reactions

The sponsor assumes responsibility for appropriate reporting of all Suspected Unexpected Serious Adverse Reactions (SUSAR) [serious adverse events that are unlisted (unexpected) and associated with the use of the study drug] to the regulatory authorities in accordance with GCP. The sponsor will also report to the investigator (and the head of the investigational institute where required) all serious adverse events that are unlisted (unexpected) and associated with the use of the study drug. The investigator (or sponsor where required) must report these events to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

12.3.4. Pregnancy

All initial reports of pregnancy 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, stillbirth, and congenital anomaly) are considered serious adverse events and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant or experiences a positive pregnancy test during the study must discontinue further study treatment. The subject should be referred to a physician experienced in teratology for evaluation and advice. Investigators should follow the local label for guidance on subject education and ensure that all subjects adhere to the local lenalidomide REMS program (when lenalidomide is supplied locally), or the lenalidomide Global Pregnancy Prevention Plan provided in Attachment 5 (when lenalidomide is supplied centrally and no local lenalidomide REMS program exists). Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

Pregnancies or positive pregnancy tests in partners of male subjects included in the study will be reported by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form.

During the long-term survival follow-up and until the end of study, pregnancy reporting will continue as described in Attachment 11 and Attachment 12.

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 on 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 on the Contact Information page(s), which will be provided as a separate document.

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drug

Daratumumab IV

The daratumumab supplied for IV infusion in this study is a colorless to yellow liquid and sterile concentrate of 20 mg/mL in a vial. It will be manufactured and provided under the responsibility of the sponsor. Refer to the Investigator's Brochure for a list of excipients.

Daratumumab SC

The daratumumab supplied for SC injection in this study is a colorless to yellow liquid and sterile concentrate of 120 mg/ml daratumumab + 2000 U/ml rHuPH20 as a liquid in vial. It will be manufactured and provided under the responsibility of the sponsor. Refer to the Investigator's Brochure for a list of excipients.

14.2. Packaging

Daratumumab IV

Daratumumab IV is supplied in glass vials containing daratumumab at a concentration of 20 mg/mL.

Daratumumab SC

Daratumumab SC is supplied in glass vials containing daratumumab at a concentration of 120 mg/mL and rHuPH20 at a concentration of 2000U/ml (~20µg/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

Daratumumab IV

All study drug vials must be stored in the original carton in a refrigerator ranging from 2°C to 8°C and must not be utilized after the expiry date printed on the label. The product must be protected from light and must not be frozen. Daratumumab does not contain preservatives; therefore any unused portion remaining in the vial must be discarded.

Daratumumab will be diluted in a sterile, pyrogen-free physiological saline solution (0.9% NaCl) prior to IV administration. Refer to the IPPI for IV dosing and SIPPM for details regarding dose preparation, storage, and handling of diluted solutions.

Daratumumab SC

All study drug vials must be stored in the original carton in a refrigerator ranging from 2°C to 8°C and must not be utilized after the expiry date printed on the label. The product must be protected from light and must not be frozen. Daratumumab does not contain preservatives; therefore any unused portion remaining in the vial must be discarded. Refer to the IPPI and SIPPM for details regarding dose preparation, storage, and handling of diluted solutions.

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, or used returned study drug for destruction, 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 supplied only to

subjects participating in the study. 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 Brochure for daratumumab
- Site Investigational Product Procedures Manual
- Laboratory manual
- PRO questionnaires and user guidelines
- eCRF completion guidelines
- Sample ICF
- Subject diaries
- Subject wallet card indicating blood type (and IAT testing for Arm B; see Section 9.8)
- Other manuals and guidance documents as needed

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

The primary safety profile of daratumumab is consistent with infusion-related reactions; see Section 6.1.4 for prevention details. Based on the mode of action of daratumumab, a potential risk could be infection; therefore the protocol requires the review of hematological laboratory results prior to daratumumab administration. CD38 is distributed in erythrocytes and platelets. A significant reduction of platelets was reported in an animal study. In a human clinical study (Study GEN501), thrombocytopenia was also reported. However, safety laboratory monitoring did not show a clinically meaningful reduction of platelets. Anemia was also reported in Study GEN501. Free hemoglobin was mildly elevated, but other parameters did not support hemolysis. No bleeding events were observed. Routine safety laboratory measurement of RBCs and platelets will be closely monitored in this study.

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 told 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 for the study is estimated at approximately 65 mL during screening and 360 mL during the first year (approximately 20-35 mL per cycle for routine testing, plus additional PK and biomarker samples). In the Follow-up Phase, subjects prior to PD will continue to have

approximately 20 mL blood drawn per month for serum disease evaluations. These blood volumes are not burdensome and fall 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), 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 Brochure 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).

Furthermore, where required, progress reports/written summaries of the study status will be submitted to the IRB/IEC annually, or more frequently if requested.

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, including permission to obtain information about his or her survival status, and agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, if needed, and subsequent disease-related treatments, or to obtain information about his or her survival status.

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/PK/immunogenicity 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, to understand multiple myeloma, to understand differential drug responders, and to develop tests/assays related to daratumumab 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 10.3, Withdrawal From the Study (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, 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 IRB (and IEC 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 (see Contact Information page(s) provided separately). 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 eCRF 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 age at initial informed consent. In cases where the subject is not randomized into the study, the date seen and age at initial informed consent 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 documentation must be available for the following to confirm data collected in the eCRF: 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 treatment administration information; and date of study completion and reason for early discontinuation of study treatment or withdrawal from the study, if applicable.

In addition, the author of an entry in the source documents should be identifiable.

At a minimum, the type and level of detail of source data available for a subject should be consistent with that commonly recorded at the study site as a basis for standard medical care. Specific details required as source data for the study will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

Subject- and investigator-completed scales and assessments designated by the sponsor (EORTC QLQ-C30 and EQ-5D-5L) will be recorded directly into an electronic device or other tool and will be considered source data.

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.

17.5. Case Report Form Completion

Case report forms are provided for each subject in electronic format.

Electronic Data Capture (eDC) will be used for this study. The study data will be transcribed by study-site personnel from the source documents onto an eCRF, and transmitted in a secure manner to the sponsor within the timeframe agreed upon between the sponsor and the study site. The electronic file will be considered to be the eCRF.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the subject's source documentation. Data must be entered into eCRFs in English. Study site personnel must complete the eCRF as soon as possible after a subject visit, and the forms should be available for review at the next scheduled monitoring visit.

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

All eCRF 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 adjust the eCRF (if applicable) and complete the query.

If corrections to an eCRF are needed after the initial entry into the eCRF, this can be done in 3 different ways:

- 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).
- Study site manager can generate a query for resolution by the study-site personnel.
- Clinical data manager can generate a query for resolution by the study-site personnel.

The sponsor will communicate the clinical cut-off date for the final CSR analysis to sites. At the time of this clinical cut-off, the study will transition to long-term survival follow-up (see Section 9.1.8). Attachment 11 describes data collection and procedures for subjects who continue to receive study treatment during the long-term survival follow up.

The sponsor will notify sites of the clinical cut-off date for the final OS analysis, which will occur when approximately 390 deaths have occurred. No additional eCRF data collection will occur after the final OS analysis. Attachment 12 describes procedures for subjects who continue to receive study treatment after the final OS analysis until the end of study (defined in Section 17.9.1).

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 database, and direct transmission of PRO data to the ePRO vendor database and then to the sponsor’s database. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided and reviewed with study-site personnel before the start of the study. The sponsor will review eCRFs 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 eCRFs 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 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 eCRFs with the hospital or clinic records (source documents). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF 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 documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the eCRF are consistent with the original source data. Findings from this review of eCRFs and source documents 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 documentation 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.

17.9. Study Completion/Termination

17.9.1. Final OS Analysis/End of Study

The sponsor will notify sites of the final OS analysis cut-off, which will occur when approximately 390 deaths have occurred. After the cut-off for the final OS analysis, no additional eCRF data will be collected, and the clinical database will be closed. Data collected in the eCRF will be included in the final OS analysis and reported in a separate addendum to clinical study report.

The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject at that study site, in the time frame specified in the Clinical Trial Agreement.

The sponsor will ensure that subjects who are benefitting from treatment with daratumumab can continue to receive study treatment after the final OS analysis until the end of study is complete. The end of study is defined as when one of the following occurs, whichever is first:

- when all subjects who are still receiving study treatment after the final OS analysis have access through another source such as a commercial availability, continued access through a dedicated long-term extension study, or a patient access program,
- when all subjects have discontinued daratumumab treatment,
- by 31 January 2026.

Attachment 12 describes data collection and reporting procedures for subjects who continue to receive study treatment after the final OS analysis.

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 and comparison with the eCRFs. 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 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 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 eCRF data from all study sites that participated in the study, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's database. 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 for the study. 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 18 months after study end date, 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 ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

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

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Attachment 1: Modified IMWG Diagnostic Criteria for Multiple Myeloma

Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma[a] AND any one or more of the following myeloma defining events:

Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:

- Hypercalcemia: serum calcium >0.25 mM/L (>1 mg/dL) higher than ULN or >2.75 mM/L (>11 mg/dL)
- Renal insufficiency: creatinine clearance[b] <40mL/min or serum creatinine >177 µM/L (>2 mg/dL)
- Anemia: hemoglobin >2 g/dL below the lower limit of normal or hemoglobin <10 g/dL[c]
- Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT[d]

Note: Subjects only meeting SLiM CRAB are not eligible.

Footnotes:

a) Clonality should be established by showing κ/λ light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and the core biopsy, the highest value should be used.

b) Measured or estimated by validated equations.

c) Hemoglobin measurement performed as part of standard of care within 42 days before randomization is acceptable for screening for CRAB criteria; but must be performed within 21 days before randomization for other eligibility requirements.

d) If bone marrow has less than 10% clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement.

Reference: Rajkumar 2014 [30]

Attachment 2: 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

Reference: Oken 1982[24]

Attachment 3: Calculated and Measured Creatinine Clearance

Cockcroft-Gault formula:

To calculate the subject's creatinine clearance (CrCl), use the following Cockcroft-Gault formula:

$$CrCl = \frac{(140 - \text{age [in years]}) \times \text{weight (kg)}}{(72 \times \text{serum creatinine [mg/dL]})} \quad (\times 0.85 \text{ for females})$$

If the serum creatinine is obtained using the International System of Units (SI) (ie, micromol/L), use the following formula to convert SI units to conventional (mg/dL) units (Manual of Laboratory & Diagnostic Tests, 2004):

- serum creatinine (micromol/L) divided by 88.4 = serum creatinine (mg/dL)

Formula to measure creatinine clearance:

$$CrCl = \frac{U_{Cr} \times U_{vol}}{P_{Cr} \times T_{min}}$$

$$\text{Corrected CrCl} = CrCl \times \frac{1.73}{BSA}$$

Notes: U_{Cr}, Urine creatinine concentration; U_{vol}, Urine volume from 24hrs collection; P_{Cr}, plasma creatinine concentration; T_{min}, collection time in minutes (24h x 60min); BSA, body surface area.

If the body mass index of a subject is >30kg/m^2, lenalidomide dosing should be based on the CrCl calculated with adjusted body weight.

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 mM/L and albumin is expressed in g/L:
Corrected calcium (mM/L) =
serum calcium (mM/L) + 0.02•(40 - serum albumin [g/L])

Source: Burtis 1999[3]

Attachment 5: Lenalidomide Global Pregnancy Prevention Plan

Where lenalidomide is supplied locally, subjects must adhere to the local lenalidomide REMS program. Where lenalidomide is supplied centrally and no local lenalidomide REMS program exists, then subjects must adhere to the lenalidomide Global Pregnancy Prevention Plan provided in this attachment.

Within this attachment only, use of the phrase "study drug" refers to lenalidomide.

1.1 Pregnancy Prevention Risk Management Plans

1.1.1 Lenalidomide Pregnancy Prevention Risk Management Plan

1.1.1.1 Lenalidomide Pregnancy Risk Minimisation Plan for Celgene Clinical Trials

This attachment applies to all patients receiving lenalidomide therapy. The following Pregnancy Risk Minimisation Plan documents are included:

1) Lenalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods (Section 1.1.1.2);
2) Lenalidomide Education and Counseling Guidance Document (Section 1.1.1.3);
3) Lenalidomide Information Sheet (Section 1.1.1.4).

1. The Lenalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods document (Section 1.1.1.2) provides the following information:
   - Potential risks to the fetus associated with lenalidomide exposure
   - Definition of Female of Childbearing Potential
   - Pregnancy testing requirements for patients receiving Lenalidomide who are females of childbearing potential
   - Acceptable birth control methods for both female of childbearing potential and male patients receiving Lenalidomide in the study
   - Requirements for counseling of all study patients receiving Lenalidomide about pregnancy precautions and the potential risks of fetal exposure to lenalidomide
2. The Lenalidomide Education and Counseling Guidance Document (Section 1.1.1.3) must be completed and signed by either a trained counselor or the Investigator at the participating clinical center prior to each dispensing of lenalidomide study treatment. A copy of this document must be maintained in the patient records.
3. The Lenalidomide Information Sheet (Section 1.1.1.4) will be given to each patient receiving lenalidomide study therapy. The patient must read this document prior to starting lenalidomide study treatment and each time they receive a new supply of study drug.

1.1.1.2 Lenalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods)

Risks Associated with Pregnancy

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

Criteria for females of childbearing potential (FCBP)

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

Counseling

For a female of childbearing potential, lenalidomide is contraindicated unless all of the following are met (i.e., all females of childbearing potential must be counseled concerning the following risks and requirements prior to the start of lenalidomide study therapy):

- She understands the potential teratogenic risk to the unborn child
- She understands the need for effective contraception, without interruption, 4 weeks before starting study treatment, throughout the entire duration of study treatment, dose interruption and 28 days after the end of study treatment
- She should be capable of complying with effective contraceptive measures
- She is informed and understands the potential consequences of pregnancy and the need to notify her study doctor immediately if there is a risk of pregnancy
- She understands the need to commence the study treatment as soon as study drug is dispensed following a negative pregnancy test
- She understands the need and accepts to undergo pregnancy testing based on the frequency outlined in this protocol (Section 1.1.1.2)
- She acknowledges that she understands the hazards and necessary precautions associated with the use of lenalidomide

The investigator must ensure that for females of childbearing potential:

- Complies with the conditions for pregnancy risk minimization, including confirmation that she has an adequate level of understanding
- Acknowledge the aforementioned requirements

For a female NOT of childbearing potential, lenalidomide is contraindicated unless all of the following are met (i.e., all females NOT of childbearing potential must be counseled concerning the following risks and requirements prior to the start of lenalidomide study therapy):

- She acknowledges that she understands the hazards and necessary precautions associated with the use of lenalidomide

Traces of lenalidomide have been found in semen. Male patients taking lenalidomide must meet the following conditions (i.e., all males must be counseled concerning the following risks and requirements prior to the start of lenalidomide study therapy):

- Understand the potential teratogenic risk if engaged in sexual activity with a pregnant female or a female of childbearing potential
- Understand the need for the use of a condom even if he has had a vasectomy, if engaged in sexual activity with a pregnant female or a female of childbearing potential.

Contraception

Females of childbearing potential (FCBP) enrolled in this protocol must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual contact during the following time periods related to this study: 1) for at least 28 days before starting study drug; 2) while participating in the study; 3) dose interruptions; and 4) for at least 28 days after study treatment discontinuation.

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

- Highly effective methods:

  Intrauterine device (IUD)

  Hormonal (birth control pills, injections, implants)

  Tubal ligation

  Partner's vasectomy

- Additional effective methods:

  Male condom

  Diaphragm

  Cervical Cap

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

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

Pregnancy testing

Medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for females of childbearing potential, including females of childbearing potential who commit to complete abstinence, as outlined below.

Before starting study drug

Female Patients:

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

Male Patients:

Must practice complete abstinence or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions and for at least 28 days following study drug discontinuation, even if he has undergone a successful vasectomy.

During study participation and for 28 days following study drug discontinuation

Female Patients:

- FCBP with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while on study, at study discontinuation, and at day 28 following study drug discontinuation. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days and then every 14 days while on study, at study discontinuation, and at days 14 and 28 following study drug discontinuation.
- At each visit, the Investigator must confirm with the FCBP that she is continuing to use two reliable methods of birth control.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in a study patient, study drug must be immediately discontinued.
- Pregnancy testing and counseling must be performed if a patient misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Study drug treatment must be discontinued during this evaluation.
- Females must agree to abstain from breastfeeding during study participation and for at least 28 days after study drug discontinuation.

Male Patients:

- Counseling about the requirement for complete abstinence or condom use during sexual contact with a pregnant female or a female of childbearing potential and the potential risks of fetal exposure to lenalidomide must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in the partner of a male study patient during study participation, the investigator must be notified immediately.

Additional precautions

- Patients should be instructed never to give this medicinal product to another person and to return any unused capsules to the study doctor at the end of treatment.
- Female patients should not donate blood during therapy, during dose interruptions and for at least 28 days following discontinuation of study drug.
- Male patients should not donate blood, semen or sperm during therapy, during dose interruptions and for at least 28 days following discontinuation of study drug.
- Only enough study drug for one cycle of therapy may be dispensed with each cycle of therapy.

1.1.1.3 Lenalidomide Education and Counseling Guidance Document

To be completed prior to each dispensing of study drug.

Protocol Number:

Patient Name (Print): DOB: / / (mm/dd/yyyy)

(Check the appropriate box to indicate risk category)

Female: □

If female, check one:

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

Male: □

Do Not Dispense study drug if:

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

FCBP:

1. I verified that the required pregnancy tests performed are negative.
2. I counseled FCBP regarding the following:
   - Potential risk of fetal exposure to lenalidomide: If lenalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby. Females are advised to avoid pregnancy

while taking lenalidomide. The teratogenic potential of lenalidomide in humans cannot be ruled out. FCBP must agree not to become pregnant while taking lenalidomide.

- Using TWO reliable methods of birth control at the same time or complete abstinence from heterosexual contact [at least 28 days prior to therapy, during therapy, during dose interruption and 28 days after discontinuation of study drug].
- That even if she has amenorrhea she must comply with advice on contraception
- Use of one highly effective method and one additional method of birth control AT THE SAME TIME. The following are examples of highly effective and additional effective methods of contraception:

  Highly effective methods:

  - Intrauterine device (IUD)
  - Hormonal (birth control pills, injections, implants)
  - Tubal ligation
  - Partner's vasectomy

  Additional effective methods:

  - Male condom
  - Diaphragm
  - Cervical Cap
- Pregnancy tests before and during treatment, even if the patient agrees not to have reproductive heterosexual contact. Two pregnancy tests will be performed prior to receiving study drug, one within 10 to 14 days and the second within 24 hours of the start of study drug.
- Frequency of pregnancy tests to be done:

  Every week during the first 28 days of this study and a pregnancy test every 28 days during the patient's participation in this study if menstrual cycles are regular or every 14 days if cycles are irregular.

  If the patient missed a period or has unusual menstrual bleeding.

  When the patient is discontinued from the study and at day 28 after study drug discontinuation if menstrual cycles are regular. If menstrual cycles are irregular, pregnancy tests will be done at discontinuation from the study and at days 14 and 28 after study drug discontinuation.
- Stop taking study drug immediately in the event of becoming pregnant and to call their study doctor as soon as possible.
- NEVER share study drug with anyone else.
- Do not donate blood while taking study drug, during dose interruptions and for 28 days after stopping study drug.
- Do not breastfeed a baby while participating in this study and for at least 28 days after study drug discontinuation.

- Do not break, chew, or open study drug capsules.
- Return unused study drug to the study doctor.

3. Provide Lenalidomide Information Sheet to the patient.

FEMALE NOT OF CHILDBEARING POTENTIAL (NATURAL MENOPAUSE FOR AT LEAST 24 CONSECUTIVE MONTHS, A HYSTERECTOMY, OR BILATERAL OOPHORECTOMY):

1. I counseled the female NOT of child bearing potential regarding the following:
   - Potential risks of fetal exposure to lenalidomide (Refer to item #2 in FCBP)
   - NEVER share study drug with anyone else.
   - Do not donate blood while taking study drug, during dose interruptions and for 28 days after stopping study drug.
   - Do not break, chew, or open study drug capsules
   - Return unused study drug capsules to the study doctor.
2. Provide Lenalidomide Information Sheet to the patient.

MALE:

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

Investigator/Counselor Name (Print):

(circle applicable)

Investigator/Counselor Signature: Date: / /

(circle applicable)

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

1.1.1.4 Lenalidomide Information Sheet

FOR PATIENTS ENROLLED IN CLINICAL RESEARCH STUDIES

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

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

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

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

   - **Do not take study drug if you are pregnant or plan to become pregnant**
   - **You must practice complete abstinence or use two reliable, separate forms of effective birth control at the same time:**

     for 28 days before starting study drug

     while taking study drug

     during dose interruptions of study drug

     for 28 days after stopping study drug
   - **You must have pregnancy testing done at the following times:**

     within 10 to 14 days and again 24 hours prior to the first dose of study drug

     weekly for the first 28 days

     every 28 days after the first month or every 14 days if you have irregular menstrual periods

     if you miss your period or have unusual menstrual bleeding

     28 days after the last dose of study drug (14 and 28 days after the last dose if menstrual periods are irregular)
   - **Stop taking study drug if you become pregnant during treatment**

     If you suspect you are pregnant at any time during the study, you must stop study drug immediately and immediately inform your study doctor. Your study doctor will report all cases of pregnancy to Celgene Corporation
   - **Do not breastfeed while taking study drug**
   - The study doctor will be able to advise you where to get additional advice on contraception.

   If you are a female not of childbearing potential:

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

If you are a male:

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

- Male patients (including those who have had a vasectomy) must practice complete abstinence or must use a condom during sexual contact with a pregnant female or a female that can become pregnant:

  While you are taking study drug

  During dose interruptions of study drug

  For 28 days after you stop taking study drug

- **Male patients should not donate sperm or semen** while taking study drug and for 28 days after stopping study drug.
- **If you suspect that your partner is pregnant any time during the study, you must immediately inform your study doctor. The study doctor will report all cases of pregnancy to Celgene Corporation. Your partner should call their healthcare provider immediately if they get pregnant.**

2. **Restrictions in sharing study drug and donating blood:**

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

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

Attachment 6: Conversion Table for Glucocorticosteroid Dose

Generic Name	Oral or Intravenous Dose (mg)
Dexamethasone	0.75
Methylprednisolone	4
Prednisolone	5
Prednisone	5
Betamethasone	0.6

Attachment 7: 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 on any day	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 FEV1 FEV1/FVC	N/A	Normal FEV_1 between exacerbations > 80% > 85%	Normal FEV_1 between exacerbations > 80% Normal	N/A	> 80% > 80%	> 80% Normal	N/A	60-80% 75-80%	60-80% Reduced 5%	N/A	< 60% < 75%	< 60% Reduced 5%
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.											

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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								
		• Maintain current step			Step up 1 step	Step up at least 1 step	• Step up 1 step	• Consider short course of oral steroids • Step up 1 2 steps		• Consider short course

Recommended Action for Treatment	• Regular follow-up every 1-6 months • Consider step down if well controlled for at least 3 months	• **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.	• Reevaluate in 2 6 weeks • For side effects, consider alternative treatment options	• **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.	of oral steroids • Step up 1-2 steps • Reevaluate in 2 weeks • For side effects, consider alternative treatment options

Attachment 8: International Staging system

International Staging System		
Stage	**Criteria**	**Median Survival (months)**
I	Serum ß$_2$ microglobulin <3.5 mg/L, serum albumin ≥3.5 g/dL	62
II	Not I or III[a]	44
III	Serum ß$_2$ microglobulin ≥5.5 mg/L	29

[a] There are 2 possibilities for Stage II:
1) Serum ß$_2$ microglobulin <3.5 mg/mL but serum albumin <3.5 g/dL, or
2) Serum ß$_2$ microglobulin 3.5 – 5.4 mg/L irrespective of the serum albumin

Attachment 9: The Family of antihistamine medications

The following antihistamines may be used for daratumumab pre-dose medication (including, but not limited to):

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

  * The IV use of promethazine should be avoided.

Attachment 10: Anticipated Adverse 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:

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

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. Each anticipated event will be assessed by the investigator at the individual case level and if considered to be drug-related will undergo expedited reporting (if appropriate) as per applicable clinical trial legislation to Health Authorities and IRB/IECs. If an anticipated event is considered disease-related or not related to study drug the event will be exempt from expedited reporting.

To meet US regulatory clinical trial legislation, the sponsor will perform aggregate review of anticipated events as outlined below, and if determined to be drug-related will implement expedited reporting of these events to Health Authorities and IRBs/IECs. If an interim analysis of trial results leads to an unblinded, aggregate review of safety data by the study team, the sponsor may terminate the review of pre-specified anticipated events outlined above.

Safety Assessment Committee (SAC)

A Safety Assessment Committee (SAC) will be established to perform reviews of pre-specified anticipated events at an aggregate level. The SAC is a safety committee within the sponsor's organization that is independent of the sponsor's study team. The SAC will meet to aid in the recommendation to the sponsor's study team as to whether there is a reasonable possibility that an anticipated event is related to the study intervention based on a review of the aggregate data by arm.

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 11: Long-term Survival Follow-up – After Final CSR Analysis Until Final OS Analysis

After the final CSR analysis, wich will provide updates to the primary CSR analysis for both efficacy and safety, all subjects, regardless of whether they are still on study treatment and those who are in follow-up, will enter the long-term survival follow-up. The subjects who are receiving treatment at the time of the cut-off for the final CSR analysis will continue to receive study treatment per protocol. The following limited schedule is applicable for the long-term survival follow-up.

Dosage and Administration

Study treatment will be administered according to the regimen established prior to Protocol Amendment 9 (see Section 6).

Once the sponsor has notified investigators that the final CSR analysis has been achieved, subjects may continue study treatment until PD per investigator evaluation, unacceptable toxicity, withdrawal of consent, the investigator decides to stop treatment, the start of subsequent anticancer therapy, or study completion (Section 17.9.1), whichever comes first.

Efficacy Evaluations

For subjects continuing study treatment during the long-term survival follow-up, investigators should monitor and assess subjects for response to treatment or disease progression according to local institutional practice and make decisions if treatment should be continued based on benefit /risk evaluation. The assessments and outcome should be entered in the subject file/source notes.

Safety Evaluations

For subjects continuing study treatment during the long-term survival follow-up, local hematology laboratory assessments, chemistry laboratory assessments, and assessment of vital signs should still be performed in accordance with good clinical practice and as per local label of drugs administered to guide safe use of study treatment. These local results do not need to be entered in the CRF.

Safety Reporting

For subjects continuing study treatment during the long-term survival follow-up, serious adverse events that occur while the subject is receiving study drug or are within 30 days after the last dose of study drug, will be collected and reported to the sponsor's global medical safety database via serious adverse event reporting process as indicated by Sponsor or designee (see Section 12.3.2). Serious adverse events that occur between 30 days after the last dose of the study drug and the end of study should be reported using the same process if considered by the investigator to be related to study drug. All serious adverse events should also be documented in the subject file/source notes.

Pregnancy reporting should continue as described in Section 12.3.4. The pregnancy should be documented in the subject file/source notes.

During long-term survival follow-up, reporting of anticipated events (Attachment 10) is no longer performed.

Patient Reported Outcomes

For subjects continuing study treatment during the long-term survival follow-up, no PRO data collection will occur.

Sample Collection and Handling

For subjects continuing study treatment during the long-term survival follow-up, there will be no PK, immunogenicity, or biomarker (MRD) assessments during this treatment period. Any sample collection or test for safety or disease evaluation should comply with local institution practice and be documented in the subject files/source notes.

Case Report Form Completion

The clinical database will remain partially open during the long-term survival follow-up. For all subjects on study, whether continuing study treatment or those in survival follow-up, CRF pages to be completed are:

- subsequent therapies
- survival follow-up
- death information
- end of treatment disposition
- end of study disposition

For survival follow up, the information can be obtained via telephone contact, medical records indicating the subject visited the hospital (laboratory, consult for other specialty), public records for deaths, etc.

Follow-up Procedures

For subjects who discontinue treatment during the long-term survival follow-up and the subjects who were in follow-up at the time of final CSR analysis, end of treatment procedures (Section 9.1.4) are not applicable, except for HBV DNA monitoring in accordance with the local label. These monitoring data should be documented in files/source notes but not entered in the CRF.

Source Documentation

At a minimum, the source data collected should include: subject and study identification, study discussion, documentation of the informed consent process including the date of consent, dates of visits, serious adverse events, pregnancy information, safety monitoring of subject as per local institution practice, drug dispensing/return records, study drug administration information, subsequent therapies, survival follow-up and death information, reason for end of treatment and for end of study.

Attachment 12: Final OS Analysis Until End of Study

Protocol Amendment 9 will allow those subjects who are benefitting from daratumumab treatment at the time of the clinical cut-off date for the final OS analysis to continue to receive daratumumab. The sponsor will ensure that subjects will be able to continue to receive daratumumab after the final OS analysis until the end of study (defined in Section 17.9.1). The following limited schedule is applicable.

Documentation of assessments performed is required only in the subject file/source notes.

Dosage and Administration

Daratumumab will be administered according to the regimen established prior to Amendment 9 (see Section 6).

Treatment Period

Once the sponsor has notified investigators that the clinical cut-off date for the final OS analysis has been achieved (end of eCRF data collection), subjects may continue treatment with daratumumab until PD per investigator evaluation, unacceptable toxicity, withdrawal of consent, the investigator decides to stop treatment, the start of subsequent anticancer therapy, or the end of the study (defined in Section 17.9.1). For subjects who continue treatment after the final OS analysis, post-treatment follow-up is not applicable, except for HBV DNA monitoring in accordance with the local label.

Efficacy Evaluations

Investigators should monitor and assess subjects for response to treatment or disease progression according to local institutional practice. The assessments and outcome should be entered in the subject file/source notes.

Safety Reporting

For subjects continuing daratumumab after the clinical cut-off date for the final OS analysis, serious adverse events that occur while the subject is receiving study drug and within 30 days after the last dose of study drug will be collected and reported to the sponsor's global medical safety database only via the same serious adverse event reporting process used over the course of the study. Serious adverse events that occur between the 30-day post-dose period and completion of the study should be reported using the same process if considered by the investigator to be related to study drug. Serious adverse events should also be documented in the subject file/source notes.

Pregnancy reporting should continue as described in Section 12.3.4. The pregnancy should be documented in the subject file/source notes.

Sample Collection and Handling

For subjects continuing daratumumab after the clinical cut-off date for the final OS analysis, there will be no PK, immunogenicity, or biomarker assessments during this treatment period, and any sample collection or test for safety or disease evaluation should comply with local institution practice.

Case Report Form Completion

No data will be collected in the eCRF after the cut-off for the final OS analysis.

Source Documentation

At a minimum, the source data collected should include: subject and study identification, study discussion, documentation of the informed consent process including the date of consent, dates of visits, serious adverse events, pregnancy information, safety monitoring of subject as per local institution practice, drug dispensing/return records, and study drug administration information.

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): PPD

Institution: Janssen Research & Development

Signature: electronic signature appended at the end of the protocol Date: _____
(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.

Signature

User	Date	Reason
PPD	22-Jul-2021 08:06:20 (GMT)	Document Approval