Janssen Research & Development *

Clinical Protocol

A Phase 3 Randomized, Multicenter Study of Subcutaneous vs. Intravenous Administration of Daratumumab in Subjects With Relapsed or Refractory Multiple Myeloma

Protocol 54767414MMY3012; Phase 3
AMENDMENT 3

JNJ-54767414 (daratumumab)

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

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

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PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	23 May 2017
Amendment 1	7 December 2017
Amendment 2	13 August 2018
Amendment 3	21 January 2020

Amendments below are listed beginning with the most recent amendment.

Amendment 3 (21 January 2020)

The overall reason for the amendment: The overall reason for the amendment is to define the end of the data collection period and to clarify access to drug treatment after data collection in the study eCRF has ended. Updates to the Anticipated Events sections and minor adjustments to study assessments in the Follow-Up Phase are also included.

Applicable Section(s)	Description of Change(s)
Rationale: To allow subjects benefitting from treatment to continue receiving treatment, the end of the study has been revised. A data collection period has been defined, after which only limited data collection will occur, as described in new Attachment 13.	
Table 1 Time and Events Schedule -Overview; Table 2 Time and Events Schedule - Pharmacokinetic/ Immunogenicity Sample Collection Times	The following note was added to the front of each Time and Events table: **Refer to Attachment 13 for a description of study procedures for subjects who continue to receive study drug provided by the sponsor after the data collection period has ended.**
3.1 Overview of Study Design	~~The study is considered completed approximately 18 months after the last subject is randomized.~~ **The data collection period will end and the clinical database will be closed approximately 24 months after the last subject was randomized or when median overall survival for both arms has been reached, whichever occurs first**.
9.1.4 Follow-Up Phase	Clarification was added that follow-up will continue until the end of the data collection period, which has been defined.
17.9.1 End of Data Collection/ End of Study (old)	The section heading has been revised: **End of Data Collection/Study Completion**~~/End of Study~~. **The end of the data collection period will be approximately 24 months after the last subject was randomized or when median overall survival for both arms has been reached, whichever occurs first.** The end of the study has been redefined: ~~The study is considered completed approximately 18 months after the last subject is randomized or when the sponsor decides to stop the study~~ **The study will be considered complete when all subjects still receiving study drug have commercial or alternative access to the appropriate formulation of daratumumab, have stopped receiving daratumumab treatment, or at approximately 5 years after the last subject was randomized, whichever occurs first.**
Attachment 13	Added Attachment 13 summarizing procedures, data collection, and data reporting methods to be followed after clinical cutoff for the final study analysis (end of the data collection period) has been reached.

Applicable Section(s)	Description of Change(s)
9.1.1 Overview; 9.1.5 Post Data Collection Period to End of Study; 9.2.1 Response Categories; 9.7 Safety Evaluations (Adverse Events, HBV DNA Tests); 9.8 Sample Collection and Handling; 17.5 Case Report Form Completion; 17.9.1 End of Data Collection/Study Completion	Cross-reference was added to Attachment 13 for detail on the scope of study procedures required after the end of the data collection period.
Rationale: Daratumumab will be provided by the sponsor to allow continued treatment for subjects benefitting from either the IV or SC formulation.	
3.1 Overview of Study Design; 9.1.5 Post Data Collection Period to End of Study; 17.9.1 End of Data Collection/ Study Completion	Detail was added regarding the sponsor's commitment to provide daratumumab to responding subjects. The sponsor will ensure that the IV or SC formulation of daratumumab is available so that subjects still on treatment may receive the appropriate daratumumab treatment after the end of the data collection period. Daratumumab will be provided until the applicable formulation is commercially available or becomes available from another source, or until the study is complete.
9.1.4 Follow-up Phase; 9.1.5 Post Data Collection Period to End of Study	Section 9.1.5 was added to describe continuation of study treatment and procedures to be followed after the end of the data collection period. Relevant text previously included in Section 9.1.4 was moved to Section 9.1.5.
Rationale: The clinical database will be closed at the end of the newly defined data collection period, and the final study analysis will be performed.	
3.1 Overview of Study Design; 17.9.1 End of Data Collection/ Study Completion	Clarification was added that the clinical database will be closed once the data collection period has ended and no additional data will be collected in the eCRF. The final study analysis will include data collected during the data collection period.
9.1.4 Follow-up Phase	New text added: **Continuation of Follow-up Phase study procedures is not required once the end of the data collection period is reached, and the End of Trial page of the eCRF should be completed at that time for subjects ongoing in the Follow-up Phase.**
Rationale: Once the data collection period has ended, subsequent safety reporting will be limited to serious adverse events and pregnancy, which will occur only through the sponsor's global medical safety database.	
12.3.1 All Adverse Events	The following text was deleted: ~~The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.~~
12.3.2 Serious Adverse Events	New text added: **Refer to Attachment 13 for details on serious adverse event reporting after the end of the data collection period.**
12.3.4 Pregnancy	New text added: **Pregnancy reporting will continue as described above after the end of the data collection period.**
Rationale: A data collection period has been defined that is distinct from the end of the study.	
3.1 Overview of Study Design	The Follow up Phase begins immediately following the End-of-Treatment Visit, and will continue until death, loss to follow up, withdrawal of consent for study participation, or end of the ~~study~~ **data collection period**, whichever occurs first.
8 Prestudy and Concomitant Therapy	Clarification was added that collection of concomitant therapy information is only required during the data collection period.

Applicable Section(s)	Description of Change(s)
9.1.4 Follow-Up Phase	Information on all new second primary malignancies will also be collected until the end of the ~~study~~ **data collection period**.
9.2.1 Response Categories	For subjects who discontinue study treatment before disease progression, disease evaluations should continue to be performed as described in the Time and Events Schedule, until confirmed disease progression, death, start of a new treatment for multiple myeloma, withdrawal of consent for study participation, or the end of the ~~study~~ **data collection period**.
9.5 Patient-reported Outcomes	The ~~schedule for completion of the~~ modified-CTSQ **will be completed per** ~~is outlined in~~ the Time and Events Schedule **until the end of the data collection period**.
9.7 Safety Evaluations (Adverse Events)	Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) from the time a signed and dated informed consent is obtained until at least 30 days after the last dose of study treatment **during the data collection period,** unless the subject withdraws consent for study participation or starts subsequent anticancer therapy… **After the data collection period has ended, only serious adverse events will be collected, as described in Attachment 13.**
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 final dose of study drug **during the data collection period.**
Rationale: The text for hepatitis B serology testing for any subject with unknown hepatitis B serology and monitoring and managing of hepatitis B virus (HBV) reactivation was added for consistency across daratumumab protocols.	
Table 1: Time and Events Schedule - Overview	Identified that the HBV DNA test will be performed during survival assessment in the Follow-up Phase. Also identified in newly added footnote 'b' that the HBV DNA test will be performed only for subjects with serologic evidence of resolved HBV infection; will be performed locally, every 4 weeks during treatment, end of treatment visit, and every 4 weeks for up to 6 months after the last dose of study treatment.
8.1.6 Management of Hepatitis B Virus Reactivation	Added a new section for information on the management of HBV reactivation.
9.7 Safety Evaluations (HBV DNA Tests)	Removed the reference (no. 7) to the Japan society of hepatology guidelines for the management of HBV infection. Additional guidance provided for subjects with serologic findings suggestive of prior HBV vaccination and known history of prior HBV vaccination.
References	Deleted reference no. 7 and renumbered subsequent references.
Rationale: To eliminate the possibility of inconsistency between the NCI-CTCAE version number being referenced 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 the NCI-CTCAE Version 4.03.

Applicable Section(s)	Description of Change(s)
Rationale: Modified the list of anticipated events to remove any events that are known adverse drug reactions of daratumumab. Clarification that after unblinding of aggregate safety data by the sponsor's study team, there is no need for independent 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 12 Anticipated 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: Medical resource utilization data collected during the Follow-up Phase will not be analyzed.	
Table 1: Time and Events Schedule - Overview	Medical resource utilization information will not be collected during the Follow-up Phase.
Rationale: To clarify when IDMC review was performed.	
3.1 Overview of Study Design	The following text was added: **The IDMC will no longer review study data after primary analysis has been completed.**
Rationale: To clarify how study data collected through the end of the data collection period will be reported.	
3.1 Overview of Study Design	Data collected through the end of the ~~study~~ **data collection period** will be **included in the final study analysis and** reported in a separate ~~an addendum to the~~ Clinical Study Report.
Rationale: To reiterate the sponsor's option to end the study at any time.	
3.1 Overview of Study Design	The following text was added: **The sponsor may decide to end the study at any time, as described in Section 17.9.2.**
Rationale: Text not relevant to study design.	
10 Subject Discontinuation of Study Treatment/ Withdrawal From the Study	The heading for Section 10 was changed as follows: SUBJECT ~~COMPLETION/~~DISCONTINUATION OF STUDY TREATMENT/ WITHDRAWAL FROM THE STUDY
10.1 Completion	Section 10.1 was deleted. Subsequent sections were renumbered.
Rationale: For consistency across daratumumab protocols.	
6.2.1 Subcutaneous Dosing	Text was revised: Doses will be administered by manual push over **approximately** 3-5 minutes in the abdominal SC tissue…
6.5 Dose Delays and Modification	• Grade 3 or higher thrombocytopenia **with bleeding** The following text was added to the last paragraph of the section: **Infusion-related reactions may occur upon re-initiation of daratumumab after a prolonged delay in treatment. Investigators should consider the applicable infusion reaction guidance provided in Section 6.4.2 when restarting treatment after a long delay.**
Rationale: To allow flexibility for some study procedures.	
6.3.1 Predose Medications	Text was revised: In an effort to prevent IRRs, all subjects will start the following medications **approximately** 1 to 3 hours prior to each study drug administration…

Applicable Section(s)	Description of Change(s)
Rationale: Minor errors were noted	
Table 1: Time and Events Schedule - Overview	For the assessment: Subsequent therapy, survival, ~~secondary~~ **second primary** malignancy information
Abbreviations	The abbreviations list has been updated.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 2 (13 August 2018)

The overall reason for the amendment: In order to meet a health authority commitment, an update to the regulatory strategy, including an update to the statistical plan, is being implemented to allow Japan to enroll beyond the initially planned 480 subjects. Clarifications have also been made to ensure accuracy and clarity throughout the protocol.

Applicable Section(s)	Description of Change(s)
Rationale: The data cutoff and primary analysis strategy has been updated to allow Japan to enroll beyond the initially planned 480 subjects.	
3.1 Overview of Study Design	The data cutoff for the primary analysis will occur approximately 6 months after ~~the last subject has~~ **480 subjects** have been randomized.
11.3 Co-primary Endpoints	The primary analysis will occur approximately 6 months after ~~the last subject has~~ **480 subjects have** been randomized.
Rationale: The Time and Events Schedules have been updated for flexibility (Table 1) and clarity (Table 2) regarding assessment timing and sample collections, respectively.	
Table 1, Time and Events Schedule - Overview	Study day windows have been added to the Follow-up phase assessments.
Table 2, Time and Events Schedule Pharmacokinetic/Immunogenicity Sample Collection Times -	Footnote d has been added to the Follow-up phase assessments to clarify that PK/immunogenicity samples should be collected even if subsequent therapy has been initiated.
Rationale: Further information added to ensure clarity in the protocol study design and conduct requirements.	
6.4.2 Infusion-related Reactions	Clarified language in the Infusion-Related Reactions of Grade 3 or Higher subsection to specify requirements for restarting the infusion after an IRR is reported, as follows "Once reaction symptoms resolve, **if continuing treatment is deemed appropriate by the investigator,** ~~consider~~ restart~~ing~~ the infusion at no more than half the rate at which the reaction occurred."
6.5 Dose Delays and Modification;	Clarified that dose modification is not permitted: "Dose modification of **16 mg/kg** Dara-IV or **1800 mg** Dara-SC (increase or decrease) is not permitted." Clarification has been made for when there is a dose delay: "Grade 3 pain associated with symptoms of multiple myeloma (bone/joint pain)" has been added as an exception to the criterion to hold study treatment.
9.1.4 Follow-Up Phase	Clarification made that "Beyond ~~the~~ 30-day**s** ~~End of Treatment Visit~~ **after the last dose,** serious adverse events considered related to study treatment will continue to be collected."

Applicable Section(s)	Description of Change(s)
9.2.2 Myeloma Protein Measurements in Serum and Urine	Text has been revised regarding the conditions for when UPEP assessments can stop after C1D1.
9.7 Safety Evaluations	Subjects who are positive for antiHBc or antiHBs will undergo testing for hepatitis B DNA by PCR every 4 weeks **(each cycle). Subjects who are positive for antiHBs antibodies due to prior immunization are not required to be monitored by HBV DNA by PCR.** During and following study treatment, subjects who have history of HBV infection will be closely monitored for clinical and laboratory signs of reactivation of HBV according to the JSH Guidelines for Prevention of HBV reactivation in patients receiving Immunosuppressive Therapy or Chemotherapy (JSH Guidelines for the Management of Hepatitis B Virus Infection[7]). **Where required by local law, the result of HBV testing may be reported to the local health authorities.**
Attachment 4: Modified Diet in Renal Disease Formula	An error in the modified diet in renal disease formula calculation has been corrected.
Rationale: Updated Attachment 10 to include SEBIA Hydrashift 2/4 Daratumumab IFE Interference assay.	
Updated Attachment 10: Interpretation of the SEBIA Hydrashift 2/4 Daratumumab IFE Interference Assay	Text updated to delete reference to the DIRA assay and include the three outcomes of the SEBIA Hydrashift 2/4 Daratumumab IFE Interference assay.
Rationale: Minor changes made to the protocol.	
4.3 Prohibitions and Restrictions; 8.3 Prohibited Therapies	The following text related to IV contrast being used in CT in subjects with multiple myeloma has been deleted from the protocol. ~~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.~~
4.2 Exclusion Criteria, Criterion #5.2; 4.2 Exclusion Criteria, Criterion #8.2; 6.2.2 Intravenous Administration, Table 4; 6.3.1 Predose medications; 6.3.2 Postdose medications;	Minor editorial and grammatical changes made to the text of the protocol for clarifications.

Amendment 1 (7 December 2017)

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

The overall reason for the amendment: The overall reason for the amendment is to address feedback from regulatory health authorities including updating inclusion criteria for measurable disease and HBV status, to provide additional instruction in the event of infusion-related reactions, and to clarify methodology of local bone marrow testing.

Applicable Section(s)	Description of Change(s)
Rationale: Clarification that chest x-rays obtained as part of the skeletal survey can be accepted as the screening chest X-ray.	
Time and Event Schedule, Table 1, Chest X-ray	Text added that chest x-rays are acceptable if performed as part of standard of care within 28 days before randomization or if performed as part of the skeletal survey
Rationale: To provide operational flexibility for study sites, ECOG assessment no longer specified to be done prior to other assessments.	
Time and Event Schedule, Table 1, ECOG performance status; 9.7. Safety Evaluations, Physical Examination and ECOG Performance Status	Text outlining that ECOG performance status be obtained prior to other study activities on scheduled days removed.
Rationale: To align with regional guidelines for management of HBV infection, safety follow-up timepoints added for subjects who are positive for antiHBc or antiHBs.	
Time and Event Schedule, Table 1, HBV DNA test	Timepoints for HBV DNA tests for subjects who are positive for antiHBc or anti-HBs added at Screening, Cycle 1 Day 1, at Day 1 of each subsequent cycle, and at EOT.
Rationale: To investigate biomarkers response and resistance to daratumumab, additional longitudinal blood collections were added. Additional text included to clarify biomarker activities.	
Time and Event Schedule, Table 1, Whole blood (biomarker)	Sample collections for biomarkers added on Cycle 6 Day 1 and Cycle 13 Day 1.
3.2. Study Design Rationale	Added text to clarify that biomarkers samples will be used to evaluate pharmacodynamic biomarkers and to evaluate the role of the immunomodulatory mechanism of action of daratumumab in response and development of resistance.
9.4. Biomarkers	Added text to clarify that biomarkers samples will be used to evaluate pharmacodynamic biomarkers and to evaluate the role of the immunomodulatory mechanism of action of daratumumab in response and development of resistance. Text added that testing may include the evaluation of specific subsets of immune cells.
Rationale: Correction of methodology for bone marrow testing	
Time and Event Schedule, Table 1, Bone marrow aspirate/biopsy;	Added text to table to indicate that FISH was the preferred method of testing and to clarify that if a fresh aspirate bone marrow sample was obtained, a portion was to be sent to the central lab for biomarker evaluation; DNA/RNA sequencing replaced with biomarker evaluation. A typographical error “and phenotyping” was corrected to read “or karyotyping”.

Applicable Section(s)	Description of Change(s)
9.2.5. Bone Marrow Examination, Table 7	Text "Cytogenetics by FISH (preferred) or karyotyping" added under Local Testing. Text under Central Testing revised to indicate that if a fresh bone marrow aspirate is collected at Screening, a portion will be sent to a central laboratory for biomarker evaluation; DNA/RNA sequencing replaced with biomarker evaluation.
Rationale: To provide operational flexibility for study sites, MRI added as an option for skeletal survey.	
Time and Event Schedule, Table 1, Skeletal survey	Added text that x-ray or MRI may be used as alternatives for skeletal surveys if applicable in local practice.
Rationale: Corrections and clarifications for PK sample collection.	
Time and Event Schedule, Table 2	PK sample collection windows on dosing days changed from ±1 day or ±3 days (depending on cycle) to ±0 days. Footnote "a" modified to indicate that samples collected on dosing days must be collected on the day of study drug administration. Text indicating collection of samples ±4 hours of the time of study drug administration on non-dosing days deleted. Samples obtained at non-dosing days Cycle 1 Day 4, Cycle 3 Day 4, Follow-up post-treatment Week 4 and Follow-up post-treatment Week 8 moved to "After dose" line in table for clarity. New footnote "c" added that end of dose samples (Dara-IV) should be collected after the end of infusion (up to 2 hours after the end of infusion).
Rationale: Inclusion criterion for measurable disease revised to align with current IMWG criteria	
4.1. Inclusion Criteria 2	Text revised to define documented multiple myeloma as serum M-protein level ≥1.0 g/dL or urine M-protein level ≥200 mg/24 hours. Text defining measurable disease for IgA, IgD, IgE, and IgM multiple myeloma as serum M-protein level ≥0.5 g/dL or urine M-protein level ≥200 mg/24 hours deleted.
Rationale: Exclusion criteria revised to align with ASCO recommendations	
4.2. Exclusion Criteria 5	Revised exclusion text to history of malignancy (other than multiple myeloma) if all treatment of that malignancy was completed at least 2 years before consent and the patient has no evidence of disease (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or breast, or other non-invasive lesion, that in the opinion of the investigator, with concurrence with the sponsor's medical monitor, is considered cured with minimal risk of recurrence within 3 years.)
Rationale: Exclusion criteria and safety follow-up for HBV revised to align with regional guidelines for management of HBV infection.	
4.2. Exclusion Criteria 8b	Revised exclusion text to define hepatitis B as hepatitis B surface antigen [HBsAg] positive, or antibodies to hepatitis B surface or core antigens [antiHBs or antiHBc] with hepatitis B virus [HBV]-DNA quantitation positive). In addition, subjects who are positive for antiHBs or antiHBc must have a negative polymerase chain reaction (PCR) for HBV-DNA quantitation result at screening, PCR positive subjects are to be excluded.

Applicable Section(s)	Description of Change(s)
9.7. Safety evaluations	Added a new section for safety follow-up for subjects who are positive for antiHBc or anti-HBs. During the study, subjects who are positive for antiHBc or antiHBs will undergo testing for hepatitis B DNA by PCR every 4 weeks (cycle). During and following study treatment, subjects who have history of HBV infection will be closely monitored for clinical and laboratory signs of reactivation of HBV. Added reference: JSH Guidelines for the Management of Hepatitis B Virus Infection 2014.
Rationale: Clarification to ensure study site alignment with IPPI in the event of drug administration interruption due to an adverse event related to the study drug.	
6.4.2. Infusion-related Reactions	Added text that the investigator/study coordinator should review the information of the dispensed study drug on the Investigational Product Preparation Form and ensure the correct drug product is being used before restarting the administration.
Rationale: Clarification of Day 1 dosing schedule delays and subsequent drug administration.	
6.5 Dose Delays and Modification	Added text that the delay of Day 1 drug dosing in any given cycle should not result in a skipped dose but should lead to a delay of the entire cycle instead. A minimum of 4 days between daratumumab doses must be observed.
Rationale: Clarification of herpes zoster prophylaxis recommendations.	
8.1.4. Prophylaxis for Herpes Zoster Reactivation	Text revised that antiviral prophylaxis within 1 week after starting study treatment and continuing for 3 months following study treatment is recommended
Rationale: Modification of disease evaluable intervals from ±3 days to ±7 days to align with other daratumumab studies.	
9.1.1 Overview; 9.2.1. Response Categories	Text revised that disease evaluations must be performed every 28 days (±7days).
Rationale: Update of estimated blood volumes to be collected to align with current Covance laboratory manual and additional biomarker samples.	
9.1.1 Overview; 16.1. Study-Specific Design Considerations	Text updated to indicate the maximum blood volume for a subject who completes 8 cycles and the post-treatment assessments is approximately 490 mL. The total blood volume to be collected is estimated at approximately 34 mL for Screening, 100 mL for Cycles 1 and 2, 161 mL for Cycles 3-6, 21 mL at each subsequent cycle…
Rationale: Clarification of study success as requested by Health Authority.	
11.3. Co-primary endpoints	Text revised that once the null non-inferiority hypothesis is rejected for both the ORR and maximum Ctrough, non-inferiority of Dara-SC to Dara-IV will be established….
Rationale: Based on oncology studies, overall survival substituted for time to next treatment in the evaluation of secondary endpoints.	
11.3. Co-primary endpoints	Text updated to indicate that hierarchical procedure for superiority testing will be implemented to control familywise Type I error rate at a two-sided significance level of 0.05 for secondary endpoints including incidence of IRR, PFS, rate of VGPR or better, and overall survival. Time to next therapy (TNT) deleted.

Applicable Section(s)	Description of Change(s)
Rationale: Clarification of adverse event reporting to align with variations based on individual country health authority requirements.	
12.3.1. All Adverse Events	Text added that while some countries require reporting of all adverse events to the health authorities, others will not identify anticipated events for the health authorities.
Rationale: Clarification of exceptions to expedited reporting to align with Health Authority request.	
12.3.3. Disease-Related Events or Outcomes Not Qualifying as Adverse Events	Text added that known consequences of the underlying disease and events common in the study population independent of drug therapy are considered adverse events. Text revised that drug-related adverse events will be recorded and reported (if appropriate) as per current legislation to Health Authorities and ECs. Disease-related or adverse events not related to the study drug will be exempt from expedited reporting. Previous text noting that events that are part of the natural course of the disease under study should not be recorded as an adverse event or serious adverse event and that clinical sequelae resulting from disease progression is to be reported if the serious event definition is fulfilled deleted.
Rationale: Text with exception to mandatory termination of pregnant subjects from the study provided to align with current daratumumab considerations.	
12.3.4. Pregnancy	Added text that pregnant subjects can continue the study if the subject (or the subject's legally acceptable representative), investigator, and sponsor agree the benefits outweigh the risks to the fetus and continuation of study treatment is in the best interests of the subject.
Rationale: Modification of template text to align with recent protocol template changes.	
10.3. Withdrawal from Study	Revised the text related to subjects withdrawing from the study.
12.3.1. All Adverse Events	Added text related to sponsor's responsibility for reporting anticipated events and SUSARs.
17.3. Subject Identification. Enrollment, and Screening Logs	Added ‘(as allowed by local regulations)’ following 2 instances of ‘date of birth’.
17.11 Use of Information and Publications	Changed the time for submitting study results for publication from ‘within 12 months of the availability of the final data (tables, listings, graphs)’ to ‘within 18 months after study end date’. Revised the text beginning ‘Authorship of publications...’ Previous text related to uniform requirements for manuscripts submitted to Biomedical journals deleted.
Rationale: Removal of non-applicable text.	
Attachment 10	Text identifying subjects assigned to the daratumumab, lenalidomide, and dexamethasone group deleted.
Rationale: Attachment update	
Attachment 11	PRO attachment replaced with current version.
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

SYNOPSIS

A Phase 3 Randomized, Multicenter Study of Subcutaneous vs. Intravenous Administration of Daratumumab in Subjects With Relapsed or Refractory Multiple Myeloma

EudraCT NUMBER: 2017-000206-38

Daratumumab is a human IgG1κ monoclonal antibody (mAb) that binds with high affinity to a unique epitope on CD38. It is a targeted immunotherapy that attacks tumor cells that overexpress CD38, a transmembrane glycoprotein, in a variety of hematological malignancies including multiple myeloma.

OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

Objectives

Primary Objectives

- To show that subcutaneous (SC) administration of daratumumab co-formulated with recombinant human hyaluronidase PH20 (Dara-SC) is non-inferior to intravenous (IV) administration of daratumumab (Dara-IV) in terms of the overall response rate (ORR)
- To show that Dara-SC is non-inferior to Dara-IV in terms of the maximum trough concentration (C_{trough})

Secondary Objectives

- To assess the pharmacokinetics and immunogenicity of Dara-SC and Dara-IV
- To evaluate the safety of Dara-SC and Dara-IV
- To evaluate the clinical benefit of Dara-SC and Dara-IV
- To evaluate the immunogenicity of recombinant human hyaluronidase (rHuPH20) following Dara-SC administration
- To evaluate patient-reported satisfaction with Dara-SC and Dara-IV

Endpoints

Primary Endpoints

The co-primary endpoints of this study are:

- ORR
- Maximum C_{trough} (Cycle 3 Day 1 predose)

Secondary Endpoints

- Rate of infusion-related reactions (IRRs)
- Progression-free survival (PFS)
- Rate of very good partial response (VGPR) or better
- Rate of complete response (CR) or better
- Time to next therapy (TNT)
- Overall survival (OS)

- Patient-reported satisfaction with therapy
- Duration of response
- Time to response

Hypothesis

The ORR and maximum C_{trough} (defined as the serum predose concentration on Cycle 3 Day 1) for Dara-SC 1800 mg are not inferior to the ORR and maximum C_{trough}, respectively, for Dara-IV 16 mg/kg in subjects with multiple myeloma who have received at least 3 prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory drug (IMiD), or whose disease is refractory to both a PI and an IMiD.

OVERVIEW OF STUDY DESIGN

This is a Phase 3, randomized, open-label, active-controlled, multicenter study to demonstrate that the efficacy and pharmacokinetics of Dara-SC are not inferior to those of Dara-IV. The study population consists of adults diagnosed with multiple myeloma who have received at least 3 prior lines of therapy including a PI and an IMiD, or whose disease is refractory to both a PI and an IMiD. Approximately 480 subjects will be assigned randomly to the Dara-SC group or the Dara-IV group in a 1:1 ratio. The randomization will be stratified by body weight at baseline (≤65 kg, 66 kg to 85 kg, >85 kg), number of prior lines of therapy (≤4 prior lines versus >4 prior lines), and type of myeloma (IgG versus non-IgG).

SUBJECT POPULATION

Key eligibility criteria include the following: ≥18 years of age; a multiple myeloma diagnosis according to the International Myeloma Working Group (IMWG) diagnostic criteria; achieved a response (partial response [PR] or better based on investigator's determination of response by IMWG criteria) to at least 1 prior treatment regimen; evidence of relapsed or refractory disease on the most recent prior treatment; have received at least 3 prior lines of therapy including a PI and an IMiD, or disease that is refractory to both a PI and an IMiD; and an Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0, 1, or 2.

DOSAGE AND ADMINISTRATION

Each treatment cycle is 28 days. Study drug will be administered once weekly in Cycles 1 and 2, every 2 weeks in Cycles 3 to 6, and every 4 weeks thereafter. All doses will be administered at outpatient visits. In the Dara-SC group, a fixed dose of Dara-SC 1800 mg will be administered by SC injection. In the Dara-IV group, a weight-based dose of Dara-IV 16 mg/kg will be administered by IV infusion.

EFFICACY EVALUATIONS

Assessment of disease will be conducted in accordance with the IMWG response criteria. Disease evaluations will include the following: measurements of myeloma proteins, bone marrow examinations, skeletal surveys and other imaging studies, and serum calcium corrected for albumin.

OTHER EVALUATIONS

Blood samples will be drawn from all subjects to characterize the pharmacokinetics of daratumumab and to assess for the generation of antibodies to daratumumab. In the Dara-SC group, additional blood samples will be assessed for the generation of antibodies to rHuPH20. Blood and bone marrow aspirate samples will be used to better understand the mechanism of action of daratumumab and to obtain information about potential markers of clinical response and resistance.

SAFETY EVALUATIONS

Safety evaluations include adverse event monitoring, physical examinations, electrocardiograms (ECGs), SC injection site evaluations, clinical laboratory parameters (hematology and chemistry), vital sign measurements, and ECOG performance status.

STATISTICAL METHODS

In a previous clinical study (MMY2002), of 106 subjects with relapsed or refractory multiple myeloma who had received at least 3 prior therapies and who were treated with Dara-IV 16 mg/kg, an ORR of 29.2% (95% CI: 20.8%, 38.9%) was observed. Non-inferiority of Dara-SC to Dara-IV in the current study is defined using a 60% retention of the lower bound (20.8%) of the 95% CI from Study MMY2002. With a planned 1:1 randomization, 480 subjects (n=240 in the Dara-SC group and n=240 in the Dara-IV group) will be needed to demonstrate non-inferiority with a power of 80% and a one-sided alpha=0.025, assuming that the true ORR is the same for both groups.

The study is also designed to establish non-inferiority of maximum C_{trough} between Dara-SC and Dara-IV. Dara-SC will be considered non-inferior to Dara-IV if the lower bound of the 90% confidence interval for the ratio of the geometric means of C_{trough} on Cycle 3 Day 1 is at least 80% (non-inferiority margin of 20%). A one-sided test is selected based on previous analyses that demonstrated a strong relationship between maximum C_{trough} and efficacy. However, there is no apparent relationship between drug exposure in the therapeutic dose range and adverse events of interest. With the planned 1:1 randomization, 480 subjects, and a one-sided alpha of 0.05, the power will be >95%. This assumes a true ratio of the maximum C_{trough} of 1 and a coefficient of variation of 0.6.

TIME AND EVENTS SCHEDULES

Table 1: Time and Events Schedule – Overview

Note: Refer to Attachment 13 for a description of study procedures for subjects who continue to receive study drug provided by the sponsor after the data collection period has ended.

			Study Visits									
			Treatment Phase (1 Cycle = 28 days)							Follow-up Phase		
		Screening Phase	Cycles 1 & 2				Cycles 3-6		Cycles 7+	EOT	FUP[a]	Survival[a]
Study Day	Notes	-28 to -1	D1	D8	D15	D22	D1	D15	D1	Post-Treatment Week 4 +7 days	Post-Treatment Week 8 ±7 days	q16wks After PD ±14 days
The start of Cycles 2 and 3 may occur ±1 day of the scheduled day. The start of each subsequent cycle may occur ±3 days of the scheduled day. Day 1 of subsequent cycles should be adjusted accordingly to maintain the 28-day cycle duration. Unless otherwise stated, all blood and urine samples must be obtained before administration of study drug (Dara-SC or Dara-IV). Blood samples must not be taken from the same arm as IV drug administration, if applicable.												
Informed consent	Subjects must sign the informed consent form before any study-specific procedures are performed											
Eligibility criteria, demography, height, medical history		X										
Forced expiratory volume test	Subjects with known or suspected COPD	X										
Chest x-ray	Acceptable if performed as part of standard of care within 28 days before randomization or if performed as part of the skeletal survey	X										
Physical examination		X	Symptom-directed physical examination only									
Weight	Prior to drug administration		X				X		X			
Pulse, temperature, and blood pressure	After ~5 minutes of rest	X	C1D1 - For Dara-SC: immediately before administration; at end of administration; and at 0.5 and 1 hour after end of administration. For Dara-IV: immediately before administration; at 0.5, 1, 1.5, 2, and 3.5 hours after the start of administration; at end of administration; and at 0.5 and 1 hour after end of administration. All other doses - immediately before administration and at the end of administration.							X		
ECOG performance status		X	X				X		X	X		
Electrocardiogram (ECG)	After ~5 minutes of rest, prior to any blood draw	X	As clinically indicated							X		

			Study Visits									
			Treatment Phase (1 Cycle = 28 days)							Follow-up Phase		
		Screening Phase	Cycles 1 & 2				Cycles 3-6		Cycles 7+	EOT	FUP[a]	Survival[a]
Study Day	Notes	-28 to -1	D1	D8	D15	D22	D1	D15	D1	Post-Treatment Week 4 +7 days	Post-Treatment Week 8 ±7 days	q16wks After PD ±14 days
Medication Administration												
Study drug (Dara-SC or Dara-IV)			X	X	X	X	X	X	X			
Predose and postdose medications			X	X	X	X	X	X	X			
Laboratory Assessments												
Blood group and type assessment and indirect antiglobulin test (IAT) results	Obtained before start of dose; includes ABO, Rh, and indirect antiglobulin test results. Results placed on subject identification wallet card		X									
Urine or serum pregnancy test	Women of childbearing potential only	Study day -14 to -1	As clinically indicated									
Chemistry	May be performed up to 3 days before study drug administration day. Results must be evaluated before each study drug administration. At Cycle 1 Day 1, tests do not need to be repeated if they were performed within the previous 5 days.	X	X				X		X	X		
Hematology		X	X	X	X	X	X	X	X	X		
HBV DNA test	Only for subjects who are positive for anti-HBc or anti-HBs	X	X				X		X	X		X[b]
Whole blood (biomarker)	Predose collection for immunophenotyping		C1				C4					
Whole blood (biomarker)	Predose plasma and PBMC collection		C1				C4 and C6		C13	X		
Pharmacokinetics and Immunogenicity Blood Samples												
Pharmacokinetics, immunogenicity	Pharmacokinetics of daratumumab; immunogenicity of daratumumab and rHuPH20		See Table 2									
Disease Evaluations (Blood/Urine) Samples must be sent to the central laboratory.												
Serum β_2-microglobulin	SPEP and UPEP are to be performed within 14 days before Cycle 1 Day 1. See Section 9.2.2 for details.	X										
QIg (IgA, IgM, IgG, IgD, IgE)		X	Every 3 months (±1 month) during treatment							X		
SPEP		X	X				X		X	X	X[a]	
UPEP (24-hr urine sample)		X	X				X		X	X	X[a]	

			Study Visits									
			Treatment Phase (1 Cycle = 28 days)							Follow-up Phase		
		Screening Phase	Cycles 1 & 2				Cycles 3-6		Cycles 7+	EOT	FUP[a]	Survival[a]
Study Day	Notes	-28 to -1	D1	D8	D15	D22	D1	D15	D1	Post-Treatment Week 4 +7 days	Post-Treatment Week 8 ±7 days	q16wks After PD ±14 days
Serum calcium corrected for albumin		X	X				X		X	X		
Serum FLC & serum/urine immunofixation		X	Serum FLC and serum/urine immunofixation are to be performed for any subject when CR is suspected or maintained; for light chain MM subjects, serum FLC will also be performed on Day 1 of every cycle, at end of treatment and at follow-up until PD.									
Disease Evaluations (Other)												
Bone marrow aspirate/biopsy	Disease characterization (morphology and either immunohistochemistry, immunofluorescence, or flow cytometry), FISH (preferred), or karyotyping. Performed locally.	Up to 42 days before randomization; if a fresh aspirate, send portion to central lab for biomarker evaluation	To confirm CR (including sCR) and if feasible, at the time of disease progression. A portion of aspirate collected at PD will be sent to a central lab for evaluation of biomarkers of resistance to daratumumab.									
Skeletal survey	Low-dose whole body CT is preferred. Depending on local practice, a skeletal survey by x-ray or MRI may be used as an alternative.	Up to 42 days before randomization	As clinically indicated and per the local standard of care for imaging (X-ray, CT, or MRI). The same methodology used at Screening should be used throughout the study for comparison purposes.									
Extramedullary plasmacytomas	For subjects with a history of extramedullary plasmacytomas, lesions should be assessed by PET-CT or MRI.	Up to 42 days before randomization	To confirm MR, PR, VGPR, CR, or sCR; as well as at suspected PD and as clinically indicated per the local standard of care									
Modified-CTSQ	To be completed prior to any other study procedures at that visit.		C2	X	X	X	X		X	X		
Medical resource utilization	See Section 9.6 for details		X	X	X	X	X	X	X			
Ongoing Subject Review												
Adverse event monitoring	See Section 12 for details.		Continuous from time of ICF signature until 30 days after last study drug dose								Treatment-related serious adverse events	
Concomitant medication recording	See Section 8 for details.		Continuous from time of ICF signature until 30 days after last study drug dose									
Subsequent therapy, survival, second primary malignancy information			Continuous from first dose of study drug until end of study									

			Study Visits									
			Treatment Phase (1 Cycle = 28 days)							Follow-up Phase		
		Screening Phase	Cycles 1 & 2				Cycles 3-6		Cycles 7+	EOT	FUP[a]	Survival[a]
Study Day	Notes	-28 to -1	D1	D8	D15	D22	D1	D15	D1	Post-Treatment Week 4 +7 days	Post-Treatment Week 8 ±7 days	q16wks After PD ±14 days

Abbreviations: Anti-HBc=antibodies to hepatitis B core antigen; Anti-HBs=antibodies to hepatitis B surface antigen; C=Cycle; COPD=chronic obstructive pulmonary disease; CR=complete response; CT=computed tomography; d/D=day(s); Dara-SC=daratumumab and recombinant human hyaluronidase for subcutaneous injection; Dara-IV=daratumumab for intravenous formulation; ECOG=Eastern Cooperative Oncology Group; EOT=End of Treatment; FISH=fluorescence in situ hybridization; FLC=free light chain; FUP=Follow-up Phase; HBV=hepatitis B virus; ICF=informed consent form; IV=intravenous; QIg=quantitative immunoglobulin; MM=multiple myeloma; modified-CTSQ=modified Cancer Therapy Satisfaction Questionnaire; MR=minimal response; MRI=magnetic resonance imaging; PBMC=peripheral blood mononuclear cells; PCR=polymerase chain reaction; PD=progressive disease; PET=positron emission tomography; PR=partial response; rHuPH20=recombinant human hyaluronidase; sCR=stringent CR; SPEP=Serum M-protein quantitation by electrophoresis; UPEP=urine M-protein quantitation by electrophoresis; VGPR=very good partial response; w=weeks.

a. For subjects who discontinue study treatment before PD, disease evaluations should continue to be performed at the frequency specified below until confirmed PD, death, start of a new treatment for multiple myeloma, withdrawal of consent to study participation, or end of the study whichever occurs first. Once PD is confirmed subsequent disease assessment time points are not required.

- Every 4 weeks: SPEP and 24-hour UPEP assessments, and serum calcium corrected for albumin
- When CR is suspected or maintained: serum FLC, serum and urine immunofixation
- As clinically indicated: skeletal survey

Evidence of clinical relapse will also be documented at the time at which it is first detected.

After PD is documented, survival status, subsequent anticancer treatment, response to subsequent anticancer treatment, date of progression, and information on all new second primary malignancies will be recorded (interview may be conducted by telephone) for all subjects until the end of the data collection period.

b. To be performed only for subjects with serologic evidence of resolved HBV infection (ie, positive anti-HBs or positive anti-HBc) at Screening, HBV DNA testing by PCR must be performed locally. Performed locally every 4 weeks during treatment, end of treatment visit, and every 4 weeks for up to 6 months after the last dose of study treatment.

Table 2: Time and Events Schedule - Pharmacokinetic/Immunogenicity Sample Collection Times

Note: Refer to Attachment 13 for a description of study procedures for subjects who continue to receive study drug provided by the sponsor after the data collection period has ended.

	Cycle 1			Cycle 2	Cycle 3		Cycle 5	Cycle 7	Cycle 12	Follow-up[d]	
Day	**1**	**4**	**15**	**1**	**1**	**4**	**1**	**1**	**1**	**Post-treatment Week 4**	**Post-treatment Week 8**
Visit window d=days, w=weeks	0	±1d	±0d	±0d	±0d	±1d	±0d	±0d	±0d	+1w	±1w
D=study drug administered	D		D	D	D		D	D	D		
Daratumumab pharmacokinetics (serum) – both groups											
Before dose[a]	X		X	X	X		X	X	X		
After dose[c]	X (Dara-IV only)	X (Dara-SC only)			X (Dara-IV only)	X (Dara-SC only)				X	X
Daratumumab immunogenicity (no additional blood draw; serum taken from pharmacokinetic sample) – both groups											
Before dose[ab]	X						X	X	X	X	X
rHuPH20 immunogenicity (plasma) – Dara-SC only											
Before dose[ab]	X						X	X	X	X	X

Dara-SC=daratumumab and recombinant human hyaluronidase for subcutaneous injection; Dara-IV=daratumumab for intravenous formulation; rHuPH20=recombinant human hyaluronidase.

[a] On dosing days, sample collection may occur up to 2 hours before but not after the start of drug administration. Samples collected on dosing days must be collected on the day of study drug administration

[b] In addition, samples for assessment of antibodies to daratumumab (Dara-IV group) or antibodies to daratumumab and rHuPH20 (Dara-SC group) should be drawn, if possible, any time an infusion-related reaction is reported (according to the Lab Manual and Section 9.3.4) in association with the second administration or beyond.

[c] End of dose samples (Dara-IV) are to be collected after the end of infusion (up to 2 hours after the end of infusion).

d Samples should be collected even if subsequent therapy has been initiated.

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
AST	aspartate aminotransferase
CDC	complement-dependent cytotoxicity
CI	confidence interval
C_{min}	minimum observed concentration
C_{max}	maximum observed concentration
COPD	chronic obstructive pulmonary disease
CR	complete response
CT	computed tomography
CTSQ	Cancer Therapy Satisfaction Questionnaire
C_{trough}	trough concentration
CV	coefficient of variation
Dara-CF	daratumumab and recombinant human hyaluronidase for subcutaneous injection: co-formulated
Dara-IV	daratumumab for intravenous infusion
Dara-MD	daratumumab and recombinant human hyaluronidase for subcutaneous injection: mix and deliver
Dara-SC	daratumumab administered subcutaneously
DRd	Dara-IV, lenalidomide, and dexamethasone
DVd	Dara-IV, bortezomib, and dexamethasone
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOT	End of Treatment
eCRF	electronic case report form
eDC	electronic data capture
EU	European Union
FEV1	forced expiratory volume in 1 second
FLC	free light chain
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
IAT	indirect antiglobulin test
ICF	informed consent form
ICH	International Council on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFE	immunofixation
IMiD	immunomodulatory drug
IMWG	International Myeloma Working Group
IRB	Institutional Review Board
IRR	infusion-related reaction
IV	intravenous
IWRS	interactive web response system
mAb	monoclonal antibody
maximum C_{trough}	serum predose concentration of daratumumab on Cycle 3 Day 1

MID	minimally important differences
modified-CTSQ	modified Cancer Therapy Satisfaction Questionnaire
M-protein	monoclonal paraprotein
MRI	magnetic resonance imaging
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NK	natural killer
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic(s)
PFS	progression-free survival
PI	proteasome inhibitor
PO	orally
PQC	Product Quality Complaint
PR	partial response
PRO	patient-reported outcome
QIg	quantitative immunoglobulin
RBC	red blood cells
Rd	lenalidomide and dexamethasone
rHuPH20	recombinant human hyaluronidase
SAC	Safety Assessment Committee
SC	subcutaneous
sCR	stringent complete response
SPEP	serum M-protein quantitation by electrophoresis
TNT	time to next therapy
ULN	upper limit of normal
UPEP	urine M-protein quantitation by electrophoresis
US	United States
Vd	bortezomib and dexamethasone
VGPR	very good partial response

1. INTRODUCTION

1.1. Multiple Myeloma

Multiple myeloma is a mostly incurable malignant plasma cell disorder diagnosed annually in approximately 86,000 patients worldwide (Becker 2011)[2]. Treatment choices for multiple myeloma vary with age, performance status, comorbidity, aggressiveness of the disease, and related prognostic factors (Palumbo 2011[20]). Current treatments include combination chemotherapy, proteasome inhibitors (PIs; bortezomib [and carfilzomib in the United States]), immunomodulatory drugs (IMiDs; thalidomide, lenalidomide, and pomalidomide), high-dose chemotherapy, and stem cell support. Chemotherapy includes the use of alkylating agents (melphalan and cyclophosphamide), anthracyclines (doxorubicin), vincristine, glucocorticoids, or combinations of these agents.

Patients who are heavily pretreated or refractory to both a PI and an IMiD have a dismal prognosis, are difficult to get back into a durable remission, and have a median overall survival (OS) of only 8 to 9 months (Kumar 2012[12]; Usmani 2016[24]; Verelst 2015[25]). For patients who are refractory to at least 3 of the common PIs (bortezomib or carfilzomib) and IMiDs (lenalidomide or pomalidomide), the median OS decreases to only 5 months (Usmani 2016[24]).

1.2. Daratumumab for Intravenous Infusion

Daratumumab is a human $IgG1_{\kappa}$ monoclonal antibody (mAb) that binds with high affinity to a unique epitope on CD38. It is a targeted immunotherapy that attacks tumor cells that overexpress CD38, a transmembrane glycoprotein, in a variety of hematological malignancies including multiple myeloma. Daratumumab induces lysis of CD38-expressing tumor cells, including multiple myeloma tumor cells that were freshly isolated from patients, by a wide spectrum of mechanisms including complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC), and antibody-dependent cellular phagocytosis (ADCP), through activation of complement proteins, natural killer (NK) cells, and macrophages, respectively (de Weers 2011[6]; Overdijk 2015[19]).

In the US, intravenously (IV) administered daratumumab (Dara-IV) is indicated for use as follows: (1) in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy; (2) as monotherapy, for the treatment of patients with multiple myeloma who have received at least 3 prior lines of therapy including a PI and an IMiD, or whose disease is refractory to both a PI and an IMiD. In the EU, Dara-IV is indicated for use as follows: (1) as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a PI and an IMiD and who have demonstrated disease progression on the last therapy; (2) in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.

For the most comprehensive nonclinical and clinical information regarding daratumumab, refer to the latest version of the Investigator's Brochure (IB Daratumumab[10]). The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

1.2.1. Clinical Studies

1.2.1.1. Single-agent Studies

Preliminary data as of 30 Jun 2016 from 2 ongoing clinical studies (GEN501 and 54767414MMY2002 [hereafter referred to as MMY2002]) and 1 completed clinical study (54767414MMY1002 [hereafter referred to as MMY1002]) are summarized below. For further details and the most up-to-date information about single-agent studies, please refer to the Investigator's Brochure (IB Daratumumab[10]).

Dara-IV as monotherapy induces deep and durable responses in subjects with heavily pretreated multiple myeloma. Phase 2 Study MMY2002 and Phase 1/2 Study GEN501 Part 2 (Part 1 was the dose-escalation phase of this first-in-human study) are ongoing single-arm, open-label studies in which subjects with relapsed and refractory multiple myeloma are administered Dara-IV as monotherapy weekly for 8 weeks, every 2 weeks for an additional 16 weeks, and every 4 weeks thereafter until disease progression or unacceptable toxicity. One hundred forty-eight (148) subjects treated with Dara-IV 16 mg/kg monotherapy were included in a combined analysis of efficacy in Study GEN501 and Study MMY2002. The overall response rate (ORR) for the combined data set was 31.1% (95% confidence interval [CI], 23.7%-39.2%). Responses included 3 subjects with stringent complete response (sCR; 2.0%), 4 subjects with complete response (CR; 2.7%), 13 subjects with very good partial response (VGPR; 8.8%) and 26 subjects with partial response (PR; 17.6%). Within the individual studies, the ORR was 35.7% (95% CI, 21.6%-52.0%) in Study GEN501 and 29.2% (95% CI, 20.8%-38.9%) in Study MMY2002. After a median duration of follow-up of 20.7 months in Study MMY2002, the Kaplan-Meier based median OS was 20.1 months.

Among 156 subjects treated with Dara-IV 16 mg/kg as monotherapy in Studies GEN501, MMY2002, and MMY1002 (a single-arm, open-label Phase 1 study of pharmacokinetics and safety conducted in Japanese subjects), 6 subjects (4%) discontinued Dara-IV treatment due to a treatment emergent adverse event. Three subjects (2%) died due to treatment emergent adverse events. The most frequently reported treatment emergent adverse events were fatigue (40%), nausea (28%), anemia (28%), back pain (26%), cough (24%), neutropenia (23%), pyrexia (22%), upper respiratory tract infection (22%), and thrombocytopenia (21%). Serious adverse events were reported in 33% of subjects; the most frequently reported serious adverse events were pneumonia (6%) and pyrexia, hypercalcemia, or general physical health deterioration (3% each).

1.2.1.2. Combination Therapy Studies

Two Phase 3 studies examined the safety and efficacy of Dara-IV in combination with other therapies in the treatment of relapsed multiple myeloma:

- In Study MMY3003, subjects with multiple myeloma received Dara-IV in combination with lenalidomide and dexamethasone (DRd). At the time of the first interim analysis, treatment with DRd resulted in a 63% reduction in the risk of disease progression or death compared to the combination of lenalidomide and dexamethasone (Rd). The median progression-free survival (PFS) was not reached in the daratumumab group; median PFS was 18.4 months in the Rd group. The ORRs were 93% for the DRd group and 76% for Rd group.
- In Study MMY3004, subjects with multiple myeloma received Dara-IV in combination with bortezomib and dexamethasone (DVd). At the time of the first interim analysis, treatment with DVd showed a 61% reduction in the risk for disease progression or death compared to the combination of bortezomib and dexamethasone (Vd). The median PFS was not estimable in the DVd group; median PFS was 7.2 months, in the Vd group. The ORRs were 83% for the DVd group and 63% for the Vd group.

For further details and the most up-to-date information about combination therapy studies, please refer to the Investigator's Brochure (IB Daratumumab[10]).

1.3. Daratumumab for Subcutaneous Injection

Dara-IV infusion requires a large volume (500 mL to 1000 mL) of infusate, resulting in a median infusion time for the first infusion of 7 hours. Subsequent infusions are approximately 3 to 4 hours. To shorten the infusion time and decrease the risk of infusion-related reactions (IRRs), a technology based on a recombinant human hyaluronidase PH20 (rHuPH20) was developed to facilitate subcutaneous (SC) administration of protein therapeutics. rHuPH20 is the active ingredient of the commercial product Hylenex® recombinant (hyaluronidase human injection), which was approved for use in the US in December 2005. Daratumumab has been administered in combination with rHuPH20 in a Phase 1 study (see Section 1.3.2, Clinical Studies). In some regions, rHuPH20 is also approved in combination with protein therapeutics for SC administration, such as HyQvia (Immune globulin infusion 10% [human] with recombinant human hyaluronidase), as well as anticancer medications such as Herceptin® SC (trastuzumab) and MabThera® SC (rituximab).

1.3.1. Nonclinical Studies

rHuPH20 is a human recombinantly expressed version of hyaluronidase that acts locally and transiently within the SC space to increase the tissue dispersion and absorption of injected drugs and fluids. rHuPH20 de-polymerizes the gel-like hyaluronan, resulting in decreased resistance to fluid flow and a transient increase in the permeability of the local SC tissue.

In a single-dose rabbit local tolerance study, male New Zealand White rabbits (n=6/group) received 14 mL SC infusions of rHuPH20 (200 or 1000 U/mL) in an aqueous solution of 25 mM sodium acetate, 60 mM NaCl, 140 mM mannitol, 0.04% polysorbate 20 at pH 5.5, alone or in combination with daratumumab (20 mg/mL) at an infusion rate of 5 mL/min. There was no mortality. Clinical signs consisting of barely perceptible erythema, flaking, and purple

discolorations at the injection site were observed in all groups. Dosing with rHuPH20 (at 200 or 1000 U/mL) in combination with daratumumab (20 mg/mL) had no effect on body weight, body weight gain, food consumption, dermal scoring, or body temperature compared to rHuPH20 alone. There were no daratumumab related macroscopic or microscopic findings.

1.3.2. Clinical Studies

Study MMY1004 is an ongoing, open-label, dose-escalation, Phase 1b study to assess the safety and pharmacokinetics of SC delivery of daratumumab. In Part 1 of this study, a mix-and-deliver SC presentation (Dara-MD) of the currently approved daratumumab IV formulation was used: rHuPH20 and daratumumab were mixed just prior to delivery. Up to 90 mL of Dara-MD was administered SC weekly for 8 weeks, every 2 weeks for 16 weeks, and then every 4 weeks thereafter. Preliminary data from this study show that SC administration is feasible and has a substantially shortened administration time compared with standard IV administration. Fifty-three subjects who received Dara-MD (1200 mg [n=8]; 1800 mg [n=45]) between November 2015 and August 2016 were evaluable for safety and efficacy. Treatment-emergent adverse events for Dara-MD in this study appeared to be similar to those reported in single-agent studies of Dara-IV (Lokhorst 2015; Lonial 2016).[14,15] After a median treatment duration of 2.6 months (range 0.7-12) for the 1200 mg cohort and 3.4 months (range 0.7-8.6) for the 1800 mg cohort, the key safety findings are as follows:

- The incidence of all-grade IRRs was 13% and 24% in the Dara-MD 1200 mg and 1800 mg cohorts, respectively. By comparison, IRRs were reported in approximately half of the subjects in single-agent studies of Dara-IV.
  - IRRs were mostly Grade 1 or 2. One subject in the Dara-MD 1200 mg cohort developed a Grade 3 IRR.
  - All IRRs developed during or within 6 hours of the start of the first SC administration and did not result in treatment discontinuation. No IRRs were reported on subsequent SC administrations.
- Local injection site reactions: SC administration of Dara-MD in the abdominal SC tissue was generally well tolerated with observations including induration and erythema, and which usually resolved within 60 minutes after the end of the infusion. Postinfusion erythema was reported in 34% of subjects (1200 mg: 63%; 1800 mg: 29%) and postinfusion induration at the injection site was observed in 26% of subjects (1200 mg; 50%; 1800 mg: 22%).
- The most frequently reported treatment-emergent adverse events (≥20% of all subjects) with Dara-MD were anemia (1200 mg: 25%; 1800 mg: 31%), thrombocytopenia (1200 mg: 38%; 1800 mg:18%), fatigue (1200 mg: 25%; 1800 mg: 20%) and pyrexia (1200 mg: 25%; 1800 mg: 22%). These events were reported with similar incidences in single-agent studies of Dara-IV 16 mg/kg.
- Grade 3 or 4 treatment-emergent adverse events were reported in 63% and 40% of subjects in the 1200 mg and 1800 mg cohorts, respectively. By comparison, Grade 3 or 4 treatment-emergent adverse events were reported in 56% of subjects in single-agent studies of Dara-IV 16 mg/kg.

- Serious adverse events were reported in 50% and 22% of subjects in the 1200 mg and 1800 mg cohorts, respectively. By comparison, serious adverse events were reported in 33% of subjects in single-agent studies of Dara-IV 16 mg/kg.
- There were no treatment-related deaths.

In the Dara-MD 1200 mg cohort, the ORR was 25% (95% CI: 3-65%), both PRs. In the Dara-MD 1800 mg cohorts, 17 responses were observed for an ORR of 38% (95% CI: 24-54%). One subject had sCR (2%), 3 subjects (7%) had VGPR, and 13 subjects (29%) had PR. The median time to first response was 4 weeks (range, 4-8). For further details and the most up-to-date information about Study MMY1004, refer to the Investigator's Brochure (IB Daratumumab[10]).

1.4. Overall Rationale for the Study

The final SC daratumumab formulation intended for commercial use will be a co-formulated drug product for fixed-dose administration, containing rHuPH20 drug substance (2000 U/mL) and daratumumab drug substance (120 mg/mL) in a single vial (approximately 15 mL). This co-formulated drug product (Dara-CF) was selected for Part 2 of Study MMY1004 to confirm the safety and pharmacokinetics of the 1800 mg dose recommended for this Phase 3 study. Hereafter, Dara-CF will be referred to as Dara-SC.

As described in Section 1.2.1.1, Single-agent Studies, Dara-IV, administered as monotherapy, induces deep and durable responses in subjects with heavily pretreated multiple myeloma. In clinical studies, a low number of subjects discontinued Dara-IV treatment due to a treatment-emergent adverse event, there was a low number of deaths due to treatment-emergent adverse events, and use of hematopoietic growth factors (ie, G-CSF) was relatively infrequent. Approximately half of the subjects receiving Dara-IV experience IRRs (mostly Grade 1 and 2). Most IRRs (>90%) occur during the first infusion. The median infusion time for Dara-IV administration is 7 hours for the first infusion and 3 to 4 hours for subsequent infusions.

Several other protein therapeutics are approved for SC administration in combination with rHuPH20. This study will investigate the efficacy and safety of SC administration of Dara-SC. Study MMY1004 provided preliminary evidence of local tolerance for SC administration of Dara-MD, consisting of Dara-IV mixed with rHuPH20 at the study center before administration. Preliminary efficacy data suggest that, in this patient population, SC administration of Dara-MD may enable comparable or better response rates compared with Dara-IV. Furthermore, to date, the rate of IRRs with SC administration of Dara-MD has been substantially lower than the rate reported with Dara-IV. The SC formulation of daratumumab would offer several tangible benefits for both patients and health care providers:

- Potential reduction in the incidence rate and severity of IRRs (compared with IV infusion), due to slower absorption of daratumumab into systemic circulation
- Shorter administration time (approximately 3 to 5 minutes compared with 4 to 7 hours for IV infusion)

- Reduced administration volume (SC administration of approximately 15 mL instead of 500 mL to 1000 mL IV infusion), which may be clinically meaningful for elderly patients with comorbid cardiac or renal insufficiency

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESES

2.1. Objectives and Endpoints

2.1.1. Objectives

Primary Objectives

- To show that SC administration of daratumumab co-formulated with recombinant human hyaluronidase PH20 (Dara-SC) is non-inferior to IV administration of daratumumab (Dara-IV) in terms of the ORR
- To show that Dara-SC is non-inferior to Dara-IV in terms of the maximum trough concentration (C_{trough})

Secondary Objectives

- To assess the pharmacokinetics and immunogenicity of Dara-SC and Dara-IV
- To evaluate the safety of Dara-SC and Dara-IV
- To evaluate the clinical benefit of Dara-SC and Dara-IV
- To evaluate the immunogenicity of rHuPH20 following Dara-SC administration
- To evaluate patient-reported satisfaction with Dara-SC and Dara-IV

2.1.2. Endpoints

Primary Endpoints

The co-primary endpoints of this study are:

- ORR, defined as the proportion of subjects with a PR or better according to the International Myeloma Working Group (IMWG) response criteria
- Maximum C_{trough}, defined as the serum predose concentration of daratumumab on Cycle 3 Day 1

Secondary Endpoints

- Rate of IRRs
- PFS, defined as the time from randomization to the date of disease progression or death due to any cause, whichever occurs first
- Rate of VGPR or better, according to the IMWG response criteria
- Rate of CR or better, according to the IMWG response criteria
- Time to next therapy (TNT), defined as the time from randomization to the start of the first subsequent anti-cancer therapy

- OS, defined as the time from randomization to the date of death
- Patient-reported satisfaction with therapy, defined as the mean of responses to 7 of 9 questions in the modified Cancer Therapy Satisfaction Questionnaire (modified-CTSQ)
- Duration of response, defined as date of onset of first response until date of disease progression or death
- Time to response, defined as the time from randomization until onset of first response

Refer to Section 9, Study Evaluations for evaluations related to endpoints.

2.2. Hypothesis

The ORR and maximum C_{trough} for Dara-SC 1800 mg are not inferior to the ORR and maximum C_{trough}, respectively, for Dara-IV 16 mg/kg in subjects with multiple myeloma who have received at least 3 prior lines of therapy including a PI and an IMiD, or whose disease is refractory to both a PI and an IMiD.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

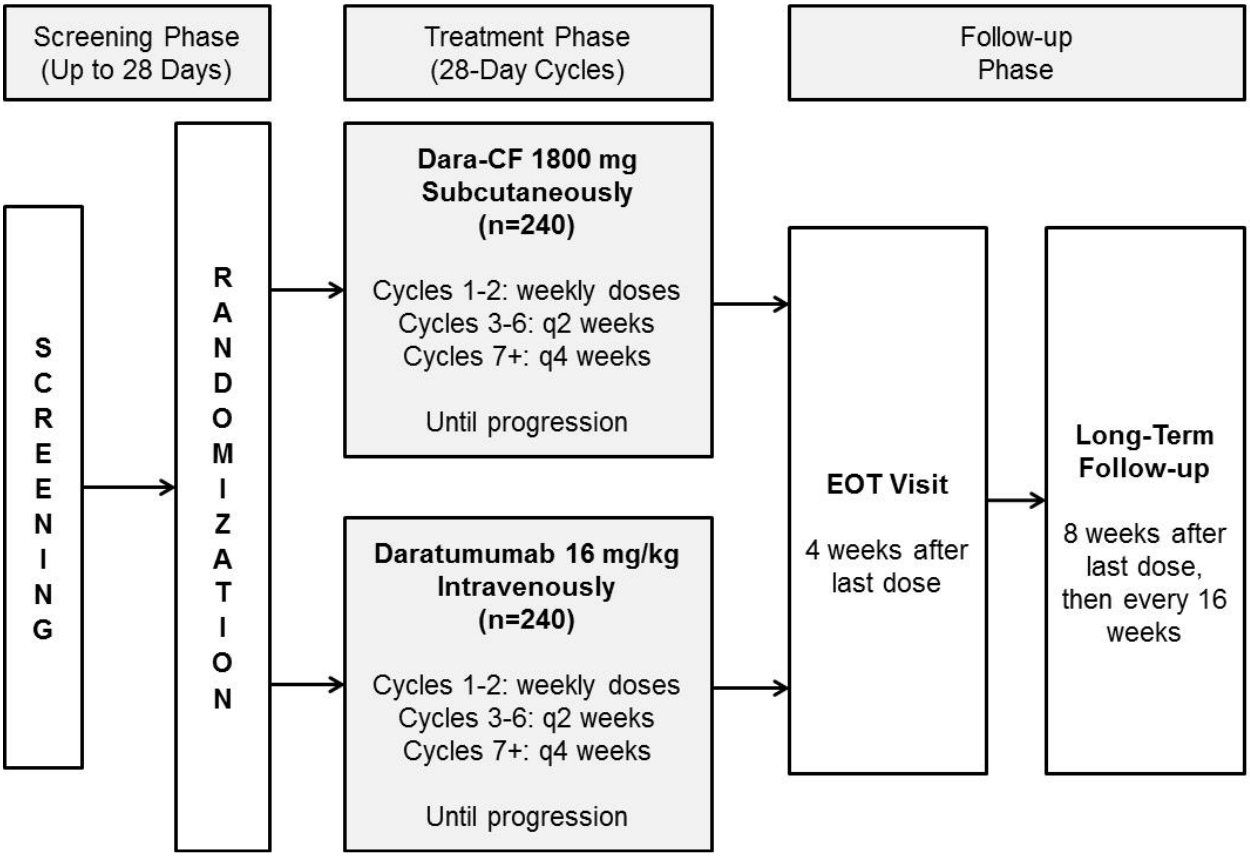
This is a Phase 3, randomized, open-label, active-controlled, multicenter study to demonstrate that the efficacy and pharmacokinetics of Dara-SC are not inferior to those for Dara-IV. The study population will consist of adults diagnosed with multiple myeloma who have received at least 3 prior lines of therapy including a PI and an IMiD, or whose disease is refractory to both a PI and an IMiD. Approximately 480 subjects will be assigned randomly to the Dara-SC group or the Dara-IV group in a 1:1 ratio. The randomization will be stratified by body weight at baseline (≤65 kg, 66 kg to 85 kg, >85 kg), number of prior lines of therapy (≤4 prior lines versus >4 prior lines), and type of myeloma (IgG versus non-IgG).

The study consists of 3 phases: a Screening Phase, a Treatment Phase, and a Follow-up Phase. A diagram of the study design is provided in Figure 1. The Screening Phase will be up to 28 days before randomization. The Treatment Phase will extend from randomization until discontinuation of study treatment. Each subject will be treated until the sponsor confirms that disease progression has occurred for that subject, the subject has unacceptable toxicity, or other reasons (refer to Section 10.1, Discontinuation of Study Treatment). The Follow-up Phase begins immediately following the End-of-Treatment Visit, and will continue until death, loss to follow up, withdrawal of consent for study participation, or end of the data collection period, whichever occurs first.

Treatment cycles are 28 days in length. The dosing schedule for both groups will be weekly for Cycles 1 and 2, every 2 weeks for Cycles 3 to 6, and every 4 weeks thereafter. Subjects who are assigned to the Dara-SC group will receive a fixed dose of Dara-SC 1800 mg (daratumumab 1800 mg co-formulated with rHuPH20 2000 U/mL). Dara-SC will be delivered by SC injection in the abdominal SC tissue in left/right locations, alternating between individual doses. All subjects in the Dara-SC group will be observed for at least 6 hours after the end of the SC injection during Cycle 1 Day 1 and, if deemed necessary by the investigator, after consecutive

injections. Subjects who are assigned to the Dara-IV group will receive Dara-IV 16 mg/kg by IV infusion pump.

Figure 1: Schematic Overview of Study Design



Assessment of disease response will be conducted in accordance with the IMWG response criteria using a computerized algorithm. Efficacy assessments will include: monoclonal paraprotein (M-protein) measurements (serum and urine), serum free light chain (FLC), examination of bone marrow aspirate, skeletal survey, documentation of extramedullary plasmacytomas, and serum calcium corrected for albumin. Safety evaluations will include adverse event monitoring, physical examinations, electrocardiogram (ECG) monitoring, SC injection site evaluations, clinical laboratory parameters (hematology and chemistry), vital sign measurements, and Eastern Cooperative Oncology Group (ECOG) performance status. The National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03 will be used to grade toxicity throughout the study. Blood samples will be drawn for assessment of pharmacokinetic and biomarker parameters. If a fresh bone marrow aspirate is collected at Screening, a portion will be sent to a central laboratory for DNA/RNA sequencing. If feasible, a bone marrow aspirate will be collected from subjects at disease progression to evaluate mechanisms of daratumumab resistance. All study evaluations will be conducted according to the Time and Events Schedule.

An Independent Data Monitoring Committee (IDMC) will review safety data at regular intervals during the study. The data cutoff for the primary analysis will occur approximately 6 months after 480 subjects have been randomized. All available data at the time of this data cutoff will be included in the Clinical Study Report. The IDMC will no longer review study data after primary analysis has been completed.

The data collection period will end, and the clinical database will be closed approximately 24 months after the last subject was randomized or when median overall survival for both arms has been reached, whichever occurs first. There will be no data collection in the eCRF after the data collection period has ended. Data collected through the end of the data collection period will be included in the final study analysis and reported in a separate Clinical Study Report.

The sponsor will ensure that subjects benefiting from treatment with either the IV or SC formulation of daratumumab are able to continue receiving the appropriate daratumumab treatment after the end of the data collection period until the applicable formulation is commercially available or available from another source, or until the study is complete.

The sponsor may decide to end the study at any time, as described in Section 17.9.2.

3.2. Study Design Rationale

Blinding, Control, Study Phase/Periods, Treatment Groups

This is a study 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 refractory to both a PI and an IMiD. The approved route of administration of daratumumab in this population is IV infusion. This study is designed to determine if the ORR and maximum C_{trough} for single-agent Dara-SC are non-inferior to the ORR and maximum C_{trough}, respectively, for single-agent Dara-IV. Therefore, important efficacy assessments will be performed symmetrically in the 2 treatment groups. Furthermore, local tolerability data will be collected from the subject and the investigator, as well as patient reported outcomes data related to the different routes of administration.

Randomization will be used to minimize bias in the assignment of subjects to treatment groups, to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. To further minimize treatment imbalance across prognostic groups, subjects will be stratified based on body weight at baseline (≤65 kg, 66 kg to 85 kg, >85 kg), number of prior lines of therapy (≤4 prior lines versus >4 prior lines), and type of myeloma (IgG versus non-IgG).

Rationale for Co-primary Endpoints

ORR has been chosen as a co-primary endpoint for this non-inferiority study due to its direct measure of a treatment effect. It is a measure of drug anti-tumor activity and is less susceptible to the influence of disease assessment schedules or patients dropping out before disease progression. It correlates well with long-term outcomes such as PFS and OS and is a well-established surrogate endpoint in the setting of refractory disease (Food and Drug

Administration 2007).[9] ORR was the basis of the recent approval of daratumumab monotherapy, carfilzomib monotherapy, and pomalidomide in combination with dexamethasone for patients with relapsed and refractory multiple myeloma. In particular, the first 2 approvals were based on single-arm studies. Moreover, its use in non-inferiority studies is supported by precedent, as ORR was a key efficacy endpoint in other non-inferiority clinical studies conducted to study SC formulations of VELCADE (approved in US in 2012), and Herceptin and MabThera, which were recently approved in the EU.

The 60% retention will result in minimal loss of benefit in terms of observed ORR. For example, if the observed ORR for Dara-IV is 30%, then an ORR of at least 25% needs to be observed for Dara-SC. The clinical relevance of the 60% retention of ORR was justified based on the benefit/risk of Dara-SC and a strong indication of similar efficacy from early efficacy and pharmacokinetics data. Subjects enrolled into MMY2002 had a median of 5 prior lines of therapy. Outcomes for this population of patients generally are measured in months. Due to prior therapies, these patients also tend to be more frail, with lower organ reserves, compared with subjects with newly diagnosed multiple myeloma. A shorter infusion time would reduce time spent in a healthcare setting and a lower incidence of IRRs could enable them to stay on therapy longer. In addition, in the daratumumab Study MMY1004 Part 1, the ORR was 38% for 45 subjects receiving Dara-MD 1800 mg, and the maximum C_{trough} was similar or higher compared to Dara-IV, strongly suggesting similar efficacy with Dara-SC.

The maximum C_{trough} for daratumumab at Cycle 3 Day 1 (at the end of 8 weeks of weekly dosing) was shown in population pharmacokinetic and exposure-response analyses to be related to ORR in multiple myeloma. A maximum C_{trough} of 274 µg/mL was associated with 90% maximal effect on ORR and a concentration of 236 µg/mL was needed to achieve 99% model-predicted target (CD38) saturation. The pharmacokinetic goal of SC delivery is to maintain maximum C_{trough} similar to or higher than that observed with IV delivery.

Rationale for Daratumumab Subcutaneous Dose Selection

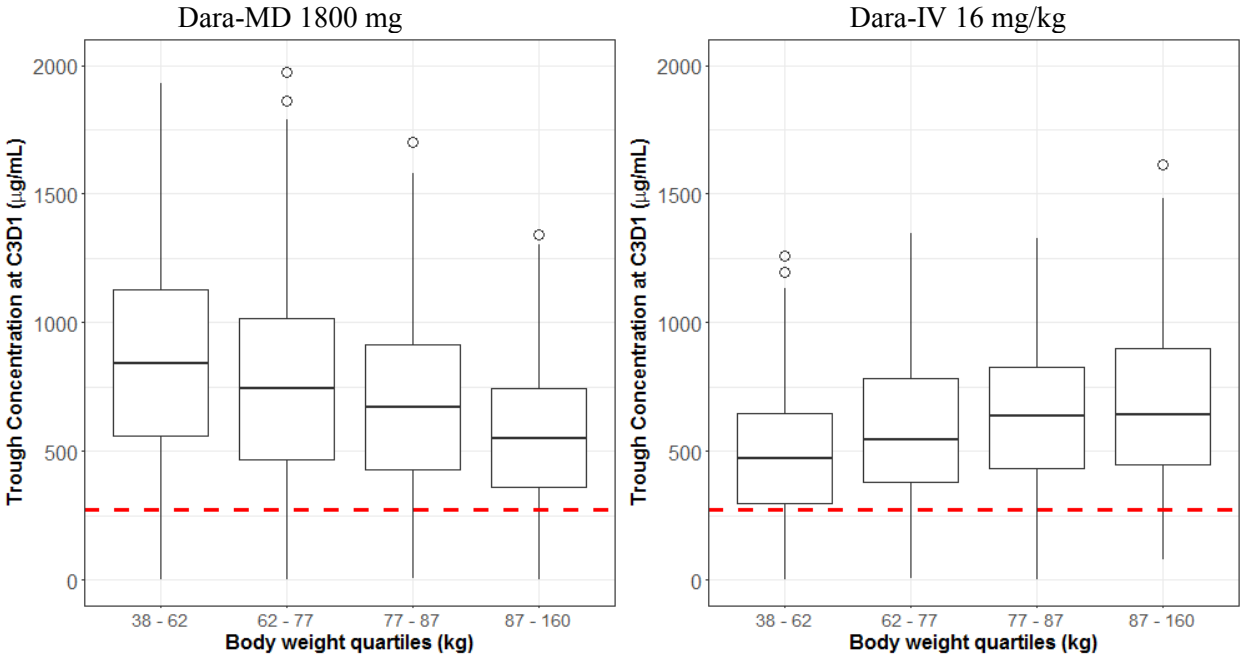
In Part 1 of Study MMY1004, starting doses of Dara-MD 1200 mg and Dara-MD 1800 mg were selected on the basis of pharmacokinetics modeling to achieve maximum C_{trough} at Cycle 3 Day 1 (at the end of weekly dosing) similar to those achieved by Dara-IV 16 mg/kg and Dara-IV 24 mg/kg, respectively, for a 75-kg person. Previously, the highest Dara-IV dose administered was 24 mg/kg. No dose-limiting toxicities were observed in the 3 subjects who received this high dose in Study GEN501. The fixed doses of Dara-MD assumed bioavailability would be 100% (ie, complete absorption). Based on emerging data from the first cohort in MMY1004, the dose was escalated to a fixed dose of Dara-MD 1800 mg. Analysis of the preliminary pharmacokinetics data indicated the 1800 mg Dara-MD dose achieved Cycle 3 Day 1 C_{trough} values comparable to or higher than those for Dara-IV 16 mg/kg.

Preliminary pharmacokinetic data for Dara-MD 1200 and 1800 mg doses in Study MMY1004 Part 1 showed a serum concentration-time curve that increased slowly and reached peak daratumumab concentrations by about 72 hours postdose. The Cycle 3 Day 1 C_{trough} was 543.90 µg/mL (coefficient of variation [CV]=44%) for Dara-MD 1200 mg (n=5) and

755.27 µg/mL (CV=51%) for Dara-MD 1800 mg (n=41). The variability in Cycle 3 Day 1 C_{trough} appeared to be similar between the Dara-IV studies (GEN501 and MMY2002) and both Dara-MD dose cohorts with %CV in the range of 44%-58% across all studies. Based on modeling, the estimated bioavailability of Dara-MD is approximately 77%. Approximately 88% of subjects dosed with Dara-MD 1800 mg would be expected to achieve the effective maximum C_{trough} of 274 µg/mL (the serum daratumumab concentration associated with 90% maximal effect on ORR in monotherapy studies), whereas only 73% of subjects dosed with Dara-MD 1200 mg would achieve the effective maximum C_{trough}. With a Dara-IV 16 mg/kg dose, approximately 80% of subjects achieve the effective maximum C_{trough}.

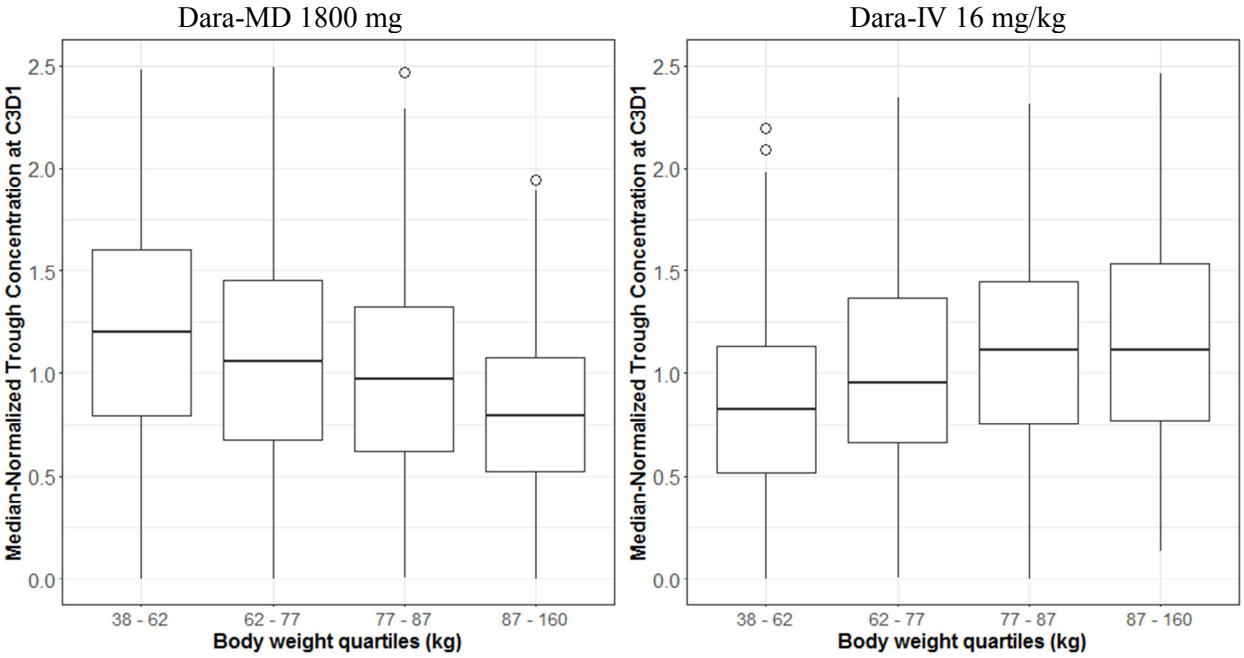
The body weight range in Part 1 of Study MMY1004 was 48 to 133 kg, which was similar to that in Dara-IV studies (MMY2002 and GEN501, 38.4 to 160.2 kg). The preliminary C_{trough} data from Cycle 3 Day 1 for the Dara-MD 1800 mg dose were assessed across a range of simulated body weights and compared with the body-weight based Dara-IV dosing. Across the quartiles of weights for the simulated patients (n=1000), similar exposure was predicted for each dosing approach (either Dara-MD 1800 mg or Dara-IV 16 mg/kg) (Figure 2). Furthermore, the variability in the exposure for Dara-MD 1800 mg in all weight quartiles was predicted to be similar compared to that for Dara-IV 16 mg/kg. The fixed Dara-MD 1800 mg dose appeared to produce a median concentration that was close to the overall population median concentration, with a ratio of approximately 1 in each weight quartile (Figure 3). Based on these simulations and observations in the ongoing MMY1004 study, fixed dosing for SC administration is a feasible approach and will be used in this study. Dara-IV exhibits a wide therapeutic window and there is no apparent relationship between drug exposure in the therapeutic dose range and adverse events of interest, which also supports the feasibility of utilizing a fixed dose approach in SC administration.

Figure 2: Predicted Maximal Trough Concentrations at Cycle 3 Day 1 for Dara-MD 1800 mg (subcutaneous administration) and Dara-IV 16 mg/kg (intravenous administration)



Dashed line is the effective concentration of 274 µg/mL.
C3D1=Cycle 3 Day 1.

Figure 3: Predicted Median-normalized Maximal Trough Concentrations at Cycle 3 Day 1 (ratio of trough concentrations and median trough concentration for overall population at each dose) for Dara-MD 1800 mg (subcutaneous administration) and Dara-IV 16 mg/kg (intravenous administration)



C3D1=Cycle 3 Day 1.
Ideal trough concentration is 1.0.

In this study, the concentration of rHuPH20 in Dara-SC will be 2000 U/mL. Products approved for commercial use, such as Herceptin SC (trastuzumab) and MabThera SC (rituximab), also contain 2000 U/mL of rHuPH20. Two studies in minipigs support the use of this concentration of rHuPH20 in Dara-SC. In the first study, 20 mg/mL of human IgG in daratumumab formulation buffer was formulated with 200, 500, or 800 U/mL of rHuPH20 and infused SC into the abdomen of sedated animals at a rate of 2 or 4 mL/min using a syringe pump. The higher infusion rate (4 mL/min) resulted in less local swelling and erythema. Erythema, when present, was mild and subsided by the next day. Infusion pressures were similar for all concentrations of rHuPH20 at both infusion rates (~40 to 60 mmHg or 1 PSI). The second study evaluated 100 mg/mL daratumumab formulated with 50, 500, 2000, or 5000 U/mL of rHuPH20. Sixteen (16) mL of each formulation was infused SC into the abdomen of sedated animals at a rate of 3 mL/minute. Infusion pressures showed a dose-dependent trend where pressures were reduced as the concentration of rHuPH20 increased. Formulations with ≥500 U/mL of rHuPH20 showed relatively small areas of local swelling that was mainly soft to the touch with mild to no erythema. These all resolved by the following day, with many resolving within an hour.

Rationale for Pharmacokinetics and Immunogenicity Assessments

Data obtained from this study will provide information about the pharmacokinetic profile of Dara-SC, as well as additional information about the pharmacokinetic profile of Dara-IV, in subjects with multiple myeloma. Therefore, samples will be obtained from all subjects for pharmacokinetic assessments. Data may also be used for a population pharmacokinetic analysis to estimate additional pharmacokinetic parameters and provide information about the determinants of inter-subject variability in this population.

Immunogenicity to daratumumab or rHuPH20 is possible. Therefore, the presence of antibodies to daratumumab (immunogenicity) will be determined from pharmacokinetic serum samples collected from all subjects and the presence of antibodies to rHuPH20 (immunogenicity) will be determined from plasma samples collected from subjects who receive Dara-SC.

Rationale for Biomarker Evaluations

Biomarker studies are designed to evaluate if there are any differences with Dara-SC and Dara-IV on daratumumab pharmacodynamic and mechanism of action biomarkers. These studies may also identify markers predictive of response or resistance to daratumumab. Biomarker samples will be collected to evaluate contributions to daratumumab response including but not limited to myeloma cell CD38 expression, resistance markers and adaptive responses via technologies such as DNA sequencing of T-cell receptor genes. Response rates in specific molecular subgroups may also be determined by DNA/RNA sequencing of myeloma cells for assessment of risk-associated genetic modifications such as del17p, amp1q21, and t(4;14), and for identification of biomarkers of response or resistance to daratumumab. The DNA and RNA sequencing data may be used for the identification of myeloma specific neoantigens to determine if antigen-specific T-cell responses are generated. Also, in previous Dara-IV studies of subjects with multiple myeloma, NK cell counts were reduced significantly following the first dose of Dara-IV and maintained at low levels on therapy while other immune cell populations were not susceptible to decreases. Therefore, the dynamics of immune cell populations may be examined

to determine whether similar changes may play a role in daratumumab response and development of resistance. Additional phenotypic and functional profiling may be performed on blood and bone marrow aspirate samples. Proteomic analysis may also be used to evaluate potential biomarkers of response and resistance.

4. SUBJECT POPULATION

Screening for eligible subjects will be performed during a 28 day period prior to randomization. The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. Prior to randomization, the sponsor will review key eligibility criteria for all subjects. Eligibility information will be provided to the sponsor for review prior to approval for randomization being granted by the sponsor. If the sponsor agrees that the eligibility criteria have been met, then the investigator will receive confirmation that the subject may be randomized into the study. If the sponsor considers that the eligibility criteria have not been met, then the sponsor will contact the investigator to discuss the subject. If there is a question about the inclusion or exclusion criteria below, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a subject in the study. Waivers are not allowed.

4.1. Inclusion Criteria

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

1. At least 18 years of age.
2. Criterion updated as per Amendment 1

2.1. Documented multiple myeloma as defined by the criteria below:

- Multiple myeloma diagnosis according to the IMWG diagnostic criteria (refer to Attachment 1).
- Measurable disease at Screening as defined by any of the following:
  - Serum M-protein level ≥1.0 g/dL or urine M-protein level ≥200 mg/24 hours; or
  - Light chain multiple myeloma without measurable disease in the serum or the urine: Serum immunoglobulin FLC ≥10 mg/dL and abnormal serum immunoglobulin kappa lambda FLC ratio.

3. Evidence of a response (PR or better based on investigator's determination of response by IMWG criteria) to at least 1 prior treatment regimen.
4. Relapsed or refractory disease as defined below:
   - Relapsed disease is defined as an initial response to previous treatment, followed by confirmed PD by IMWG criteria >60 days after cessation of treatment.
   - Refractory disease is defined as <25% reduction in M-protein or confirmed PD by IMWG criteria during previous treatment or ≤60 days after cessation of treatment.
5. Received at least 3 prior lines of therapy (refer to Attachment 2) including a PI (≥2 cycles or 2 months of treatment) and an IMiD (≥2 cycles or 2 months of treatment) in any order during the course of treatment (except for subjects who discontinued either of these

treatments due to a severe allergic reaction within the first 2 cycles/months). A single line of therapy may consist of 1 or more agents, and may include induction, hematopoietic stem cell transplantation, and maintenance therapy. Radiotherapy, bisphosphonate, or a single short course of corticosteroids (no more than the equivalent of dexamethasone 40 mg/day for 4 days) would not be considered prior lines of therapy.

or

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

6. ECOG Performance Status score of 0, 1, or 2 (refer to Attachment 3).
7. Pretreatment clinical laboratory values meeting the following criteria during the Screening Phase:
   a. hemoglobin ≥7.5 g/dL (≥5 mmol/L) (without prior red blood cells [RBC] transfusion within 7 days before the laboratory test; recombinant human erythropoietin use is permitted);
   b. absolute neutrophil count $\geq 1.0 \times 10^9$/L (prior growth factor support is permitted);
   c. platelet count $\geq 50 \times 10^9$/L (transfusions are not permitted within 7 days of testing to achieve this minimum platelet count);
   d. aspartate aminotransferase (AST) ≤2.5 × upper limit of normal (ULN);
   e. alanine aminotransferase (ALT) ≤2.5 × ULN;
   f. total bilirubin ≤2.0 × ULN; except in subjects with congenital bilirubinemia, such as Gilbert syndrome (in which case direct bilirubin ≤2.0 × ULN is required);
   g. estimated creatinine clearance >20 mL/min per 1.73m^2 (refer to Attachment 4);
   h. albumin-corrected serum calcium ≤14 mg/dL (≤3.5 mmol/L) or free ionized calcium ≤6.5 mg/dL (≤1.6 mmol/L) (refer to Attachment 5).
8. 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, hormonal [birth control pills, injections, hormonal patches, vaginal rings or implants] 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. Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy.
9. Women of childbearing potential must have a negative urine or serum pregnancy test at screening within 14 days prior to randomization.
10. 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. Subjects 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. Received daratumumab or other anti-CD38 therapies previously.
2. Received anti-myeloma treatment within 2 weeks or 5 pharmacokinetic half-lives of the treatment, whichever is longer, before the date of randomization. The only exception is emergency use of a short course of corticosteroids (equivalent of dexamethasone 40 mg/day for a maximum of 4 days [refer to Attachment 6]) before treatment. A list of anti-myeloma treatments with the corresponding pharmacokinetic half-lives is provided in the Site Investigational Product Procedures Manual.
3. Received autologous stem cell transplant within 12 weeks before the date of randomization, or the subject has previously received allogeneic stem cell transplant (regardless of timing).
4. Plans to undergo a stem cell transplant prior to progression of disease on this study (these subjects should not be enrolled to reduce disease burden prior to transplant).
5. Criterion updated as per Amendment 1

5.1 Criterion updated as per Amendment 2

5.2 History of malignancy (other than multiple myeloma) unless all treatment of that malignancy was completed at least 2 years before consent and the patient has no evidence of disease. Further exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or breast, or other non-invasive lesion, that in the opinion of the investigator, with concurrence with the sponsor's medical monitor, is considered cured with minimal risk of recurrence within 3 years.

6. Clinical signs of meningeal involvement of multiple myeloma.
7. Either of the following:
   a. Known chronic obstructive pulmonary disease (COPD) with a forced expiratory volume in 1 second (FEV1) is <50% of predicted normal. Note that FEV1 testing also is required for subjects suspected of having COPD and subjects must be excluded if FEV1 is <50% of predicted normal.
   b. Known moderate or severe persistent asthma, or a history of asthma within the last 2 years, or currently has uncontrolled asthma of any classification (refer to Attachment 7). (Subjects who currently have controlled intermittent asthma or controlled mild persistent asthma are allowed to participate in the study.)
8. Criterion updated as per Amendment 1

8.1 Criterion updated as per Amendment 2

8.2 Any of the following:

   a. Known to be seropositive for human immunodeficiency virus (HIV)
   b. Known to be seropositive for hepatitis B (defined by a positive test for hepatitis B surface antigen [HBsAg]). Subjects with resolved infection (ie, subjects who are positive for antibodies to hepatitis B core antigen [anti-HBc] and/or antibodies to hepatitis B surface antigen [anti-HBs]) must be screened using real-time polymerase chain reaction

(PCR) measurement of hepatitis B virus (HBV) DNA levels. Those who are PCR positive will be excluded. EXCEPTION: Subjects with serologic findings suggestive of HBV vaccination (anti-HBs positivity as the only serologic marker) AND a known history of prior HBV vaccination, do not need to be tested for HBV DNA by PCR.

c. Known to be seropositive for hepatitis C (except in the setting of a sustained virologic response [SVR], defined as aviremia at least 12 weeks after completion of antiviral therapy).

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

10. Clinically significant cardiac disease, including:

    - Myocardial infarction within 6 months before date of randomization, or unstable or uncontrolled disease/condition related to or affecting cardiac function (eg, unstable angina, congestive heart failure, New York Heart Association Class III-IV [refer to Attachment 8]).
    - Uncontrolled cardiac arrhythmia (Grade 2 or higher by NCI-CTCAE Version 4.03) or clinically significant ECG abnormalities.
    - Screening 12-lead ECG showing a baseline QT interval as corrected by Fridericia's formula >470 msec.

11. Known allergies, hypersensitivity, or intolerance to any of the study drugs, hyaluronidase, mAbs, human proteins, or their excipients (refer to daratumumab IB[10]), or known sensitivity to mammalian-derived products.

12. Plasma cell leukemia (>2.0 × 10^9/L circulating plasma cells by standard differential) or Waldenström's macroglobulinemia or POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes) or amyloidosis.

13. Known or suspected of not being able to comply with the study protocol (eg, because of alcoholism, drug dependency, or psychological disorder) or the 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 their well-being) or that could prevent, limit, or confound the protocol-specified assessments.

14. Pregnant, breast-feeding, or planning to become pregnant while enrolled in this study or within 3 months after the last dose of study drug.

15. Plans to father a child while enrolled in this study or within 3 months after the last dose of study drug.

16. Received an investigational drug (including investigational vaccines) or used an invasive investigational medical device within 4 weeks before the planned first dose of study drug (except for investigational anti-myeloma treatments, which cannot be taken within 2 weeks before Cycle 1 Day 1).

17. Major surgery within 2 weeks before randomization, or has not fully recovered from an earlier surgery, or has major surgery planned during the time the subject is expected to participate in the study or within 2 weeks after the last dose of study drug administration.

Kyphoplasty or vertebroplasty are not considered major surgery. Note: subjects with planned surgical procedures to be conducted under local anesthesia may participate. If there is a question whether a procedure is considered a major surgery, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a subject in the study.

18. Plasmapheresis within 28 days before randomization.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study drug 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, Source Documentation, describes the required documentation to support meeting the enrollment criteria. Subjects who fail to meet the inclusion criteria or who fulfill any of the exclusion criteria (ie, screen failures) may be rescreened 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 the study after rescreening must sign a new ICF and then will 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, Prohibited Therapies.

1. For women of childbearing potential, adequate contraception as specified in Section 4.1, Inclusion Criteria must continue during the Treatment Phase, during any dose interruptions, and for 3 months after the last dose of daratumumab. In addition, women must not donate ova during the study and for 3 months after the last dose of daratumumab.
2. A man who is sexually active with a woman of childbearing potential must always use a latex or synthetic condom during the study and for 3 months after discontinuing daratumumab. All men must not donate sperm during the study and for 3 months after the last dose of daratumumab.

5. TREATMENT ALLOCATION AND BLINDING

Treatment Allocation

Central randomization will be implemented in this study. Subjects will be assigned randomly to 1 of 2 treatment groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by body weight at baseline (≤65 kg, 66 kg to 85 kg, >85 kg), number of prior lines of therapy (≤4 prior lines versus >4 prior lines), and type of myeloma (IgG versus non-IgG). The interactive web response system (IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study drug kit for the subject. The requestor must use his or her own user identification and personal

identification number when contacting the IWRS, and will then give the relevant subject details to uniquely identify the subject.

6. DOSAGE AND ADMINISTRATION

In this protocol, "study drug" refers to Dara-SC or Dara-IV. The Investigational Product and Procedures Manual and Investigational Product Preparation Instructions contain detailed descriptions for preparation and administration of daratumumab and will be supplied to each pharmacy and site.

6.1. Preparation

6.1.1. Subcutaneous Preparation

In the Dara-SC group, Dara-SC will be provided as a fixed-dosed, combination drug product containing rHuPH20 drug substance (2000 U/mL) and daratumumab drug substance (120 mg/mL) in a single vial.

6.1.2. Intravenous Preparation

In the Dara-IV group, infusion solution will be prepared as a 1,000-mL (first dose) or 500-mL (second and subsequent doses) dilution of Dara-IV in sterile, pyrogen-free 0.9% NaCl.

6.2. Treatment Schedule and Administration

Each treatment cycle is 28 days. Study drug will be administered once weekly in Cycles 1 and 2, every 2 weeks in Cycles 3 to 6, and then every 4 weeks thereafter. Dosing days may be adjusted to accommodate the schedule of the site or the subject, as shown in Table 3. Tight visit windows (±1 day) are required for Day 1 in the first 3 treatment cycles because of the co-primary endpoint assessments at those visits. Changes to within-cycle dosing should not affect Day 1 of the next cycle. Subjects will continue to receive study treatment until disease progression, unacceptable toxicity, or other reasons as listed in Section 10.1, Discontinuation of Study Treatment.

Table 3: Study Drug (Dara-SC or Dara-IV) Administration Schedule

Cycle	Schedule	Day 1	Day 8	Day 15	Day 22
Cycles 1-2	Weekly	Day 1	Day 8 (±1d)	Day 15 (±1d)	Day 22 (±1d)
Cycle 3	Every 2 weeks	Day 1 (±1d)	–	Day 15 (±3d)	–
Cycles 4-6	Every 2 weeks	Day 1 (±3d)	–	Day 15 (±3d)	–
Cycles 7+	Every 4 weeks	Day 1 (±3d)	–	–	–

Every effort should be made to keep subjects on the planned dosing schedule. Refer to Section 6.5, Dose Delays and Modification for information on the management of cycle delays.

All doses will be administered at outpatient visits. Subjects will receive predose medications and postdose medications as detailed in Section 6.3, Predose and Postdose Medications.

As noted in the Time and Events Schedule, all subjects should have vital signs monitored at each dose. If a subject experiences any significant medical event, then the investigator should assess whether the subject should stay overnight for observation. If the subject has not experienced a

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

6.2.1. Subcutaneous Dosing

In the Dara-SC group, Dara-SC will be administered by SC injection at a fixed dose of 1800 mg. Doses will be administered by manual push over approximately 3-5 minutes in the abdominal SC tissue in left/right locations, alternating between individual doses. The volume of the SC solution will be 15 mL for the 1800 mg dose. Refer to the Investigational Product Preparation Instructions for additional guidance on SC administration of Dara-SC. All subjects in the Dara-SC group will be observed for at least 6 hours after the end of the SC injection during Cycle 1 Day 1 and, if deemed necessary by the investigator, after consecutive injections.

6.2.2. Intravenous Administration

In the Dara-IV group, Dara-IV 16 mg/kg will be administered by IV infusion. Each subject's dose will be calculated based on the subject's weight rounded to the nearest kilogram, but does not need to be recalculated for weight changes that are <10% from baseline. The dilution volumes, infusion rates, and increment of infusion rates for the first, second, and subsequent doses in the absence of an IRR >Grade 1 are provided in Table 4. The first infusion, with a volume of 1,000 mL, takes approximately 7 hours; the second and subsequent infusions, with volumes of 500 mL, take approximately 4 hours. The maximum infusion rate for all infusions is 200 mL/hour.

Refer to the Investigational Product Preparation Instructions for additional guidance on IV administration of daratumumab.

Table 4: Dara-IV Intravenous Infusion Rates

	Dilution Volume	Initial Infusion Rate (first hour)	Rate Increment[a]	Maximum Infusion Rate
First infusion	1000 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Second infusion[b]	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Subsequent infusions[c]	500 mL	100 mL/hour	50 mL/hour every hour	200 mL/hour

[a] Consider incremental escalation of the infusion rate only in the absence of infusion reactions.
[b] Use a dilution volume of 500 mL only if there were no infusion reactions >Grade 1 during the first 3 hours of the first infusion. Otherwise, continue to use a dilution volume of 1000 mL and instructions for the first infusion.
[c] Use a modified initial rate after the second infusion only if there were no infusion reactions >Grade 1 during a final infusion rate of ≥100 mL/hr in the first two infusions. Otherwise, continue to use instructions for the second infusion.

6.3. Predose and Postdose Medications

6.3.1. Predose Medications

In an effort to prevent IRRs, all subjects will start the following medications approximately 1 to 3 hours prior to each study drug administration (1 hour prior to study drug administration is preferred):

- An antipyretic: paracetamol (acetaminophen) 650-1000 mg IV or orally (PO)
- An antihistamine: diphenhydramine 25-50 mg IV or PO, or equivalent. Avoid the use of IV promethazine. (See Attachment 9 for a list of antihistamines that may be used)
- A corticosteroid: methylprednisolone 100 mg IV or PO or equivalent for the first 2 doses and 60 mg for all subsequent doses (in the absence of IRR adverse events in the first 2 doses). Substitutions for methylprednisolone are allowed (refer to Attachment 6).

Predose administration of a leukotriene inhibitor (montelukast 10 mg PO, or equivalent) is optional on Cycle 1 Day 1. If necessary, all PO predose medications may be administered outside of the clinic on the day of study drug administration, provided they are started within 1 to 3 hours before study drug administration.

6.3.2. Postdose Medications

In an effort to prevent delayed IRRs, all subjects will receive a long- or intermediate-acting corticosteroid (20 mg methylprednisolone PO or IV or equivalent [refer to Attachment 6], in accordance with local standards) on the 2 days following each study drug administration (beginning the day after study drug administration). In the absence of IRR adverse events after the first 3 doses, postdose corticosteroids should be administered per investigator discretion.

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

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

In addition, these at-risk subjects may be hospitalized for monitoring for up to 2 nights after study drug administration. If these at-risk subjects are hospitalized, then their FEV1 should be measured before discharge. If these subjects are not hospitalized, then a follow-up telephone call should be made to monitor their condition within 48 hours after each study drug administration. If the subject has not experienced a significant medical event but is hospitalized overnight only for observation, then the hospitalization should not be reported as a serious adverse event. Investigators may prescribe bronchodilators, antihistamines, and corticosteroids that are deemed necessary to provide adequate supportive care in the event a bronchospasm occurs after subjects

are released from the hospital/clinic. If an at-risk subject experiences no major IRRs, then these postdose medications may be waived after 4 doses at the investigator's discretion.

6.4. Management of Injection-site and Infusion-related Reactions

6.4.1. Local Injection-site Reactions

In Study MMY1004 Part 1, SC administration of Dara-MD in abdominal SC tissue was associated with local injection-site reactions such as induration and erythema in some subjects. The reactions usually resolved within 60 minutes. Injection-site reactions should be managed per institutional standards.

6.4.2. Infusion-related Reactions

Subjects should be observed carefully during study drug administrations. Trained study staff at the clinic should be prepared to intervene in case of any IRRs, and resources necessary for resuscitation (eg, agents such as epinephrine and aerosolized bronchodilator, also medical equipment such as oxygen tanks, tracheostomy equipment, and a defibrillator) must be available at the bedside.

If an IRR develops, then the infusion or injection should be temporarily interrupted or slowed down. Subjects who experience adverse events during the infusion must be treated for their symptoms. Subjects should be treated with acetaminophen, antihistamine, or corticosteroids as needed. 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 IRR (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. In case of interruption of the administration of the study drug due to an adverse event related to the study drug, the investigator/study coordinator should review the information of the dispensed study drug on the Investigational Product Preparation Form and ensure the correct drug product is being used before restarting the administration.

If an infusion/injection is paused or the infusion rate is decreased, then a longer-than-anticipated infusion/injection time may occur. Overnight stays at the hospital because of slow infusion/injection times should not be reported as serious adverse events. However, if the underlying cause of the delayed infusion/injection time is an adverse event or serious adverse event, then that should be reported as such.

Infusion-Related Reactions of Grade 1 or Grade 2

If the investigator assesses a Grade 1-2 IRR adverse event to be related to administration of study drug, then the Dara-IV infusion or Dara-SC injection should be paused. Once IRR symptoms resolve and the subject's condition is stable, the Dara-IV infusion or Dara-SC injection may be restarted at the investigator's discretion. Upon restart of Dara-IV infusion, the infusion rate should be half of that employed before the interruption. If the subject does not experience any

further IRR symptoms, infusion rate escalation may resume at increments and intervals as clinically appropriate up to the maximum rate of 200 mL/hour (Table 4).

If the subject experiences a Grade 2 or higher event of laryngeal edema, or a Grade 2 or higher event of bronchospasm that does not respond to systemic therapy and does not resolve within 6 hours from onset, then the subject must be withdrawn from daratumumab treatment.

Infusion-Related Reactions of Grade 3 or Higher

For IRR adverse events that are Grade 4, the Dara-IV infusion or Dara-SC injection must be stopped and the subject withdrawn from daratumumab treatment.

For IRR adverse events that are Grade 3, the Dara-IV infusion or Dara-SC injection must be stopped and the subject must be observed carefully. Once reaction symptoms resolve, if continuing treatment is deemed appropriate by the investigator, restart the infusion at no more than half the rate at which the reaction occurred. If the subject does not experience additional symptoms, resume infusion rate escalation at increments and intervals as outlined in Table 4. If the intensity of the adverse event returns to Grade 3 after restart of the Dara-IV infusion or Dara-SC injection, then the procedure described in this section should be repeated, or the subject may be withdrawn from treatment. Should the intensity of the adverse event increase to Grade 3 for a third time, then the subject must be withdrawn from daratumumab treatment.

6.5. Dose Delays and Modification

Dose modification of 16 mg/kg Dara-IV or 1800 mg Dara-SC (increase or decrease) is not permitted. Dose delay is the primary method for managing daratumumab-related toxicities. On the first day of each new treatment cycle and before each dose of study drug, the subject will be evaluated by the treating physician for possible toxicities that may have occurred after the previous dose(s). Toxicities are to be assessed according to NCI-CTCAE, Version 4.03. Cycle delays will be based on the toxicity experienced during the previous cycle of therapy or newly encountered on Day 1 of a cycle.

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

- Grade 4 hematologic toxicity, except for Grade 4 lymphopenia
- Grade 3 or higher thrombocytopenia with bleeding
- Febrile neutropenia
- Neutropenia with infection, of any grade
- Grade 3 or higher non-hematologic toxicities <u>with the following exceptions</u>:
  - 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
- Grade 3 pain associated with symptoms of multiple myeloma (bone/joint pain)

Study treatment should be resumed when the toxicity has resolved to ≤Grade 2. If study drug administration does not commence within the prespecified window of the scheduled administration date (Table 5), 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 5: Daratumumab Administration Schedule

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

Any dose hold of more than 28 days due to toxicity will result in permanent discontinuation of daratumumab. Dose holds of more than 28 days for other reasons should be discussed with the sponsor. If a dose delay occurs, then pharmacokinetic and pharmacodynamic assessments should be performed on (or relative to, in the case of C1D4 and C3D4 PK collections in the Dara-SC group) the actual day of study drug administration, not on the original scheduled administration day.

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

A study drug dose held for more than 3 days 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 missing ≥3 consecutive planned doses of study drug for reasons other than toxicity should be withdrawn from treatment, 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. Investigators should consider the applicable infusion reaction guidance provided in Section 6.4.2 when restarting treatment after a long delay.

7. TREATMENT COMPLIANCE

Study drug (Dara-IV or Dara-SC) will be administered by qualified site staff, and the details of each administration will be recorded in the electronic case report form (eCRF). Additional details are provided in the Investigational Product and Procedures Manual.

8. PRESTUDY AND CONCOMITANT THERAPY

All prestudy antineoplastic and multiple myeloma therapies must be recorded at screening. Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 8.3, Prohibited Therapies. 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 during the data collection period or until the start of subsequent anticancer 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 postinfusion systemic reactions, bisphosphonates, and any anticancer therapy (including radiation). Concomitant medications to manage adverse events and serious adverse events will be recorded as per Section 12.3, Procedures.

8.1. Recommended Therapies

8.1.1. Bisphosphonate Therapy

Bisphosphonate therapy is strongly recommended for all subjects with evidence of lytic destruction of bone or with osteopenia. Bisphosphonate therapy is recommended to be continued per treatment guidelines (NCCN 2013[17]; Moreau 2013[16]). Commercially available IV bisphosphonates (pamidronate and zoledronic acid) are preferred when available, and should be used according to the manufacturer's recommendations, as described in the prescribing information, for subjects with osteolytic or osteopenic myelomatous bone disease. Oral bisphosphonates may be used as alternatives if IV bisphosphonates are not available at the study site. Investigators should use the same route of bisphosphonate therapy for all subjects at their sites.

8.1.2. Therapy for Tumor Lysis Syndrome

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

8.1.3. Therapy for *Pneumocystis carinii/jirovecii*

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

8.1.4. Prophylaxis for Herpes Zoster Reactivation

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

8.1.5. 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), sucralfate, or H2 blockers (ranitidine or equivalent).

8.1.6. Management of Hepatitis B Virus Reactivation

Primary antiviral prophylaxis is permitted as per local standard of care. Per protocol, HBV DNA testing by PCR is mandatory for subjects at risk for HBV reactivation, see Section 9.7.

For subjects with evidence of positive HBV serology, monitor for clinical and laboratory signs of HBV reactivation during, and for at least 6 months following the end of study treatment. Manage subjects according to current clinical guidelines. Consider consulting a hepatitis disease expert as clinically indicated.

For subjects who develop reactivation of HBV while on study treatment, suspend study treatment and institute appropriate treatment for HBV or follow country-specific clinical guidelines. Resumption of study treatment in subjects whose HBV reactivation is adequately controlled should be discussed with physicians with expertise in managing HBV.

8.2. Permitted Therapies

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

- Antivirals
- Colony stimulating factors, erythropoietin, and transfusion of platelets and red cells is allowed, except as prophylaxis during Cycle 1
- Laxatives or stool softeners
- Adequate hydration is recommended for prevention of myeloma-related kidney disease.

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

8.3. Prohibited Therapies

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered. Concomitant administration of any other antineoplastic therapy for the intention of treating multiple myeloma is prohibited, including medications that target CD38, as well as medications used for other indications that have anti-myeloma properties (eg, interferon and clarithromycin). Continuation of study treatment (during or after emergency orthopedic surgery or radiotherapy because of subject benefit) may only occur in the absence of disease progression and after consultation with and approval by the sponsor.

Emergency radiotherapy may consist of localized radiotherapy for pain control or for stabilization of an extensive bone lesion at high risk of pathologic fracture or damage to surrounding tissues in a subject for whom delay of systemic therapy is not appropriate. Radiotherapy must occur within the first 2 cycles of treatment and only if disease progression has not occurred. Before radiotherapy, the sponsor will review the evidence and confirm that disease progression has not occurred.

Concomitant administration of investigational agents and of commercially available agents with activity against or under investigation for multiple myeloma are prohibited. Systemic corticosteroids (>10 mg prednisone per day or equivalent) (other than those given for IRRs as described in Section 6.3, Predose and Postdose Medications) should be avoided. Nonsteroidal anti-inflammatory agents should be avoided to prevent myeloma-related kidney disease.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedules (Table 1 and Table 2) summarize the frequency and timing of measurements applicable to this study. Every effort should be made to keep subjects on the planned study schedule. At each visit, study assessments should be completed before study treatment administration. The modified-CTSQ should be conducted and completed before any tests, procedures, or other consultations for that visit, to prevent influencing subject perceptions.

Disease evaluations must be performed every 28 days (±7days) starting from Cycle 1 Day 1. Any missed visits, tests not performed, or examinations that are not conducted must be reported as such on the eCRF. 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 maximum blood volume for a subject who completes 8 cycles and the post-treatment assessments is approximately 490 mL. The total blood volume to be collected is estimated at approximately 34 mL for Screening, 100 mL for Cycles 1 and 2, 161 mL for Cycles 3-6, 21 mL at each subsequent cycle, 55-85 mL for pharmacokinetics (depending on treatment group), 5 mL when CR is suspected or maintained, and 50 mL at the End-of-Treatment visit. 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. In the Follow-up Phase, subjects who discontinue study drug prior to PD will continue to have approximately 20 mL blood drawn every 2 months for serum disease evaluations.

Subjects benefiting from daratumumab after the data collection period has ended may continue receiving study drug (see Attachment 13).

9.1.2. Screening Phase

The Screening Phase begins when the ICF is signed. During the Screening Phase, eligibility criteria will be reviewed and a complete clinical evaluation will be performed as specified in the Time and Events Schedule. Screening procedures will be performed within 28 days before randomization, with the exceptions of disease evaluations, laboratory tests, and pregnancy tests. Serum and urine baseline disease evaluations are to be performed by the central laboratory within 14 days before randomization. It is not mandatory to collect these samples again at the Cycle 1, Day 1 visit. Results from skeletal survey and radiologic plasmacytoma assessments performed as routine follow up for subject's disease within 42 days before randomization and bone marrow aspirate/biopsy within a maximum of 42 days before randomization may be used without these tests being repeated. If the 24h collection of urine M-protein quantitation by electrophoresis (UPEP) began before informed consent was obtained as part of routine patient care, the sample can be used in this study as long as it was sent to the central lab for analysis after the informed consent was obtained. During Screening, a pregnancy test must be performed within 14 days prior to dosing. If approved by the sponsor, subjects who are screen failures may be rescreened if their condition changes (see Section 4.2, Exclusion Criteria, for details).

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

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. Subjects will be closely monitored for adverse events, laboratory abnormalities, and clinical response. Clinical evaluations and laboratory studies may be repeated more frequently, if clinically indicated. If disease progression is confirmed, then the subject will discontinue study treatment, complete the End-of-Treatment Visit, and enter the Follow-up Phase.

End-of-Treatment Visit

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

9.1.4. Follow-Up Phase

Each subject is to have a follow-up visit 8 weeks after the last dose of study treatment. Beyond 30 days after the last dose, serious adverse events considered related to study treatment will continue to be collected. For a subject who discontinues study treatment before disease progression, disease evaluations should continue to be performed as specified in the Time and Events Schedule. After disease progression is documented, survival status, subsequent anticancer treatment, response to subsequent anticancer treatment, and date of progression will be recorded. Information on all new second primary malignancies will also be collected until the end of the data collection period. If the information is obtained via telephone contact, then written documentation of the communication must be available for review in the source documents. If the subject has died, then the date and cause of death will be collected and documented on the eCRF.

Follow-up will continue until the end of the data collection period, approximately 24 months after the last subject was randomized or when median overall survival for both arms has been reached, whichever occurs first.

Continuation of Follow-up Phase study procedures is not required once the end of the data collection period is reached, and the End of Trial page of the eCRF should completed at that time for subjects ongoing in the Follow-up Phase.

9.1.5. Post Data Collection Period to End of Study

The sponsor will ensure that subjects benefiting from treatment with either the IV or SC formulation of daratumumab will be able to continue receiving treatment after the end of the data collection period until the applicable formulation is commercially available or available from another source, or until the study is complete (Section 17.9.1). Attachment 13 describes study procedures to be followed for subjects who continue treatment with study drug after the end of the data collection period.

9.2. Efficacy Evaluations

9.2.1. Response Categories

Disease evaluations must be performed every 28 days (±7days), regardless of any changes to the dosing regimen, until disease progression. Disease evaluations will be performed by a central laboratory (unless otherwise specified). This study will use the IMWG consensus recommendations for multiple myeloma treatment response criteria (Durie 2006[7]; Kumar 2016[11]; Rajkumar 2011[22]) presented in Table 6. For quantitative immunoglobulin (QIg), M-protein, and immunofixation measurements in serum and 24 hour urine, the investigator will use results provided by the central laboratory. For subjects with light chain multiple myeloma, only serum FLC assay will be performed routinely. Otherwise, serum FLC assay test results will be analyzed by the central laboratory only for the assessment of sCR. For subjects with suspected daratumumab interference on serum M-protein quantitation by electrophoresis (SPEP) and immunofixation, a reflex assay will be performed (Attachment 10). Subjects with confirmed daratumumab interference who meet all other clinical criteria for CR or sCR will be considered CR/sCR.

Table 6: 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 • If serum and urine M-protein are not measurable, and serum free light assay is also not measurable, ≥50% reduction in bone marrow PCs is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥30% • In addition to the above criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required.
Minimal response (MR)	• ≥25% but ≤49% reduction of serum M-protein, *and* • Reduction in 24-h urine M-protein by 50–89% • In addition to the above criteria, if present at baseline, a 25% to 49% reduction in the size of soft tissue plasmacytomas also is required
Stable disease (SD)	• Not meeting criteria for CR, VGPR, PR, MR, or PD
Progressive disease (PD)[†]	• Increase of 25% from lowest response value in any one of the following: • Serum M-component (absolute increase must be ≥0.5 g/dL), • Urine M-component (absolute increase must be ≥200 mg/24 hours), • Only in subjects without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL) • Only in subjects without measurable serum and urine M-protein levels and without measurable disease by FLC levels, bone marrow PC percentage (absolute percentage must be ≥10%) • Bone marrow plasma cell percentage: the absolute percentage must be >10% • Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas • Development of hypercalcemia (corrected serum calcium >11.5 mg/dL) that can be attributed solely to the PC proliferative disorder

Table 6: International Uniform Response Criteria Consensus Recommendations

Response	Response Criteria
CR=complete response; FLC=free light chain; IMWG=International Myeloma Working Group; M-protein=monoclonal paraprotein; MR=minimal response; PC=plasma cell; PD=progressive disease; PR=partial response; sCR=stringent complete response; SD=stable disease; VGPR=very good partial response All response categories (CR, sCR, VGPR, PR, and PD) require 2 consecutive assessments made at any time before the institution of any new therapy; CR, sCR, VGPR, PR, and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable on serum, urine, both, or neither. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. For PD, serum M-component increases of more than or equal to 1 g/dL are sufficient to define relapse if starting M-component is ≥5 g/dL. * Clarifications to IMWG criteria for coding CR and VGPR in subjects in whom the only measurable disease is by serum FLC levels: CR in such subjects indicates a normal FLC ratio of 0.26 to 1.65 in addition to CR criteria listed above. VGPR in such subjects requires a >90% decrease in the difference between involved and uninvolved FLC levels. † Clarifications to IMWG criteria for coding PD: Bone marrow criteria for PD are to be used only in subjects without measurable disease by M protein and by FLC levels; "25% increase" refers to M protein, FLC, and bone marrow results, and does not refer to bone lesions, soft tissue plasmacytomas, or hypercalcemia and the "lowest response value" does not need to be a confirmed value. [a] Presence/absence of clonal cells is based upon the kappa/lambda ratio. An abnormal kappa/lambda ratio by immunohistochemistry or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is kappa/lambda of >4:1 or <1:2. **Clinical Relapse** Clinical relapse is defined using the definition of clinical relapse in IMWG criteria (Durie 2006[7]; Kumar 2016[11]; Rajkumar 2011[22]). In IMWG criteria, clinical relapse is defined as requiring one or more of the following direct indicators of increasing disease or end-organ dysfunction that are considered related to the underlying plasma cell proliferative disorder: 1. Development of new soft tissue plasmacytomas or bone lesions on skeletal survey, magnetic resonance imaging, or other imaging 2. Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion 3. Hypercalcemia (>11.5 mg/dL; >2.875mM/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.	

M-protein levels need to meet the definition of disease progression (see Table 6) for subjects to have disease progression. Disease evaluations will continue beyond relapse from CR until disease progression is confirmed.

Disease progression must be consistently documented across clinical study sites using the criteria in Table 6. It is important that instances of disease progression be reported to the sponsor as soon as possible. Diagnosis and documentation of disease progression will be reported to the sponsor within 24 hours of suspected disease progression. The medical monitor will review the information to confirm that the IMWG criteria for disease progression have been met. If the medical monitor agrees that disease progression has occurred, then a confirmation will be returned to the investigator, and the subject will be withdrawn from study treatment. If the medical monitor considers that the IMWG criteria for disease progression have not been met, then the medical monitor will contact the investigator to discuss the subject.

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

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

Refer to Attachment 13 details on efficacy evaluations after the end of the data collection period.

9.2.2. Myeloma Protein Measurements in Serum and Urine

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

- Serum QIgs: All subjects will be evaluated for IgG, IgA, IgM, IgE, and IgD at Screening. During the study, 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 quantification by electrophoresis (SPEP)
- Serum immunofixation at Screening and thereafter when a CR is suspected. If daratumumab interference is suspected based on SPEP and immunofixation (IFE) results, additional reflex IFE testing may be performed.
- Serum FLC assay
- 24-hour UPEP
- Urine immunofixation at Screening and thereafter when a CR is suspected

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

Subjects with a urine M-protein on UPEP ≥100 mg/24h at Screening will provide samples for UPEP assessment on the same schedule as SPEP throughout the study according to the Time & Events Schedule. Subjects can stop collecting samples for UPEP assessments after C1D1 only if 1) they have urine M-protein <100 mg/24h at Screening, or 2) they have measurable urine M-protein ≥100 mg/24h at Screening but then urine M-protein <100 mg/24h at 2 consecutive post-baseline measurements. A urine sample for UPEP assessment should be obtained to document VGPR, CR, and sCR and at suspected disease progression for all subjects with measurable

disease by SPEP or UPEP (non-FLC), regardless of UPEP collection exemptions as described above.

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

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

9.2.3. Serum Calcium Corrected for Albumin

Blood samples for calculating serum calcium corrected for albumin will be collected as specified in the Time and Events Schedule and analyzed centrally until the development of confirmed disease progression. Development of hypercalcemia (corrected serum calcium >11.5 mg/dL or 2.8 mmol/L) can indicate disease progression or relapse if it is not attributable to any other cause (see disease response criteria in Table 6). 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 5.

When blood is analyzed at a local laboratory, measurement of free ionized calcium is an acceptable alternative to corrected serum calcium to determine hypercalcemia. Free ionized calcium levels greater than the ULN (local laboratory reference ranges) are considered to be hypercalcemic for this study.

9.2.4. β2-microglobulin and Albumin

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

9.2.5. Bone Marrow Examination

Bone marrow assessments to be performed locally and centrally are summarized in Table 7.

Table 7: Bone Marrow Testing

	Local Testing	Central Testing
Screening **Bone marrow aspirate/biopsy**	Disease characterization (morphology and either immunohistochemistry, immunofluorescence, or flow cytometry). Cytogenetics by FISH (preferred) or karyotyping.	If a fresh bone marrow aspirate is collected at Screening, a portion will be sent to a central laboratory for biomarker evaluation.
CR, sCR **Bone marrow aspirate or biopsy (or both)**	For response confirmation, additional bone marrow aspirates or biopsies (or both) will be performed locally (Disease characterization [morphology and either immunohistochemistry, immunofluorescence, or flow cytometry]) to confirm sCR or CR. For sCR: immunohistochemistry, immunofluorescence (requires kappa/lambda ratio from analysis of ≥100 cells) or 2- to 4-color flow cytometry.	
Disease Progression **Bone marrow aspirate or biopsy (or both)**	Not applicable	If feasible, a bone marrow aspirate may be collected from subjects **at disease progression** to evaluate mechanisms of daratumumab resistance.

CR=complete response; FISH=fluorescence in situ hybridization; sCR=stringent complete response

9.2.6. Assessment of Lytic Bone Disease

A complete skeletal survey (including skull, entire vertebral column, pelvis, chest, humeri, femora, and any other bones for which the investigator suspects involvement by disease or the local standard of care imaging, [eg, low-dose CT]) is to be performed and evaluated at the study site during the Screening Phase. The same methodology used at Screening should be used throughout the study for comparison purposes. During the Treatment Phase and before disease progression is confirmed, x-rays should be performed to document response or progression whenever clinically indicated based on symptoms. Magnetic resonance imaging (MRI) or low-dose CT are acceptable methods for evaluation of bone disease and may be included at the discretion of the investigator (see the disease response criteria in Table 6). 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. In these cases, disease progression may be documented by skeletal survey or other radiographs, depending on the symptoms that the subject experiences. If the diagnosis of disease progression is obvious by radiographic investigations, then no repeat confirmatory x-rays are necessary. In instances where changes may be more subtle, a repeat x-ray may be needed in 1 to 3 weeks.

9.2.7. Documentation of Extramedullary Plasmacytomas

Sites of known extramedullary plasmacytomas must be documented during the Screening Phase. Clinical examination or MRI may be used to document extramedullary sites of disease. Computed tomography scan evaluations are an acceptable alternative if there is no

contraindication to the use of IV contrast. Positron emission tomography scan or ultrasound tests are not acceptable to document the size of extramedullary plasmacytomas.

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

To qualify for PR or better, the sum of products of the perpendicular diameters of the existing extramedullary plasmacytomas must have decreased by at least 50%, and new plasmacytomas must not have developed (see the disease response criteria in Table 6). To qualify for CR or better, all extramedullary plasmacytomas must have resolved. To qualify for disease progression, either the sum of products of the perpendicular diameters of the existing extramedullary plasmacytomas must have increased by at least 50% or a new plasmacytoma must have developed. In the cases where not all existing extramedullary plasmacytomas are reported, but the sum of products of the perpendicular diameters of the reported plasmacytomas have increased by at least 50%, this will also qualify as disease progression.

9.3. Pharmacokinetics and Immunogenicity

9.3.1. Evaluations

Samples to assess both the serum concentration (pharmacokinetics) of daratumumab and the generation of anti-daratumumab antibodies (immunogenicity) will be drawn from all subjects according to the Time and Events Schedule. At specified time points, venous blood samples (5 mL per sample) will be collected and the serum will be divided into 3 aliquots (1 aliquot for pharmacokinetic analysis, 1 aliquot for immunogenicity assessment [when appropriate], and 1 aliquot as a back-up).

Samples will also be collected from all subjects receiving Dara-SC to evaluate the immunogenicity of rHuPH20 according to the Time and Events Schedule. At specified time points, 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 for sample collection requirements. Collected samples must be stored under the specified and controlled conditions for the temperatures indicated in the laboratory manual. 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.

9.3.2. Analytical Procedures

Samples will be analyzed to determine concentrations of daratumumab or generation of antibodies to daratumumab or rHuPH20 using validated immunoassay methods by or under the supervision of the sponsor. For the daratumumab immunogenicity assessments, serum samples will be screened for antibodies binding to daratumumab and serum titer will also be determined

from confirmed positive samples. Other immunogenicity analyses (eg, assessment of neutralizing capabilities) may be performed to further characterize the immune responses that are generated.

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:

Maximum C_{trough}	Serum predose concentration of daratumumab on Cycle 3 Day 1
C_{max}	Maximum observed concentration
C_{min}	Minimum observed concentration

Other pharmacokinetic parameters may be calculated. The Maximum C_{trough}, C_{min}, and C_{max} will be determined based on the assigned collection timepoints. If there are sufficient data, population pharmacokinetic analysis of serum concentration-time data of daratumumab may be performed and may include data from other clinical studies. If performed, details will be provided in a population pharmacokinetic analysis plan and results of the analysis will be presented in a separate report.

9.3.4. Immunogenicity Assessments

Serum from venous blood samples collected from all subjects will be assessed for the generation of anti-daratumumab antibodies (immunogenicity) according to the Time and Events Schedule. Daratumumab concentration will be evaluated at all immunogenicity time points to ensure appropriate interpretation of immunogenicity data. When both daratumumab serum concentration and immunogenicity analyses are specified, they will be performed on aliquots from the same blood draw and no additional sampling is required. Plasma samples will be collected from all subjects receiving Dara-SC and assessed for antibodies to rHuPH20. Procedures for sample collection, preparation, identification, storage, and shipment will be provided in the laboratory manual or equivalent document.

When an IRR occurs associated with the second administration or beyond, 1 blood sample should be obtained, if possible, from subjects in the Dara-IV group for determination of antibodies to daratumumab; in the Dara-SC group, 2 blood samples should be obtained, if possible, for determination of both antibodies to daratumumab and antibodies to rHuPH20. No unscheduled samples need to be collected for IRRs associated with the first administration of daratumumab. Daratumumab serum concentration will also be determined from the daratumumab infusion reaction sample for the purpose of interpreting immunogenicity data. 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. Procedures for sample collection, preparation, identification, storage, and shipment will be provided in the Laboratory Manual or equivalent document. 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.

Subjects who discontinue treatment or withdraw from the study before confirmation of PD should have samples collected at the time of early discontinuation. Subjects who discontinue treatment will also be asked to return for immunogenicity evaluation during the Follow-up Phase. These samples will be tested by the sponsor or sponsor's designee.

9.4. Biomarkers

Samples for biomarker evaluations will be collected as specified in the Time and Events Schedule. Baseline bone marrow aspirate samples are required, if feasible, and may be subjected to DNA and RNA sequencing in order to identify multiple myeloma antigens to evaluate the generation of antigen specific immune responses, to classify subjects into high-risk molecular subgroups and to evaluate biomarkers of response and resistance to daratumumab.

In addition to planned bone marrow aspirate assessment, whole blood samples will be collected from subjects as outlined in the Time and Events Schedule for processing to plasma and peripheral blood mononuclear cells (PBMCs). These samples will be drawn from all subjects to evaluate pharmacodynamic biomarkers and to evaluate the role of the immunomodulatory mechanism of action of daratumumab in response and development of resistance. Testing may include evaluation of specific subsets of immune cells such as cytotoxic T cells, regulatory T cells, myeloid-derived suppressor cells, B cells, and NK cells. Cells may also be used for additional phenotypic and functional profiling. Previous clinical studies indicate CD8+ T cell expansion, which could be an additional mechanism for daratumumab activity. If CD8+ T cell expansion is noted in this study, then T-cell receptor sequences may be analyzed on PBMC DNA to assess clonal expansion of cytotoxic T cells. 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 and to evaluate potential biomarkers of response and resistance.

Stopping Analysis

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

9.5. Patient-reported Outcomes

The modified-CTSQ is included in the clinical study as a measure to assess patient satisfaction with daratumumab treatment, support market access and the payer request for patient-reported outcomes (PRO) data, and assess superiority of Dara-SC. The modified-CTSQ is a secondary

endpoint, not part of the statistical hierarchy. Non-inferiority will not be analyzed for this endpoint. Details on the statistical analyses will be included in the Statistical Analysis Plan.

The Cancer Therapy Satisfaction Questionnaire (CTSQ) is a 16-item PRO measure that assesses satisfaction with and preference for chemotherapy, hormonal and biological therapies based on efficacy, tolerability, and convenience. The CTSQ was developed to compare IV administration with oral medication (Abetz 2005[1]; Trask 2008[23]). Minimally important differences for the Satisfaction with Therapy domain were estimated using distribution based methods and based on known-group differences (Trask 2008[23]). Using known groups of perceived change in cancer the average difference between groups was 3.7 points and using distribution-based methods the minimally important difference was 6.88 for 0.5 standard deviation and 5.84 for 1 standard error or measure using internal consistency reliability (Trask 2008[23]).

The modified-CTSQ was adapted, with approval from the instrument developer, to contain 9 items specific to satisfaction with therapy and for comparison of IV with SC administration (Attachment 11). A domain score for Satisfaction with Therapy is calculated based on 7-items. Each item asks about the most recent cancer therapy using a 5-point verbal rating scale. The modified-CTSQ takes less than 10 minutes to complete and will be completed by the subject using paper administration.

The modified-CTSQ assesses previous administration of daratumumab, not the current visit administration. To achieve unbiased assessments, the modified-CTSQ should be administered before the subject's clinical examination, the subject receives any tests or test results, and the subject's health, health data, or emotions are discussed. The modified-CTSQ will be completed per the Time and Events Schedule until the end of the data collection period.

9.6. Medical Resource Utilization

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

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

9.7. Safety Evaluations

Details regarding the IDMC are provided in Section 11.12, Safety Data Monitoring. Safety will be measured by adverse events, physical examination findings, ECG, SC injection site evaluations, laboratory test results, vital sign measurements, and assessment of ECOG

performance status score. All toxicities will be graded according to the NCI-CTCAE Version 4.03. Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the eCRF. Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached.

Based on previous experience with daratumumab, IRRs, allergic reactions, hemolysis, and thrombocytopenia will be closely monitored. As daratumumab is a biologic agent, immunogenicity will also 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. Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the eCRF.

The study will include the following evaluations of safety and tolerability according to the time points provided in the Time and Events Schedule.

Adverse Events

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) from the time a signed and dated informed consent is obtained until at least 30 days after the last dose of study treatment during the data collection period, unless the subject withdraws consent for study participation or starts subsequent anticancer therapy. Adverse events will be followed by the investigator as specified in Section 12, Adverse Event Reporting. After the data collection period has ended, only serious adverse events will be collected, as described in Attachment 13.

Clinical Laboratory Tests

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

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

- Hematology Panel

  -hemoglobin
  -white blood cell count, absolute neutrophil count, and absolute lymphocyte count
  -platelet count

- Serum Chemistry Panel

-AST	-alkaline phosphatase
-ALT	-uric acid
-total bilirubin[a]	-blood urea nitrogen or urea
-glucose	-calcium and albumin-adjusted calcium[b]
-creatinine	-lactic acid dehydrogenase
-sodium	-potassium

[a] If Gilbert's disease, assessment of direct bilirubin.
[b] These parameters will be part of the efficacy evaluations as specified in Section 9.2.3, Serum Calcium Corrected for Albumin, and will be analyzed at a central laboratory.

Serum or Urine Pregnancy Testing

Serum or urine pregnancy testing will be performed for women of childbearing potential as specified in the Time and Events Schedule.

Indirect Antiglobulin Test (IAT)

Blood Type, Rh, and Indirect Antiglobulin Test (IAT) should be done before the first dose of daratumumab. Subject RBC phenotyping (standard or extended) is an alternative option to the IAT test, if locally required. Either method must be completed prior to first study drug administration.

Daratumumab interferes with the 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 or phenotyping) determined before the first study drug administration, along with information on the IAT interference for healthcare providers/blood banks. Subjects are to carry this card throughout the treatment period and for at least 6 months after treatment ends. Blood banks can eliminate the daratumumab interference with IAT by treating reagent RBCs with dithiothreitol (DTT) (Chapuy 2015[5]; Chapuy 2016[4]).

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

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

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

Despite daratumumab binding to CD38 on erythrocytes, no indication of clinically significant hemolysis has been observed in daratumumab studies. For additional details, refer to the daratumumab Investigator's Brochure (IB daratumumab[10]).

HBV DNA Tests

Subjects who are positive for anti-HBc or anti-HBs will undergo testing for hepatitis B DNA by PCR every 4 weeks (each cycle). Subjects who are positive for anti-HBs antibodies due to prior immunization are not required to be monitored by HBV DNA by PCR. During and following study treatment, subjects who have history of HBV infection will be closely monitored for clinical and laboratory signs of reactivation of HBV as specified in the Time and Events Schedule. Subjects with serologic findings suggestive of prior HBV vaccination (anti-HBs positivity as the only serologic marker) AND a known history of prior HBV vaccination do not need to be tested for HBV by PCR and do not need to be followed by repeat HBV PCR. Where required by local law, the result of HBV testing may be reported to the local health authorities.

Subjects benefiting from daratumumab after the data collection period has ended may continue receiving study drug, and HBV DNA testing will be performed as detailed in Attachment 13.

Pulmonary Function Test

Subjects with known or suspected COPD must have a FEV1 test during screening.

Electrocardiogram (ECG)

A 12-lead ECG will be performed as described 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 blood pressure measurement is scheduled for the same time point as ECG recording, then the procedures should be performed in the following order: ECG(s), blood pressure, blood draw.

Vital Signs

Vital signs (pulse, temperature, blood pressure) will be performed as specified in the Time and Events Schedule. It is recommended that blood pressure and pulse measurements be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

Physical Examination and ECOG Performance Status

A complete physical examination (including neurological examination) should be performed during the Screening Phase. Thereafter, only a symptom-directed physical examination is required. Height will be measured at screening only; weight will be measured on Day 1 of each treatment cycle. Abnormalities will be recorded in the appropriate section of the eCRF. ECOG performance status will be used to evaluate the effect of the disease status on the activities of daily living.

9.8. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the laboratory requisition form. Refer to the Time and Events Schedule for the timing and frequency of all sample collections. Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual 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.

After the end of the data collection period, sample collection and handling will occur as detailed in Attachment 13.

10. SUBJECT DISCONTINUATION OF STUDY TREATMENT/ WITHDRAWAL FROM THE STUDY

10.1. Discontinuation of Study Treatment

Discontinuation of Study Treatment

If a subject's study treatment must be discontinued, this will not result in automatic withdrawal of the subject from the study. The End-of-Treatment Visits and Follow-up visit assessments should continue as specified in the Time and Events Schedule.

A subject's study treatment must be discontinued if:

- The investigator believes that for safety or tolerability reasons (eg, adverse event) it is in the best interest of the subject to discontinue study treatment.
- The subject becomes pregnant unless the subject (or the subject's legally acceptable representative), investigator, and sponsor agree the benefits outweigh the risks to the fetus and continuation of study treatment is in the best interests of the subject
- The subject (or the subject's legally acceptable representative) withdraws consent for administration of study drug
- The subject experiences unacceptable toxicity, including IRRs described in Section 6.4, Management of Injection-site and Infusion-related Reactions
- The subject’s dose is held for more than 28 days, or if 3 consecutive planned doses of daratumumab are missed for reasons other than toxicity unless, upon consultation with the sponsor and the review of safety and efficacy, continuation is agreed upon
- The subject experiences disease progression (please see below); relapse from CR is not considered as disease progression
- The subject experiences a second primary malignancy that cannot be treated by surgery alone (however, a subject who develops a malignancy that can be cured surgically may continue to receive the assigned study treatment and should continue to be followed for subsequent progression of multiple myeloma)

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

Study treatment will continue until confirmation of PD. Before subjects are discontinued from study treatment because of suspected PD:

1. The investigator (or designee) will provide documentation of disease progression (for example, by completing a disease progression form or by contacting the IWRS) as soon as possible and within 48 hours of confirmation of disease progression.
2. The sponsor's medical monitor will review the provided documentation and confirm PD has occurred per IMWG criteria (see Section 9.2.1, Response Categories) and that study treatment should be discontinued.
3. After confirmation of PD by the sponsor, the subject will discontinue study treatment and enter the Follow-up Phase.

If a subject's study treatment must be discontinued, this will not result in automatic withdrawal of the subject from the study; instead, the subject will enter the Follow-up Phase. The End-of-Treatment Visit and Follow-up Visit assessments should continue as specified in the Time and Events Schedule.

10.2. 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
- Death
- Sponsor terminates 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 before completing the study, the reason for withdrawal is documented in the eCRF and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject. If subjects withdraw from the study, additional subjects will not be enrolled. If a subject discontinues study drug and withdraws from the study before the end of the Treatment Phase, End-of-Treatment assessments should be obtained. If the withdrawal from the study is withdrawal of consent then no additional assessments are allowed.

10.3. 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, Long-term Retention of Samples for Additional Future Research). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF.

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 main analysis populations are:

- Intent-to-treat population, defined as all randomized subjects
- Safety population, defined as randomized subjects who receive at least 1 dose of study agent
- Per-protocol population, defined as all treated subjects who have measurable disease at baseline and have no major protocol deviations with respect to eligibility
- Pharmacokinetic evaluable population, defined as subjects who received all 8 weekly doses of Dara-IV or Dara-SC in Cycle 1 and Cycle 2 according to the Time and Events Schedule and provide a predose pharmacokinetic sample on Cycle 3 Day 1

The intent-to-treat population will be used to summarize the study population and efficacy. The safety population will be used to summarize the safety data. The per-protocol population will be used for critical sensitivity analyses of ORR in the context of the non-inferiority design. The pharmacokinetic evaluable population will be used to summarize the maximum C_{trough}.

Descriptive statistics will be used to summarize data. For continuous parameters, number of observations, mean, standard deviation, median, and range will be used. For discrete parameters, frequency will be summarized. For time-to-event parameters, Kaplan-Meier estimates will be produced. When sample sizes are small, sample listings may be provided instead.

11.2. Sample Size Determination

In a previous clinical study (MMY2002), of 106 subjects with relapsed or refractory multiple myeloma who had received at least 3 prior therapies and who were treated with Dara-IV 16 mg/kg, an ORR of 29.2% (95% CI: 20.8%, 38.9%) was observed. Non-inferiority of Dara-SC to Dara-IV in the current study is defined using a 60% retention of the lower bound (20.8%) of the 95% CI from Study MMY2002. With a planned 1:1 randomization, 480 subjects (n=240 in the Dara-SC group and n=240 in the Dara-IV group) will be needed to demonstrate non-inferiority with a power of 80% and a one-sided alpha=0.025, assuming that the true ORR is the same for both groups. The sample size calculation is based on the methodology for the non-inferiority test for non-unity null, as described by Farrington and Manning (1990).[8]

The study is also designed to establish non-inferiority of the co-primary pharmacokinetics endpoint, maximum C_{trough}, between Dara-SC and Dara-IV. Dara-SC will be considered non-inferior to Dara-IV if the lower bound of the 90% CI for the ratio of the geometric means of C_{trough} on Cycle 3 Day 1 is at least 80% (non-inferiority margin of 20%). A one-sided test is selected based on previous analyses that demonstrated a strong relationship between maximum C_{trough} and efficacy. However, there is no apparent relationship between drug exposure in the therapeutic dose range and adverse events of interest. With the planned 1:1 randomization,

480 subjects a one-sided alpha=0.05, the power will be >95%. This assumes a true ratio of the maximum C_{trough} of 1, a non-inferiority margin of at least 80% of the geometric mean ratio, and a coefficient of variation of 0.6.

11.3. Co-primary Endpoints

1. ORR: The number and proportion of subjects who achieve PR or better will be calculated for each group. The primary analysis will use the non-inferiority test for non-unity null according to Farrington and Manning (1990).[8] The relative risk and its two-sided 95% CI will be provided. If the lower bound of the 95% CI is ≥60%, the non-inferiority of Dara-SC relative to Dara-IV will be concluded. If non-inferiority in ORR is established and the lower limit of the 95% CI of the relative risk is ≥100%, the superiority of Dara-SC relative to Dara-IV will be concluded. The primary analysis will occur approximately 6 months after 480 subjects have been randomized.
2. Maximum C_{trough} (Predose on Cycle 3 Day 1): see Section 11.5, Pharmacokinetic Analyses.

Once the null non-inferiority hypothesis is rejected for both the ORR and maximum C_{trough}, non-inferiority of Dara-SC to Dara-IV will be established and a hierarchical procedure for superiority testing will be implemented to control familywise Type I error rate at a two-sided significance level of 0.05 for secondary endpoints including incidence of IRR, PFS, rate of VGPR or better, and overall survival. The detailed procedure will be specified in the statistical analysis plan.

11.4. Secondary Endpoints

1. IRR: The proportion of subjects who have an IRR and the 95% CI will be calculated for each treatment group. The IRR rate will be compared between the 2 groups using the stratified Cochran-Mantel-Haenszel test. The Mantel-Haenszel odds ratio will be provided along with its 2-sided 95% CI.
2. PFS: The median PFS and 95% CI in each treatment group will be estimated using the Kaplan-Meier method. The PFS distributions between the 2 treatment groups will be compared using the stratified log-rank test. The treatment effect (hazard ratio) and its two-sided 95% CI will be estimated using a stratified Cox regression model with treatment as the sole explanatory variable.
3. VGPR or better: The proportion of subjects who have a VGPR or better and the 95% CI will be calculated for each treatment group. The rate of VGPR or better will be compared between the 2 treatment groups using the stratified Cochran-Mantel-Haenszel test. The Mantel-Haenszel odds ratio will be provided along with its 2-sided 95% CI.
4. CR or better: The proportion of subjects who have a CR or better and the 95% CI will be calculated for each treatment group. The rate of CR or better will be compared between the 2 treatment groups using the stratified Cochran-Mantel-Haenszel test. The Mantel-Haenszel odds ratio will be provided along with its two-sided 95% CI.
5. TNT: The median TNT and 95% CI in each treatment group will be estimated using the Kaplan-Meier method. The TNT distributions will be compared between the 2 treatment groups using the stratified log-rank test. The treatment effect (hazard ratio) and its two-sided

95% CI will be estimated using a stratified Cox regression model with treatment as the sole explanatory variable.

6. OS: The median OS and 95% CI in each treatment group will be estimated using the Kaplan-Meier method. The OS distributions will be compared between the 2 treatment groups using the stratified log-rank test. The treatment effect (hazard ratio) and its 2-sided 95% CI will be estimated using a stratified Cox regression model with treatment as the sole explanatory variable.
7. Duration of response: A descriptive summary for duration of response will be provided. No statistical comparison will be made.
8. Time to response: A descriptive summary for time to response will be provided. No statistical comparison will be made.

11.5. Pharmacokinetic Analyses

For the co-primary endpoint of maximum C_{trough}, the ratio of the geometric means and the corresponding 90% CI utilizing logarithmic transformation of maximum C_{trough} values will be provided. The 2 formulations of daratumumab will be considered similar if the lower bound of the 90% CI for the ratio of the geometric means of maximum C_{trough} is at least 80% (non-inferiority margin of 20%). Summary statistics such as the geometric mean, coefficient of variation, median, and range will be provided by treatment group.

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

Descriptive statistics will be used to summarize daratumumab serum concentrations at each sampling time point and other pharmacokinetic parameters of daratumumab: C_{min}, and C_{max}. Additional pharmacokinetic parameters, when available, will also be summarized.

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

11.6. Immunogenicity Analyses

The incidence of anti-daratumumab antibodies will be summarized for all subjects who receive at least 1 dose of Dara-SC or Dara-IV and have appropriate samples for detection of antibodies to daratumumab (ie, subjects with at least 1 sample obtained after their first dose of daratumumab). The incidence of antibodies to rHuPH20 will be summarized for all subjects who receive a dose of Dara-SC and have appropriate samples for detection of antibodies to rHuPH20. A listing of subjects who are positive for antibodies to daratumumab or rHuPH20 will be provided.

11.7. Biomarker Analyses

Biomarker studies are designed to evaluate if there are any differences with Dara-SC and Dara-IV on biomarkers for daratumumab pharmacodynamics and mechanism of action. These studies also may identify markers predictive of response or resistance to daratumumab. Analyses will be stratified by clinical covariates or molecular subgroups using the appropriate statistical methods (eg, parametric or non-parametric, univariate or multivariate, analysis of variance, or survival analysis, depending on the endpoint). Correlation of baseline expression levels or changes in expression levels with response to time-to-event endpoints will identify responsive (or resistant) subgroups in addition to genes and pathways attenuated following treatment with daratumumab.

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

11.8. Pharmacokinetic/Pharmacodynamic Analyses

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

11.9. Patient-reported Outcomes

The modified-CTSQ item scores and Satisfaction with Therapy domain score will be summarized for each time point, by treatment arm and descriptively reported. Mean Satisfaction with Therapy domain score will be compared between treatment arms at each time point.

11.10. Medical Resource Utilization Analyses

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

11.11. 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). Treatment-emergent adverse events are adverse events with onset during the Treatment Phase or that are a consequence of a pre-existing condition that has worsened since baseline. All reported adverse events will be included in the analysis. For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group. In addition, comparisons between treatment groups will be provided if appropriate.

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

Clinical Laboratory Tests

Laboratory data will be summarized for each treatment group 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). A listing of subjects with any laboratory results outside the reference ranges will be provided. A listing of subjects with any markedly abnormal laboratory results will also be provided.

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

Electrocardiogram (ECG)

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

Vital Signs

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

Physical Examination

Physical examination findings will be summarized at baseline. Descriptive statistics will be calculated. Frequency tabulations of the abnormalities will be made.

11.12. Safety Data Monitoring

An IDMC, consisting of 2 clinicians and 1 statistician, will be established to review safety data periodically. 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 Council for Harmonisation [ICH]).

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

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

Serious Adverse Event

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

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

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

If a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the study drug and the event (eg, death from anaphylaxis), the event must

be reported as a suspected unexpected serious adverse reaction (SUSAR) even if it is a component of the study endpoint (eg, all-cause mortality).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. The expectedness of an adverse event will be determined by whether or not it is listed in the daratumumab Investigator's Brochure (IB daratumumab[10]). Anticipated events will be recorded and reported as described in Attachment 12.

Adverse Event Associated With the Use of the Drug

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

12.1.2. Attribution Definitions

Not Related

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

Doubtful

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

Possible

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

Probable

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

Very Likely

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

12.1.3. Severity Criteria

The severity assessment for an adverse event or serious adverse event should be completed using NCI-CTCAE Version 4.03. Any adverse event or serious adverse event not listed in that 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 or safety evaluation include, but are not limited to:

- Overdose of a sponsor study drug
- Suspected abuse/misuse of a sponsor study drug
- Accidental or occupational exposure to a sponsor study drug
- Any failure of expected pharmacologic action (ie, lack of effect) of a sponsor study drug
- Unexpected therapeutic or clinical benefit from use of a sponsor study drug
- Medication error involving a sponsor product (with or without subject/patient exposure to the sponsor study drug, eg, name confusion)
- Exposure to a sponsor study drug from breastfeeding

Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious 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 final dose of study drug during the data collection period. The only exception is for subjects who have withdrawn informed consent for study participation or for subjects who have received additional treatment with therapeutic intent for multiple myeloma within 30 days after the final dose of Dara-IV or Dara-SC. For subjects who have received additional 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 study drug must be reported (unless the subject has been withdrawn from the study).

Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study drug, and those that are considered related to study drug within the Follow-up Phase, must be reported using the Serious Adverse Event Form

Death should not be recorded as an adverse event or serious adverse event, but as the outcome of an adverse event. The 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 12. Note: Some countries require

reporting of all adverse events to the health authorities, while others will not identify anticipated events for the health authorities.

All adverse events, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document and the 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 sponsor assumes responsibility for appropriate reporting of anticipated events to the regulatory authorities according to requirements of the countries in which the studies are conducted. The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review (ICE/IRB) that approved the protocol unless otherwise required and documented by the IRB/IEC.

The subject (or their designee, if applicable) must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

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

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:

- 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.
- A standard procedure for protocol therapy administration will not be reported as a serious adverse event. In addition, hospitalization due to a longer than anticipated infusion time. Hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as a serious adverse event.
- The administration of blood or platelet transfusions. Hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable serious adverse event.
- A procedure for protocol-related investigations (eg, scans, endoscopy, sampling for laboratory tests, bone marrow sampling, pharmacokinetic, or biomarker blood sampling). Hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable serious adverse event.

Refer to Attachment 13 for details on serious adverse event reporting after the end of the data collection period.

12.3.3. Disease-Related Events or Outcomes Not Qualifying as Adverse Events

Known consequences of the underlying disease under investigation (eg, symptoms) and events common in the study population independent of drug therapy are adverse events. If they are considered drug-related they will be recorded and reported (if appropriate) as per current legislation to Health Authorities and ECs. If they are considered disease-related or not related to the study drugs they will be exempt from expedited reporting.

12.3.4. Pregnancy

All initial reports of pregnancy in female subjects or partners of male subjects must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study treatment unless the subject (or the subject's legally acceptable representative), investigator, and sponsor agree the benefits outweigh the risks to the fetus and continuation of study treatment is in the best interests of the subject. Because the effect of the study drug on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported as noted above. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

Pregnancy reporting will continue as described above after the end of the data collection period.

12.4. Contacting Sponsor Regarding Safety

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

13. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

13.1. Procedures

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

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

13.2. Contacting Sponsor Regarding Product Quality

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

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drugs

Dara-SC

The Dara-SC 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. The study agent should be essentially free of visible particulate matter at the time of syringe preparation and drug product administration. It will be manufactured and provided under the responsibility of the sponsor. Refer to the Investigator's Brochure (IB daratumumab[10]) for a list of excipients.

Dara-IV

The Dara-IV supplied for IV infusion in this study is a colorless to yellow liquid and sterile concentrate of 20 mg/mL as a liquid vial. The study agent should be essentially free of visible particulate matter at the time of dosage preparation and drug product administration. It will be manufactured and provided under the responsibility of the sponsor.

14.2. Packaging

Dara-SC

Dara-SC is supplied in glass vials containing daratumumab at a concentration of 120 mg/mL and rHuPH20 at a concentration of 2000 U/mL (~20 µg/mL). It will be supplied to the site/pharmacy as open-label supply.

Dara-IV

Dara-IV is supplied in glass vials containing daratumumab at a concentration of 20 mg/mL. It will be supplied to the site/pharmacy as open-label supply.

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

Dara-SC

Dara-SC must be stored in the original carton in a refrigerator at controlled temperatures ranging from 2°C to 8°C until it is removed for dose preparation. Dara-SC must not be utilized after the expiry date printed on the label. Dara-SC must be protected from light and must not be frozen. The product does not contain preservatives; therefore, any unused portion remaining in the vial must be discarded. Refer to the Investigational Product Preparation Instructions for additional guidance on study drug preparation, handling, and storage.

Dara-IV

Dara-IV must be stored in the original carton in a refrigerator at controlled temperatures ranging from 2°C to 8°C until it is removed for dose preparation. Dara-IV must not be utilized after the expiry date printed on the label. Dara-IV must be protected from light and must not be frozen. Dara-IV does not contain preservatives; therefore, any unused portion remaining in the vial must be discarded. Refer to the Investigational Product Preparation Instructions for additional guidance on study drug preparation, handling, and storage.

14.5. Drug Accountability

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

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

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

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

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Investigator's Brochure for daratumumab
- Investigational Product Preparation Instructions
- Investigational Product and Procedures Manual
- Laboratory manual
- IWRS Manual
- eCRF completion guidelines
- Sample ICF
- Modified-CTSQ and PRO training materials
- Subject identification wallet card, including space for blood type and IAT result
- Subject diaries for recording predose and postdose medications that are administered at home (Section 6.3, Predose and Postdose Medications)
- Other manuals and guidance documents as needed

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

As discussed in Section 1.4, Overall Rationale for the Study, preliminary efficacy data suggest that SC administration of Dara-SC may provide comparable or better response rates compared with IV administration of Dara-IV. Additional benefits of Dara-SC compared with Dara-IV include:

- Potential reduction in the incidence rate and severity of IRRs (compared with IV infusion), due to slower absorption of daratumumab into systemic circulation
- Shorter administration time (approximately 3 to 5 minutes compared with 4 to 7 hours for IV infusion)
- Reduced administration volume (SC administration of approximately 15 mL instead of 500 mL to 1000 mL IV infusion), which may be clinically meaningful for elderly patients with comorbid cardiac or renal insufficiency

The primary safety profile of Dara-IV is consistent with IRRs; see Section 6.3, Predose and Postdose Medications, 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 study drug 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.

In a previous study with SC administration of daratumumab (MMY1004), a lower incidence of IRRs was observed compared to IRR rate reported from studies with IV administration of daratumumab. However, IRRs may still occur and may develop at a later time point than previously observed with IV administration due to the more gradual absorption. Subjects will therefore be observed for at least 6 hours on their first day of SC daratumumab administration. Apart from IRRs, a similar toxicity profile has been shown for SC versus IV administration for anemia, thrombocytopenia, and other toxicities. During this study local tolerability at the SC injection site will be closely monitored as well.

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 maximum blood volume for a subject who completes 8 cycles and the post-treatment assessments is approximately 490 mL. The total blood volume to be collected is estimated at approximately 34 mL for Screening, 100 mL for Cycles 1 and 2, 161 mL for Cycles 3-6, 21 mL at each subsequent cycle, 55-85 mL for pharmacokinetics (depending on treatment group), 5 mL when CR is suspected or maintained, and 50 mL at the End-of-Treatment visit. In the Follow-up Phase, subjects who discontinue study drug prior to PD will continue to have approximately 20 mL blood drawn every 2 months 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 Independent Ethics Committee/Institutional Review Board [IEC/IRB] with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments

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

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

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

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- New edition(s) of the Investigator's 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).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required. The reapproval should be documented in writing (excluding the ones that are purely administrative, with no consequences for subjects, data, or study conduct). At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion (if applicable, the notification will be submitted through the head of investigational institution).

16.2.3. Informed Consent

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

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

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.

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 DNA, biomarker, and 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 and rHuPH20, to understand multiple myeloma, to understand differential drug responders, and to develop tests/assays related to daratumumab. 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 Use of Samples in Future Research).

16.2.6. Country Selection

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

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involves only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the 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 date of birth (as allowed by local regulations). In cases where the subject is not randomized into the study, the date seen and date of birth (as allowed by local regulations) will be used. The investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

17.4. Source Documentation

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

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

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

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

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

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

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

17.5. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each subject in electronic format. All eCRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the eCRF are accurate and correct. The study data will be transcribed by study-site personnel from the source

documents onto an electronic eCRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

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 documents. Data must be entered into eCRF in English. The eCRF must be completed as soon as possible after a subject visit and the forms should be available for review at the next scheduled monitoring visit. 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.

If necessary, queries will be generated in the electronic data capture (eDC) tool. If corrections to an eCRF are needed after the initial entry into the eCRF, this can be done in either of the following ways:

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

There will be no data collection in the eCRF after the database is locked for the final analysis. Attachment 13 describes procedures for subjects who continue study treatment after the end of the data collection period.

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, periodic monitoring visits by the sponsor, and direct transmission of clinical laboratory data into the sponsor's data base. 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 eCRF 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 eCRF and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

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

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

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

17.8. Monitoring

The sponsor will use a combination of monitoring techniques central, remote, or on-site monitoring to monitor this study. The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the eCRF with the source documents (eg, hospital/clinic/physician's office medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the 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 documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

17.9. Study Completion/Termination

17.9.1. End of Data Collection/Study Completion

The end of the data collection period will be approximately 24 months after the last subject was randomized or when median overall survival for both arms has been reached, whichever occurs first. Only data collected in the eCRF during the data collection period will be included in the final study analysis. The final data from the study site will be sent to the sponsor (or designee)

after completion of the final subject assessment at that study site, in the time frame specified in the Clinical Trial Agreement.

The sponsor will ensure that subjects benefiting from treatment with either the IV or SC formulation of daratumumab are able to continue receiving daratumumab treatment after the end of the data collection period (final analysis) until the applicable formulation is commercially available or available from another source, or the study is complete. After the end of the data collection period, the clinical database will be closed, and no additional data will be collected in the eCRF. Attachment 13 describes data collection and reporting procedures for subjects who continue study treatment after the end of the data collection period.

The study will be considered complete when all subjects still receiving study drug have commercial or alternative access to the appropriate formulation of daratumumab, have stopped receiving daratumumab treatment, or at approximately 5 years after the last subject was randomized, whichever occurs first.

17.9.2. Study Termination

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

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

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

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

17.10. On-Site Audits

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

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

17.11. Use of Information and Publication

All information, including but not limited to information regarding 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 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 data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator for the study. Results of 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 disclose the existence of and the results of clinical studies as required by law.

REFERENCES

1. Abetz L, Coombs JH, Keininger DL, et al. Development of the cancer therapy satisfaction questionnaire: Item generation and context validity testing. Value in Health. 2005; 8:S41-S53.
2. Becker N. Epidemiology of multiple myeloma. Recent Results Cancer Res, 2011;183:25-36.
3. Burtis CA, Ashwood ER. Tietz textbook of clinical chemistry, 3rd Edition, Philadelphia; WB Saunders: 1998.
4. Chapuy CI, Aguad MD, Nicholson RT, et al; DARA-DTT Study Group* for the BEST Collaborative. International validation of a dithiothreitol (DTT)-based method to resolve the daratumumab interference with blood compatibility testing. Transfusion. 2016;56:2964-2972.
5. Chapuy CI, Nicholson RT, Aguad MD, et al. Resolving the daratumumab interference with blood compatibility testing. Transfusion. 2015;55:1545-1554.
6. de Weers M, Tai YT, van der Veer MS, et al. Daratumumab, a novel therapeutic human CD38 monoclonal antibody, induces killing of multiple myeloma and other hematological tumors. J Immunol. 2011;186:1840-1848.
7. Durie BG, Harousseau JL, Miguel JS, et al. International uniform response criteria for multiple myeloma. Leukemia 2006;20:1467–1473. Corrigenda/Erratum in: Leukemia. 2007;21:1134-1135.
8. Farrington CP, Manning G. Test statistics and sample size formulae for comparative binomial trials with null hypothesis of non-zero risk difference or non-unity relative risk. Stat Med. 1990;9:1447-1454.
9. Food and Drug Administration (FDA). US Department of Health and Human Services. Guidance for Industry: Clinical Trial Endpoints the Approval of Cancer Drugs and Biologics. May 2007. Available at: http://www.fda.gov/downloads/Drugs/.../Guidances/ucm071590.pdf. Accessed 16 January 2017.
10. Investigator's Brochure: JNJ-54767414 (daratumumab). Edition 13; Janssen Research & Development (06Oct2016).
11. Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol. 2016;17:e328-346.
12. Kumar SK, Lee JH, Lahuerta JJ, et al. Risk of progression and survival in multiple myeloma relapsing after therapy with IMiDs and bortezomib: a multicenter international myeloma working group study. Leukemia. 2012;26:149-157.
13. Levey AS, Coresh J, Greene T, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med. 2006;145:247-254.
14. Lokhorst HM, Plesner T, Laubach JP, et al. Targeting CD38 with daratumumab monotherapy in multiple myeloma. N Engl J Med. 2015;373:1207-1219.
15. Lonial S, Weiss B, Usmani S, et al. Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomized, phase 2 trial. Lancet. 2016;387:1551-1560.
16. Moreau P, San Miguel J, Ludwig H, et al. Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals Oncol. 2013; 24 Suppl 6:vi133-7.
17. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Multiple Myeloma, version 2.2014. Fort Washington, PA: National Comprehensive Cancer Network; 2013.
18. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-655.
19. Overdijk MB, Verploegen S, Bogels M, et al. Antibody-mediated phagocytosis contributes to the anti-tumor activity of the therapeutic antibody daratumumab in lymphoma and multiple myeloma. MAbs. 2015;7:311-321.
20. Palumbo A, Anderson K. Multiple myeloma. N Engl J Med. 2011;364:1046-1060.
21. Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol. 2014;15:e538-e548.

22. Rajkumar SV, Harousseau JL, Durie B, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. Blood. 2011;117:4691-4695.

23. Trask PC, Tellefsen C, Espindle D, Getter C, Hsu MA. Psychometric validation of the cancer therapy satisfaction questionnaire. Value Health. 2008;11:669-679.

24. Usmani S, Ahmadi T, Ng Y, et al. Analysis of real-world data on overall survival in multiple myeloma patients with ≥3 prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory drug (IMiD), or double refractory to a PI and an IMiD. Oncologist. 2016;21:1355-1361.

25. Verelst SGR. PHAROS myeloma data comparison for registration file of daratumumab. Erasmus University Medical Center, July 2015. Data on file.

Attachment 1: International Myeloma Working Group Diagnostic Criteria

Multiple myeloma is defined as 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:

- 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 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL)
    - Renal insufficiency: creatinine clearance <40 mL per min[b] or serum creatinine >177 µmol/L (>2 mg/dL)
    - Anemia: hemoglobin value of >20 g/L below the lower limit of normal, or a hemoglobin value <100 g/L
    - Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT[c,d]
- Any one or more of the following biomarkers of malignancy:
  - Clonal bone marrow plasma cell percentage[a] ≥60%
  - Involved:uninvolved serum free light chain ratio[e] ≥100
  - >1 focal lesions on MRI studies[f]

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 core biopsy, the highest value should be used.
b. Measured or estimated by validated equations.
c. 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.
d. PET-CT=^{18}F-fluorodeoxyglucose positron emission tomography with computed tomography.
e. These values are based on the serum Freelite assay (The Binding Site Group, Birmingham, UK). The involved free light chain must be ≥100 mg/L.
f. Each focal lesion must be 5 mm or more in size.

(Rajkumar 2014[21])

Attachment 2: Prior Cancer Therapy for Multiple Myeloma

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

Source: Rajkumar 2011[22]

Attachment 3: Eastern Cooperative Oncology Group Performance Status Score

Grade	Eastern Cooperative Oncology Group 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 self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair (Oken 1982[18]).

Attachment 4: Modified Diet in Renal Disease Formula

For creatinine in **mg/dL**, the estimated glomerular filtration rate (e-GFR) for the modified diet in renal disease (MDRD) formulas is:

e-GFR (MDRD) mL/min per $1.73m^2$= 175 × [serum creatinine (mg/dL)]$^{-1.154}$ × [age]$^{-0.203}$ × [1.212 if black] × [0.742 if female]

For creatinine in **µmol/L**, the estimated glomerular filtration rate (e-GFR) for the modified diet in renal disease (MDRD) formulas is:

e-GFR (MDRD) mL/min per $1.73m^2$= 175 x [serum creatinine (µmol/L)/88.4]$^{-1.154}$ × [age]$^{-0.203}$ × [1.212 if black] × [0.742 if female]

(Levey 2006[13])

Attachment 5: Serum Calcium Corrected for Albumin

If calcium is expressed in mg/dL and albumin is expressed in g/dL:
Corrected calcium (mg/dL) =
serum calcium (mg/dL) + 0.8 × (4 - serum albumin [g/dL])

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

(Burtis 1998[3])

Attachment 6: Conversion Table for Glucocorticosteroid Dose

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

Attachment 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	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 FEV1 between exacerbations > 80% > 85%	Normal FEV1 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
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	Step 3 and consider short course of oral steroids	Step 3 and consider short course of oral steroids	Step 3: medium dose ICS OR Step 4 and consider short course of oral steroids	Step 4 or 5 and consider short course of oral steroids
		In 2-6 weeks, evaluate level of asthma control that is achieved. 0-4 years: If no clear benefit is observed in 4-6 weeks, stop treatment and consider alternate diagnosis or adjusting therapy. 5-11 and 12+ years: adjust therapy accordingly.											

Components of Control		Classification of Asthma Control								
		Well Controlled			Not Well Controlled			Very Poorly Controlled		
		0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs
	Symptoms	≤ 2 days/week but not more than once on each day		≤ 2 days/ week	> 2 days/week or multiple times on ≤2 days/week		> 2 days/ week	Throughout the day		
Impairment	Nighttime awakenings	≤ 1x/month		≤ 2x/month	> 1x/month	≥ 2x/month	1-3x/week	> 1x/week	≥ 2x/week	≥ 4x/week
	Interference with normal activity	None			Some limitation			Extremely limited		
	SABA use for symptom control (not prevention of EIB)	≤ 2 days/week			> 2 days/week			Several times per day		
	Lung function FEV_1 or peak flow FEV_1/FVC	N/A	> 80% > 80%	> 80%	N/A	60-80% 75-80%	60-80%	N/A	< 60% < 75%	< 60%
	Validated questionnaires ATAQ ACQ ACT			0 ≤ 0.75 ≥ 20			1-2 ≥ 1.5 16-19			3-4 N/A ≤ 15
Risk	Exacerbations requiring oral systemic corticosteroids	0-1/year			≥ 2/year					
		Consider severity and interval since last exacerbation								
	Reduction in lung growth/ Progressive loss of lung function	Evaluation requires long-term follow-up								
Recommended Action for Treatment		• Maintain current step • Regular follow-up every 1-6 months • Consider step down if well controlled for at least 3 months			Step up 1 step • **Before step up**: Review adherence to medication, inhaler technique, and environmental control. If alternative treatment was used, discontinue it and use preferred treatment for that step. • **Reevaluate the level of asthma control in 2-6 weeks to achieve control**. 0-4 years: If no clear benefit is observed in 4-6 weeks, consider alternative diagnoses or adjusting therapy. 5-11 years: Adjust therapy accordingly. • **For side effects**, consider alternative treatment options.	Step up at least 1 step	• Step up 1 step • Reevaluate in 2-6 weeks • For side effects, consider alternative treatment options	• Consider short course of oral steroids • Step up 1-2 steps • **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.		• Consider short course of oral steroids • Step up 1-2 steps • Reevaluate in 2 weeks • For side effects, consider alternative treatment options

Attachment 8: New York Heart Association (NYHA) Functional Classification

NYHA Class	Symptoms
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity (eg, shortness of breath when walking or climbing stairs).
II	Mild symptoms (mild shortness of breath or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity (eg, walking short distances [20–100 m]). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while *at rest*. Mostly bedbound patients.

Attachment 9: Antihistamines That May Be Used Predose

The following antihistamines may be used predose, before Dara-IV infusion or Dara-SC injection (including, but not limited to):

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

* The IV use of promethazine should be avoided.

Attachment 10: Interpretation of The SEBIA Hydrashift 2/4 Daratumumab IFE Interference Test

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

Implementation: To mitigate this interference, the sponsor will use the SEBIA Hydrashift 2/4 Daratumumab IFE Interference test to distinguish a positive SPEP/IFE due to the presence of daratumumab versus the presence of the underlying (endogenous) monoclonal protein. The SEBIA Hydrashift 2/4 Daratumumab IFE Interference test will be sent automatically to the central laboratory if a subject with IgG kappa multiple myeloma has an SPEP at or below 0.2 g/dL on 2 or more consecutive cycles. In addition, the SEBIA Hydrashift 2/4 Daratumumab IFE Interference test will be sent automatically to the central laboratory if a subject has an SPEP of zero, but persistently positive IFE for IgG kappa on 2 or more occasions.

Interpretation of results:

The results will be available to the investigator via the central laboratory interface and will be reported as follows:

DARAHydra Impress1: result defined as “DARA detected”, “DARA not detected”, OR “DARA indeterminate”
DARAHydra Impress2: result defined as “M-protein not detected” OR the specific protein detected (i.e. “IgG,k” or “IgA”)
DARAHydra Impress3: result defined as “M-protein not detected” OR the specific protein detected (i.e. “IgG,k” or “IgA”)

- If Impress1 result is “DARA detected” and Impress2 and 3 results are “M-protein not detected”, the patient may be in complete response (CR) if the other criteria for CR (including negative bone marrow aspirate/biopsy) are achieved.
- If Impress1 result is “DARA not detected” or “DARA indeterminate”, the patient is still positive for underlying (endogenous) monoclonal protein and Impress2 and 3 can inform as to the type of endogenous protein still present. Therefore, this patient is not in a complete response (CR), because the CR response criteria requires a negative SPEP and serum IFE.
- If Impress1 result is “DARA detected” but there is also protein present and reported by Impress2 or 3, the patient is still positive for underlying (endogenous) monoclonal protein and Impress2 and 3 can inform as to the type of endogenous protein still present. Therefore, this patient is not in a complete response (CR), because the CR response criteria requires a negative SPEP and serum IFE.

Attachment 11: Modified Cancer Therapy Satisfaction Questionnaire

Modified Cancer Therapy Satisfaction Questionnaire
US English

The following pages ask some questions about your cancer therapy (IV/SC). Within this questionnaire, "Cancer therapy (IV/SC)" refers to your current or most recent cancer therapy (including: IV therapy and subcutaneous therapy (SC)). Please read each question and answer as honestly as you can without the help of anyone. There are no right or wrong answers; the answers should be based on your own personal experiences.

Your Thoughts about Cancer Therapy (IV/SC)

The following statements ask you to share your **thoughts about cancer therapy (IV/SC)**. Please answer each question below by *checking the box* that best represents your opinion (check only one box per question).

In general, in the last four weeks, how *often did you feel*:	**Always**	**Most of the time**	**Some-times**	**Rarely**	**Never**
1. That cancer therapy (IV/SC) was worth taking even with the side effects?	☐5	☐4	☐3	☐2	☐1

2. In general, **in the last four weeks**, how often did you think about stopping your cancer therapy (IV/SC)?

☐5	☐4	☐3	☐2	☐1
Always	Most of the time	Sometimes	Rarely	Never

Satisfaction with Cancer Therapy (IV/SC)

The following statements are about your satisfaction with your **most recent cancer therapy (IV/SC)**. Please answer each question below by *checking the box* that best describes your level of satisfaction (check only one box per question).

3. **Overall**, how worthwhile was your cancer therapy (IV/SC)?

☐5	☐4	☐3	☐2	☐1
Very worthwhile	Quite worthwhile	Moderately worthwhile	A little worthwhile	Not worthwhile at all

4. **Overall**, was taking cancer therapy (IV/SC) as difficult as you expected?

☐5	☐4	☐3	☐2	☐1
Much more difficult than I thought it would be	Somewhat more difficult than I thought it would be	As difficult as I thought it would be	Somewhat easier than I thought it would be	Much easier than I thought it would be

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5. **Overall,** how well did the **benefits** of cancer therapy (IV/SC) meet your expectations?

☐5	☐4	☐3	☐2	☐1
Much better than my expectations	Somewhat better than my expectations	Met my expectations	Somewhat worse than my expectations	Much worse than my expectations

6. **Overall,** were the **side effects** of cancer therapy (IV/SC) as you expected?

☐5	☐4	☐3	☐2	☐1
Much better than I expected	Somewhat better than I expected	Exactly as I expected	Somewhat worse than I expected	Much worse than I expected

7. How satisfied were you with the **form** of your cancer therapy (IV/SC)?

☐5	☐4	☐3	☐2	☐1
Very satisfied	Satisfied	Neither satisfied nor dissatisfied	Dissatisfied	Very dissatisfied

8. **Overall,** how satisfied were you with your most recent cancer therapy (IV/SC)?

☐5	☐4	☐3	☐2	☐1
Very satisfied	Satisfied	Neither satisfied nor dissatisfied	Dissatisfied	Very dissatisfied

9. Taking everything into consideration, if given the choice again, would you decide to take this cancer therapy treatment?

☐5	☐4	☐3	☐2	☐1
Yes, definitely	Probably Yes	I don't know	Probably not	Definitely not

Thank you.

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Attachment 12: Anticipated Events

Anticipated Event

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

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

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

Reporting of Anticipated Events

All adverse events will be recorded in the eCRF 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 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/ECs. 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)

An 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 13: Continuation of Treatment After Clinical Cutoff for the Final Analysis (End of the Data Collection Period)

Protocol Amendment 3 will allow those subjects who are benefitting from daratumumab treatment after the clinical cutoff date for the final analysis (end of the data collection period) to continue receiving study drug. The sponsor will ensure that subjects will be able to continue receiving the appropriate formulation of IV or SC daratumumab after the data collection period has ended until the applicable formulation is commercially available or available from another source, or until the study is complete (see 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 3 (see Section 6).

Treatment Period

Once the sponsor has notified investigators that the clinical cutoff for the final analysis has been achieved (end of the data collection period), subjects may continue treatment with daratumumab until PD per investigator evaluation, unacceptable toxicity, withdrawal of consent, the investigator decides to stop treatment, or the start of subsequent anticancer therapy. Post-treatment follow-up is not applicable for subjects who discontinue study treatment in this period, except for HBV DNA testing as described below.

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

Once the data collection period has ended, 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 (see Section 12.3.2). Serious adverse events that occur between the end of 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.

HBV DNA Tests

Subjects who are positive for anti-HBc or anti-HBs will undergo testing for HBV DNA by PCR every 4 weeks (±1 month) after entering this treatment period. Testing will continue for 6 months after the last dose of study treatment. Subjects with serologic findings suggestive of HBV vaccination (anti-HBs positivity as the only serologic marker) and a known history of prior HBV vaccination do not need to be tested for HBV by PCR.

Sample Collection and Handling

There are no PK, immunogenicity, or biomarker assessments during this treatment period, and any sample collection or test for safety or disease evaluation should comply with standard local institution practice. Please note that local bone marrow analysis is required for the assessment of CR.

Case Report Form Completion

No data will be collected in the eCRF during this treatment period.

Source Documentation

At a minimum, the type and level of detail of source data collected should be consistent with that commonly recorded at the site as a basis for standard medical care. This should include: subject identification and study identification, study discussion, documentation of the informed consent process including the date, dates of visits, drug dispensing/return records, and study drug administration information.

INVESTIGATOR AGREEMENT

JNJ-54767414 (daratumumab)
Clinical Protocol 54767414MMY3012 Amendment 3

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): Ming Qi, MD PhD

Institution: Janssen Research & Development

Signature: PPD Date: 21 Jan 2020 (Day Month Year)

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

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Approved, Date: 21 January 2020