Janssen Research & Development *

Clinical Protocol

A Randomized Phase 2 Trial to Evaluate Three Daratumumab Dose Schedules in Smoldering Multiple Myeloma

Protocol 54767414SMM2001; Phase 2
AMENDMENT 6

JNJ-54767414 Daratumumab

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EudraCT NUMBER: 2014-005139-14

Status:	Approved
Date:	29 March 2021
Prepared by:	Janssen Research & Development, LLC
EDMS number:	EDMS-ERI-95497760, 10.0

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

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PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	25 November 2014
Amendment 1	20 January 2015
Amendment 2	27 July 2015
Amendment 3	20 June 2017
Amendment 4	28 January 2019
Amendment 5	01 April 2020
Amendment 6	29 March 2021

Amendments are listed beginning with the most recent amendment.

Amendment 6 (29 March 2021)

The overall reason for the amendment: The overall reason for the amendment is to extend the study duration up to a maximum of 7 years following Last Patient First Dose (LPFD) by redefining the End of Study.

Applicable Section(s)	Description of Change(s)
Rationale: The end of the study was extended to collect long-term safety and efficacy data and to allow subjects to have the option to continue to receive study treatment.	
Synopsis, Overview of Study Design (including figure); 3.1. Overview of Study Design; Figure 1; 3.2. Study Design Rationale; 9.1.4. Follow-up Phase; 17.9.1. Study Completion	The end of study definition was changed to occur up to approximately 7 years after the last subject's first dose, not approximately 5 years. Text regarding the evaluation of data from a Phase 3 study to potentially extend drug treatment beyond the end of study was deleted.
Rationale: Text was added to specify permitted and prohibited vaccinations.	
8.1. Permitted Therapies	Text was added indicating vaccinations are allowed per local guidelines with a reference to Section 8.2.
8.2. Prohibited Therapies	Text was added clarifying the restriction of live attenuated and replication-competent viral vector vaccines.
Rationale: Clarified procedures in Attachment 4.	
Attachment 4	Clarified that on Day 1 of each cycle, only subjects receiving daratumumab IV may require a recalculation of weight and should have vital signs measured. Added text to the table to indicate that the administration of pre-dose methylprednisolone should be administered in the absence of infusion-related adverse events in the first 2 doses.
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 5 (01 April 2020)

The overall reason for the amendment: Overall reasons for the amendment are 1) to extend the study duration and 2) to provide flexibility for study investigators as it relates to the global coronavirus (COVID-19) pandemic.

The overall reason for the amendment is to extend the study duration to approximately 5 years following Last Patient First Dose (LPFD) by redefining the End of Study. This amendment also reduces required assessments in the Time and Events Schedule for ongoing subjects.

Additionally, this amendment provides flexibility for study investigators to prioritize the safety of their subjects during the global coronavirus (COVID-19) pandemic. To ensure continuity of study treatment, while limiting subjects' time spent at the study center, subjects will be given the option to switch from daratumumab intravenous (IV) (16 mg/kg) to daratumumab subcutaneous (SC) (1800 mg), at the discretion of the investigator. Alternatively, for subjects who continue to receive daratumumab IV, the duration of infusion may be shortened to a 90-minute infusion for subjects without a history of an infusion-related reaction after the third dose, at the discretion of the investigator. Detailed information regarding daratumumab IV administration, including infusion rates and duration, has been removed from the protocol and will only be provided in the Site Investigational Product Procedures Manual (SIPPM).

Applicable Section(s)	Description of Change(s)
Rationale: A new formulation of daratumumab for SC administration has been developed to avoid the long infusion time with IV administration of daratumumab and to lessen the rate and severity of infusion-related reactions (IRRs) observed with daratumumab IV. The SC formulation of daratumumab has been evaluated in the Phase 3 randomized Study 54767414MMY3012 (COLUMBA), which compared efficacy, pharmacokinetics, and safety of SC vs IV daratumumab in 522 subjects which met the predefined non-inferiority criteria, demonstrating that daratumumab SC is non-inferior to IV. As such, subjects who are being treated in the Treatment Extension Phase at the time of this amendment will have the option to switch to SC daratumumab dosing (1800 mg dose) at the discretion of the investigator.	
Synopsis Overview of Study Design, Dosage and Administration; 3.1 Overview of Study Design; 6 Dosage and Administration; 9.1.3 Treatment Phase; 10.1 Completion of Treatment	Text has been added to describe the option of daratumumab SC administration for subjects receiving daratumumab IV.
1.2.2.4 Daratumumab Subcutaneous (new); 1.3 Overall Rationale for the Study; 3.2 Study Design Rationale; 6.3 Daratumumab SC Administration (new)	Sections, sub-sections, and text have been added to support daratumumab SC dosing including background information regarding the SC formulation of daratumumab, rationale for daratumumab SC dose regimen, and daratumumab SC dose administration.
6.4.2 Post-dose Medication	Instruction for post-dose medications for subjects who switch from daratumumab IV to daratumumab SC was added.
14.1 Physical Description of Study Drug	Text was added to describe the physical characteristics of daratumumab SC supplied to the site.
14.2 Packaging	Text was added to provide details on the packaging of daratumumab IV and daratumumab SC.
14.4 Preparation, Handling, and Storage	Text was added to provide instruction on the preparation, handling, and storage of daratumumab SC.

Applicable Section(s)	Description of Change(s)
Throughout the protocol (including 6.4.1 Pre-dose Medication; 6.4.2 Post-dose Medication; 6.4.3.1 Infusion-related Events of Grade 1 or Grade 2 and 6.4.3.2 Infusion-related Reactions of Grade 3 or Higher)	Language and terminology were updated to differentiate between IV infusion and SC administration.
Rationale: Daratumumab SC is co-formulated with rHuPH20 and sorbitol.	
Synopsis Overview of Study Design, Dosage and Administration; 1.2.2.4 Daratumumab Subcutaneous; 3.1 Overview of Study Design; 6 Dosage and Administration; 6.3 Daratumumab SC Administration; 9.1.3 Treatment Phase; 10.1 Completion of Treatment	Subjects with known allergies/intolerance to sorbitol will not be allowed to switch from daratumumab IV to daratumumab SC.
Rationale: Infusion-related reactions are systemic reactions related to daratumumab administration, regardless of route of administration.	
6.4.3 Management of Infusion-related Reactions	Text has been added to describe IRRs and the applicability to both daratumumab IV or SC administration.
Rationale: Subcutaneous administration of daratumumab is associated with local injection site reactions.	
6.4.3.3 Injection-Site Reactions (new)	Text has been added to describe injection-site reactions and management of such events.
Rationale: To obtain longer term safety, overall survival, and progression-free survival data in the Smoldering Multiple Myeloma population, the End of Study was redefined. Required assessments were reduced to focus the remaining study conduct on the above aspects of data collection and are described in the new Attachment 4.	
Synopsis Overview of Study Design; 3.1 Overview of Study Design; 9.1.4 Follow-up Phase; 17.9.1 Study Completion	Extended the end of study to **approximately 5 years after the last subject's first dose, following a decision by the sponsor to end the study based on data from the smoldering multiple myeloma Phase 3 study (54767414SMM3001), or for reasons as outlined in Section 17.9.2, whichever occurs first.**
3.2 Study Design Rationale	Indicated that **long-term** data on PFS will be analyzed in the final study analysis which is expected to occur **approximately 5 years after the last subject's first dose**.
Synopsis Pharmacokinetic and Immunogenicity Evaluations, Biomarker Evaluations; 9.3 Pharmacokinetics and Immunogenicity; 9.4 Biomarkers	PK, immunogenicity, and biomarker evaluations will not be collected.
Synopsis Overview of Study Design, Efficacy Evaluations/Endpoints; Table 1; Table 2; Table 3; 3.1 Overview of Study Design; 3.2 Study Design Rationale; 9.1.1 Overview; 9.1.3 Treatment Phase; 9.1.4 Follow-up Phase; 9.2 Efficacy; 9.2.1 Evaluations; 9.3 Pharmacokinetics and Immunogenicity; 9.4 Biomarkers; 9.5.2 Other Safety Evaluations; 10.3 Premature Discontinuation of Study Treatment	Refer investigators and staff to Attachment 4 for a description of dose administration and study procedures for subjects who continue in the Treatment Extension Phase or who have discontinued treatment but remain in Follow-up.

Applicable Section(s)	Description of Change(s)
Rationale: To specify that a protocol amendment will be issued if treatment beyond the end of study is permitted for subjects included in the Treatment Extension Phase (and who have not yet entered the Follow-up period as of the end of study). Potential extension of treatment will be based on data from the smoldering multiple myeloma Phase 3 study (54767414SMM3001).	
Synopsis Overview of Study Design; 3.1 Overview of Study Design; ; 9.1.4 Follow-up Phase; 17.9.1 Study Completion	Added: **For subjects included in the Treatment Extension Phase (and who have not yet entered the Follow-up period as of the end of study) as described in Amendment 4, potential drug treatment beyond the end of study will be evaluated after data from the smoldering multiple myeloma Phase 3 study (54767414SMM3001) are available. A protocol amendment will be issued if further treatment is permitted.**
Rationale: To eliminate the possibility of inconsistency between the NCI-CTCAE version numbering used in the protocol and the standard grade descriptions included in the protocol.	
12.1.3 Severity Criteria	Severity Criteria Section: Eliminated definitions of severity criteria; the definitions are specified in NCI-CTCAE version 4.
Rationale: Results reported from assessments facilitated by central laboratories will not be required. Results from the primary analysis have been described in a clinical study report and additional data have been collected for approximately 3 years. Use of local laboratories will continue as described in the newly added Attachment 4.	
Attachment 4	Added: **central laboratory evaluations are not applicable**
Rationale: Changes for clarity/consistency noted in the protocol were corrected.	
Synopsis Overview of Study Design; 3.1 Overview of Study Design	Clarified that the data collected at the end of the study will be reported in a clinical study report.
Synopsis Efficacy Evaluations/Endpoints; 9.2.2.2 Major Secondary Endpoints; 11.3.2 Secondary Efficacy Endpoints	Updated the secondary endpoint of overall survival rate to exclude the 4-year time period.
Table 2	Clarified that as of Amendment 4, the QTc substudy was considered complete and the data collection outlined was not applicable.
Synopsis Overview of Study Design; 3.1 Overview of Study Design	Added a statement to cross-reference Section 6.4 which details guidelines to prevent infusion-related reactions.
6.4.3 Management of Infusion-related Reactions	Included tracheostomy equipment as an example of resources necessary for resuscitation.
6.5.1 Daratumumab Toxicity Management	Clarified that Grade 3 thrombocytopenia **with bleeding** is a criterion for a dose delay.
9.1.3 Treatment Phase	Specified that due to the addition of the treatment extension outlined in Amendment 4, it is possible for subjects to have 2 EOT visits with the requirement to complete 2 EOT visit CRFs.
9.1.4 Follow-up Phase	Added: **If included in the Treatment Extension Phase, it is possible that subjects will have 2 Follow-up Phase portions of the study (1 after the planned 20 cycles, and 1 after the last dose in the treatment extension). As of Amendment 5, these additional protocol-specified Follow-up assessments should be conducted as specified in Attachment 4.**
9.5.2 Other Safety Evaluations	Added information detailing the conduct for subjects with evidence of positive HBV serology.

Applicable Section(s)	Description of Change(s)
14.1 Physical Description of Study Drug	Added additional detail regarding the physical appearance of the daratumumab IV liquid supplied to the site.
14.4 Preparation, Handling, and Storage	Added additional detail regarding the preparation, handling, and storage of daratumumab IV.
Rationale: Daratumumab IV infusion rates were redefined with added flexibility.	
Synopsis Dosage and Administration; 6.2 Daratumumab IV Administration	Indicated that daratumumab IV infusion rates have been redefined with added flexibility and **may be shortened to a 90-minute infusion for subjects without a history of an infusion-related reaction after the third dose, at the discretion of the investigator.** Removed Table 4 Infusion Rates for Daratumumab; renumbered subsequent tables.
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 4 (28 January 2019)

The overall reason for the amendment: The overall reason for the amendment is to allow extended treatment with IV daratumumab (Q8W) after 20 treatment cycles in long intense (Arm A) and intermediate arm (Arm B) if, as per investigator discretion, there is a positive benefit/risk ratio, absence of Grade ≥3 treatment related toxicity, and at least stable disease has been achieved. In the case of subjects who already completed EOT and the end of Cycle 20 occurred <6 months, these subjects can continue receiving IV daratumumab administrations every 8 weeks. Additionally, modifications have been made in response to identification of a new important risk (hepatitis B virus [HBV] reactivation), and text related to evaluation of circulating multiple myeloma cells as an exploratory objective or biomarker has been modified.

Applicable Section(s)	Description of Change(s)
Rationale: Instructions for extension of IV daratumumab treatment beyond Cycle 20 were provided.	
Synopsis; Table 1 (footnote c); 3.1 Overview of Study Design; Figure 1; 6 Dosage and Administration; 6.2 Daratumumab Administration; 9.1.3 Treatment Phase; 10.1 Completion of Treatment;	Added the following text: **For subjects in Arm A (long intense) and Arm B (intermediate), there is a possibility to extend treatment with IV daratumumab (Q8W) after the end of Cycle 20 if, as per investigator discretion, there is a positive benefit/risk ratio, absence of Grade ≥3 treatment related toxicity, and at least stable disease has been achieved. In the case of subjects who already completed EOT and end of Cycle 20 occurred <6 months, these subjects can also continue receiving IV daratumumab administrations every 8 weeks.**
6.2 Daratumumab Administration; Table 4 (footnote f);	Provided clarification regarding treatment re-initiation relative to EOT: **If EOT took place ≥3 months but < 6months before re-initiation, the same instructions on infusion rates are applicable as per table 4, meaning that slower infusion rates are to be applied during the first infusion, with acceleration during the subsequent infusions to avoid the occurrence of IRR.**

Applicable Section(s)	Description of Change(s)
Table 1 footnote b; 6.2 Daratumumab Administration	Provided clarification on the timing of disease assessment: **The assessment of disease progression will be based on the last disease evaluation performed. In case last disease evaluation was performed ≥5 months at treatment re-initiation, a new disease evaluation is to be performed to make sure that patient has not progressed. Every case of treatment re-initiation is to be discussed with the medical monitor prior to re-initiation.**
Synopsis; 3.1 Overview of Study Design; 9.1.4 Follow-up Phase	Clarified the language for the Follow-up Phase: The Follow-up Phase will begin once subjects complete the planned number of cycles**, and no treatment extension will be given as per investigator's discretion. In case of treatment extension or treatment re-initiation, the same procedures are to be followed as outlined in Section 9.1.3 and TABLE 1.**
9.1.4 Follow-up Phase; 17.9.1 Study Completion	Added the following text: **For subjects that will continue treatment or re-initiate treatment as part of treatment extension, the duration of treatment extension will be re-evaluated at the time of the interim analysis of the Phase 3 study (Study 54767414SMM3001), evaluating subcutaneous daratumumab in patients with high risk smoldering myeloma.**
Table 1; Table 3; 6.4.2 Daratumumab Delays; 9.1.3 Treatment Phase; 9.2 Efficacy; 10.3 Premature Discontinuation of Study Treatment	Added text to indicate that instructions also pertain to treatment extension or re-initiation.
Rationale: Added instructions for assessment of hepatitis B prior to treatment re-initiation.	
Table 1 (and footnote a)	Added to Table 1 Laboratory Assessments, instructions for HBV serology and HBV DNA testing prior to treatment re-initiation.
4.2 Exclusion Criteria (Criterion 6)	Updated and added text regarding subjects who are: • **known to be seropositive for human immunodeficiency virus (HIV).** • **known to have a history of hepatitis C.** • **seropositive for hepatitis B (defined by a positive test for hepatitis B surface antigen [HBsAg]). Subjects with resolved infection (ie, subjects who are HBsAg negative but positive for antibodies to hepatitis B core antigen [anti-HBc] and/or antibodies to hepatitis B surface antigen [anti-HBs]) must be tested 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 (antiHBs 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.** **For subjects who enter extension treatment period, HBV serology (HBsAg, anti-HBs, and anti-HBc) testing is to be performed locally prior to re-initiation. HBV serology is not required at re-initiation if this was performed as part of standard of care within 3 months prior to the re-initiation or the start of extension treatment is within 3 months of last daratumumab dose.**

Applicable Section(s)	Description of Change(s)
8.3 Management of Hepatitis B Virus Reactivation	Added the following text to the new Section 8.3: **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 9.5.2.** **For subjects who are diagnosed with HBV reactivation while on treatment, study treatment should be interrupted until the infection is adequately controlled. If the benefits outweigh the risks, study treatment may be resumed with concomitant antiviral prophylaxis as per local standard of care. Consult a liver disease specialist as clinically indicated.**
9.5.2 Other Safety Evaluations	Added instructions for HBV Serology and DNA testing.
Rationale: Evaluation of circulating multiple myeloma cells (CMMCs) is no longer performed.	
Table 1 Time and Events Schedule; 9.4 Biomarkers	Added the following text: **As of Amendment 4, these samples will no longer be collected.**

Amendment 3 (20 June 2017)

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

The overall reason for the amendment: To incorporate changes from practical experience with implementing study evaluations and to address feedback from investigators and the steering committee. The resulting changes include the clarification that a subject with disease progression, assessed by serum FLC only, may continue to receive study treatment if the subject continues to show clinical benefit per investigator assessment and if agreed upon by the sponsor.

Applicable Section(s)	Description of Change(s)
Rationale: In a subset of subjects, daratumumab disproportionally decreases the uninvolved light chain. It was unanticipated at the time of writing the protocol that this would lead to artificially elevated FLC ratios. The artificially elevated FLC ratios have led to ambiguous cases in interpretation of disease progression. To allow for investigator clinical judgment, clarification was made to allow a subject to remain on study treatment following disease progression which is based only on FLC criteria.	
9.2.1.3. Free Light Chain Ratio	Added a new section and the text in bold: **In a subset of subjects, daratumumab disproportionally decreases the uninvolved light chain, thus artificially skewing the FLC ratio. The artificially elevated FLC ratios have led to ambiguous cases in interpretation of disease progression. In cases where the subject's disease progresses solely based on FLC criteria, if the subject continues to benefit from the study treatment based on investigator assessment, the subject is allowed to continue the study treatment if agreed by the sponsor. The investigator or designee must consult with the subject and discuss the considerations for recommending continuation of study treatment. The agreement of the subject to continue treatment with daratumumab must be documented in the medical record. Disease evaluations must continue at a frequency of at least every 8 weeks.** Renumbered subsequent sections.

Applicable Section(s)	Description of Change(s)
Rationale: MRD assessment via whole blood samples is no longer proceeding because it has been confirmed that whole blood MRD is not sensitive enough for the depth of MRD negativity that is being determined in this study.	
Synopsis, Overview of Study Design; 3.1. Overview of Study Design	Deleted text in strikethrough: An assessment of MRD will be conducted on ~~whole blood and~~ bone marrow aspirate samples.
Synopsis, Biomarker Evaluations	In addition, blood samples will be obtained for assessment of ~~MRD,~~ CMMCs, immunophenotyping, and plasma and PBMC biomarker assessments.
Table 1 Time and Events Table	Deleted the row for Blood sample for MRD
3.2 Study Design Rationale, Rationale for Biomarker Evaluations, MRD assessment	In the present study, we will assess for MRD in ~~both blood and~~ bone marrow aspirate when samples are obtained at screening, at confirmation of CR, and at 12 months and 18 months after first dose for subjects who maintain CR.
9.4 Biomarkers	Baseline bone marrow aspirates ~~and a whole blood sample~~ will be subjected to DNA sequencing in order to establish the myeloma clone for MRD monitoring. A fresh bone marrow aspirate ~~and whole blood sample~~ at Screening is required if at all possible, for MRD assessment. For subjects who achieve a CR or sCR, additional bone marrow aspirate ~~and a whole blood sample~~ will be utilized for assessment of MRD by next-generation sequencing (NGS) of immunoglobulin heavy and light chains (Vij 2014)[24]. For subjects who maintain a CR, MRD will also be assessed at 12 and 18 months after first dose in bone marrow aspirate ~~and whole blood~~.
Rationale: After the End-of-Treatment Visit, clinic visits are limited to disease evaluations by laboratory tests only. Therefore, ECOG assessments cannot be performed.	
Table 1 Time and Events Table, ECOG	Added text in bold: **Once a subject discontinues or completes therapy prior to PD, ECOG will only be assessed at the End-of-Treatment Visit and additionally when PD is suspected.** Replaced text in strikethrough with text in bold: Week 5, Week 9, and then every 8 weeks in the first year, thereafter q16wk ~~until PD~~ **during the Treatment Phase**
Rationale: Clarified timing of repeated urine UPEP analysis for a subgroup of subjects to minimize urine collections to increase subject adherence.	
Table 1 Time and Events Table, Urine disease evaluations (UPEP); 9.2.1.5 Myeloma Protein Measurements in Serum and Urine	Added text in bold: In subjects with baseline UPEP result below the level of quantification, UPEP analysis will be repeated only **(1)** at the time of disease progression **and (2) to confirm a CR**.

Applicable Section(s)	Description of Change(s)
Rationale: Corrected typographical errors from Amendment 2 (value for anemia should be >2 g/dL, not ≥2 g/dL) and added a missing symbol for anemia value (should be >2 g/dL).	
4.2. Exclusion Criteria #1d	Replaced text in strikethrough (≥) with text in bold (>): Anemia, defined as hemoglobin <10 g/dL and/or ~~≥~~**>**2 g/dL below LLN in the absence of transfusion support or concurrent treatment with erythropoietin stimulating agents (ESAs)
9.2.1.4. CRAB Criteria-Related Laboratory Assessments, Hemoglobin	Added text in bold (>): Development of anemia (according to CRAB criteria; hemoglobin <10 g/dL or **>**2 g/dL lower than LLN) indicates progression to symptomatic MM if it is not attributable to any other cause.
Rationale: To comply with Janssen protocol template standards, the Company Sponsorship Statement was updated, language in Case Report Form Completion was updated, and the version number was added to the EDMS number.	
Title page	Added text in bold: Deleted strikethrough text: **Janssen Pharmaceutica NV;** **Janssen Sciences Ireland UC;** ~~Janssen R&D Ireland;~~ ~~Janssen Infectious Diseases BVBA;~~ EDMS-ERI-95497760**, 5.0**
17.5. Case Report Form Completion	Deleted sentence: ~~All data relating to the study must be recorded in eCRFs prepared by the sponsor.~~
Rationale: Footnote letters were added to the text descriptions to match the letters in a table which were missing in previous editions of this protocol.	
6.2. Daratumumab Administration, Table 4	Added text in bold: Added footnote letters "**a**, **b**, **c**, **d**, **e**" to the text descriptions at the bottom of the table.
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment INT-2 (27 July 2015)

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

The overall reason for the amendment: To address feedback from health authorities and investigators. The resulting changes include the clarification of requirements for radiologic assessment to reduce exposure, addition of a disease evaluation to capture early response, adjustment of the entry criteria and visit windows, as well as other minor edits throughout the protocol.

Applicable Section(s)	Description of Change(s)
Rationale: Clarified the requirement for radiologic assessment during the study in order to reduce radiation exposure to asymptomatic patients.	
Table 1, Time and Events Table, Disease Evaluations, Skeletal radiography or low-dose CT; 9.2.1.7. Assessment of Bone Lesions	Added text in bold. **U**se same methodology during study as used at screening: Skeletal radiography **or low-dose CT** q12 months and at **biochemical progression (eg, increase of SPEP >25%) or** at suspected PD.~~;or low-dose CT q6 months **for the first year, then q12 months,** and at suspected PD.~~ **For subjects with (1) negative MRI results at baseline, (2) M-protein increase ≤25%, and (3) no other signs of clinical progression, only an MRI needs to be performed. For these subjects, low-dose whole body CT or skeletal survey does not need to be repeated unless focal lesions have been identified by MRI.**
Rationale: Added one additional disease evaluation at Cycle 1 Week 5 to capture early response and provide a more accurate measure of the duration of response. This timepoint was selected because the median time to response for daratumumab is 4 weeks for relapse and refractory MM.	
Synopsis, Efficacy Evaluations/Endpoints; Table 1 Time and Events Table, Heading, ECOG, Serum disease evaluations (SPEP), Urine disease evaluations (UPEP), Serum free light chain, Calcium, albumin; 9.2. Efficacy	Disease assessments will be performed **at Week 5, Week 9, and then** every 8 weeks in the first year**, thereafter** ~~and then~~ every 16 weeks until disease progression.
Rationale: Updated information on the statistical hypotheses to be tested.	
Synopsis, Objectives and Hypothesis and Statistical Methods; 2.2. Hypothesis; 11.2. Sample Size Determination	Replaced text in strikethrough with text in bold. **Two hypotheses will be tested:** **1. H0: CR rate ≤ 15%** **Ha: CR rate ≥ 35%** **2. H0: PD/death rate ≥ 0.346/patient-year (median PFS < 24 months)** **Ha: PD/death rate ≤ 0.185/patient-year (median PFS > 45 months)** 1. The CR rate at 6 months after the last subject is randomized is greater than or equal to 35%. 2. The disease progression [PD]/death rate one year after the last subject is randomized is less than or equal to 0.185

Applicable Section(s)	Description of Change(s)
Rationale: Added clarification that the antihistamine administered preinfusion and postinfusion is an H1-antihistamine.	
Synopsis; Overview of Study Design; Table 3 Time and Events Table Dose Administration; 3.1. Overview of Study Design; 6.3.1. Preinfusion Medication; 6.3.2. Postinfusion Medication; 6.3.3. Management of Infusion-related Reactions	Added text in bold. **H1-**antihistamine
Rationale: Changed allowable time window for disease evaluations from 5 days to 7 days.	
Synopsis; Efficacy Evaluations/Endpoints; Table 1, Time and Events Table, Disease Evaluations Heading; 9.2. Efficacy; 9.2.1.1. Assessment of Response	Replaced text in strikethrough with text in bold. A window of ±~~5~~**7** days before the scheduled assessment date is allowed.
Rationale: Clarified the definition of PFS.	
Synopsis Efficacy Evaluations/Endpoints; 9.2.2.2 Major Secondary Endpoints	Added text in bold: PFS, defined as the time from the date of randomization to the date of initial documented PD according to the CRAB criteria**, myeloma defining events,** or date of death, whichever occurs first.
Rationale: Added that the pregnancy test for women of childbearing potential must be performed within 14 days prior to randomization to the Time and Events table for consistency within the protocol.	
Table 1, Time and Events Table, Laboratory Assessments	Added text in bold. For women of childbearing potential only **within 14 days prior to randomization.**
Rationale: Added time window of 7 days for the End-of-Treatment Visit.	
Table 1, Time and Events Table, EOT Heading; 3.1 Overview of Study Design; 9.1.3. Treatment Phase, End of Treatment Visits	Replaced text in strikethrough with text in bold. Unless a subject withdraws consent for study participation or is lost to follow up, an End-of-Treatment Visit is to occur ~~within~~**at** 28 **±7 days** after the last dose of all study treatments.
Rationale: Removed the requirement for a FEV1 test for subjects with asthma during screening.	
Table 1, Time and Events Table, Procedures; 9.5.2. Other Safety Evaluations, Pulmonary Function Test	Deleted strikethrough text. Subjects with known or suspected COPD ~~or asthma~~ must have a FEV1 test during screening.
Rationale: Clarified language for samples needed for MRD assessment.	
Table 1 Time and Events Table, Disease Evaluations, Bone marrow aspirate/biopsy; 9.2.1.6. Bone Marrow Examination, Table 7, Screening, Central Testing; 9.4. Biomarkers	Added text in bold. If a fresh bone marrow aspirate will not be performed at screening because a sample is available within 56 days prior to randomization, then **unstained,** non-decalcified diagnostic tissue [bone marrow aspirate slides**, touch prep from biopsy (rolled biopsy) slides, or clot specimen slides** ~~or FFPE tissue~~)] ~~should~~ **must** be collected for MRD assessment.

Applicable Section(s)	Description of Change(s)
Rationale: Added that MRI can be performed on a yearly basis starting three years after the first dose of daratumumab.	
Table 1, Time and Events Table, Disease Evaluations, MRI of spine and pelvis; 9.2.1.7. Assessment of Bone Lesions	Added text in bold. q6 months **for the first 3 years, then q12 months,** and **at biochemical progression (eg, increase of SPEP >25%) or** at suspected PD; whole body MRI per local practice or when clinically indicated.
Rationale: Added monteleukast as an optional preinfusion medication, to be used based upon investigator discretion.	
Table 3, Time and Events Table Dose Administration, Preinfusion Medication; 6.3.1 Preinfusion Medication	Added text in bold. **Monteleukast 10 mg approximately 1 hr prior to every infusion of daratumumab; use is optional per investigator discretion.**
Rationale: Added cetirizine as an example of a H1-antihistamine that can be used preinfusion and postinfusion.	
Table 3, Time and Events Table Dose Administration, Preinfusion Medication; 6.3.1 Preinfusion Medication	Added text in bold. An H1-antihistamine (diphenhydramine 25-50 mg IV or PO, **cetirizine 10 mg PO,** or equivalent) approximately 1 hour prior to daratumumab infusion
6.3.2. Postinfusion Medication	Added text in bold. H1-antihistamine (diphenhydramine, **cetirizine,** or equivalent) on the 2 days following all daratumumab infusions (beginning the day after the infusion)
Rationale: Added lactate dehydrogenase to the list of clinical laboratory tests to be performed by the local laboratory.	
Table 3 Time and Events Schedule Dose Administration, Other Study Procedures; 9.5.2. Other Safety Evaluations, Clinical Laboratory Tests	Added text in bold. Serum Chemistry Panel: **lactate dehydrogenase (LDH)**
Rationale: Clarified that the specified laboratory tests need to be drawn for infusions 2 through 8 during Cycle 1, and not for each infusion during Cycle 1.	
Table 3 Time and Events Schedule Dose Administration, Other Study Procedures; 9.5.2. Other Safety Evaluations, Clinical Laboratory Tests	Replaced text in strikethrough with text in bold. **At Screening and during** Cycle 1 only, before ~~each~~ **the second through eighth** infusion**s** of daratumumab
Rationale: Amended inclusion criteria to allow enrollment of subjects with light chain only myeloma.	
4.1 Inclusion Criteria #3.1	Added text in bold. - **The absolute involved serum free light chain (sFLC) is ≥100 mg/L with abnormal FLC ratio (<0.126 or >8).**
Rationale: Clarified the duration of contraceptive administration in the inclusion criteria.	
4.1 Inclusion Criteria #6.1	Added text in bold. Contraception must begin prior to dosing **and continue until 4 months after the last dose of daratumumab.**

Applicable Section(s)	Description of Change(s)
Rationale: Edited exclusion criteria to clarify that subjects who are on corticosteroids with a dose >10 mg prednisone per day or equivalent are not allowed in the study, and subjects who are on a stable dose of bone-protecting agents for a nonmalignant condition are allowed in the study.	
4.2 Exclusion Criteria #3.1	Replaced text in strikethrough with text in bold. ~~- To concurrent treatment with bone-protecting agents (eg, bisphosphonates, denosumab) or corticosteroids with a dose not exceeding 10 mg prednisone per day or equivalent are only allowed if given in a stable dose and for a nonmalignant condition~~. **-To concurrent treatment with corticosteroids with a dose >10 mg prednisone per day or equivalent**. **-To concurrent treatment with bone-protecting agents (eg, bisphosphonates, denosumab) for treatment of SMM or MM. The subjects who are on a stable dose of these medications for a nonmalignant condition are allowed in the study.**
Rationale: Updated the url for the website that contains the list of medications known to affect the QT interval, which are prohibited during Cycle 1 for subjects in the QTc substudy. Aligned protocol language with terminology used in the referenced website.	
4.2 Exclusion Criteria #15.1	Replaced text in strikethrough with text in bold. Received medications **with a** known **or possible risk of torsades de pointes** ~~to affect the QT interval~~ (see https://www.crediblemeds.org~~/~~) within 4 weeks prior to ECG screening day
8.2. Prohibited Therapies	For subjects in the QTc substudy, medications **with a known or possible risk of torsades de pointes** ~~known to affect the QT interval~~ (see ~~http://www.azcert.org/~~ **https://www.crediblemeds.org**) are prohibited during Cycle 1.
Rationale: Updated information on daratumumab interference with Indirect Antiglobulin Test (IAT) results. Streamlined the display of this information by including in only one section of the protocol, and removing redundant information elsewhere.	
4.3. Prohibitions and Restrictions	Deleted section, which only included information on the IAT. Text on the IAT was relocated to Section 9.5.2.
9.5.2. Other Safety Evaluations; Daratumumab Interference with Indirect Antiglobulin Test (IAT) results	The text for the IAT was updated to be consistent across all daratumumab protocols.
Rationale: Added table to show infusion rates for daratumumab over time. Edited text to state that further information on daratumumab administration can be found in the SIPPM.	
6.2. Daratumumab Administration	Added Table 4 Infusion Rates for Daratumumab, which shows infusion rates for the first, second and subsequent infusions of daratumumab. Replaced text in strikethrough with text in bold. For **further information** ~~recommendations~~ on daratumumab **administration** ~~infusion rate~~, please refer to the SIPPM.

Applicable Section(s)	Description of Change(s)
Rationale: Added the clarification that postinfusion corticosteroids are long- or intermediate-acting corticosteroids.	
6.3.2. Postinfusion Medication	Added text in bold. For the prevention of delayed infusion-related reactions, all subjects will receive **long- or intermediate-acting** corticosteroid**s** orally (20 mg methylprednisolone or equivalent in accordance with local standards) on the 2 days following daratumumab infusions in Cycle 1 (beginning the day after the infusion).
Rationale: Clarified instructions for postinfusion medications for at-risk subjects.	
6.3.2. Postinfusion Medication	Added text in bold. If, after 4 full doses, an at-risk subject experiences no major infusion-related reactions, then postinfusion medications **(except Cycle 1 corticosteroids)** may be stopped at the investigator's discretion.
Rationale: Amended instructions for the management of infusion-related reactions.	
6.3.3. Management of Infusion-related Reactions	Removed text in strikethrough. If an infusion-related reaction develops, then the infusion should be ~~temporarily interrupted~~ **paused** ~~or slowed down~~.
6.3.3. Management of Infusion-related Reactions	If an infusion is paused ~~or the infusion rate is decreased~~, then a longer-than-anticipated infusion time may occur.
Rationale: Edited criteria for daratumumab dose delay due to toxicity by removing the requirement for bleeding with Grade 3 thrombocytopenia.	
6.4.1. Daratumumab Toxicity Management	Removed text in strikethrough. The criteria for a dose delay are: – Grade 3 thrombocytopenia ~~with bleeding~~
Rationale: Reorganized and modified text for cases where consecutive doses of daratumumab are missed.	
6.4.2. Daratumumab Delays	Relocated text, and added text in bold. If more than 2 consecutive planned doses of daratumumab are missed due to **daratumumab-related** AEs, treatment should be permanently discontinued. Replaced text in strikethrough with text in bold. If 2 consecutive **planned** doses of daratumumab are missed ~~for any reason other than AEs~~, this should be brought to the attention of the Sponsor at the earliest possible time ~~and study treatment should be discontinued, unless, upon consultation with the sponsor and the review of safety and efficacy, continuation is agreed upon~~**; subject continuation can occur if agreed by the Sponsor.**

Applicable Section(s)	Description of Change(s)
Rationale: Edited instructions on prohibited therapies and discontinuation of study drug to allow greater flexibility for the retention of subjects in the Treatment Phase. Replaced specific examples of prohibited therapies with general classes of medications that are prohibited, to align with text used in the exclusion criteria.	
8.2. Prohibited Therapies	Replaced text in strikethrough with text in bold. Use of the ~~prohibited~~ treatments listed below **is prohibited** during the study ~~will result in discontinuation of study drug for subjects~~: • Administration of ~~commercially available agents or agents under investigation for SMM or MM, including systemic corticosteroids (>10 mg prednisone per day or equivalent other than those given per Section 6.3.1 and Section 6.3.2), clarithromycin, interferon, bortezomib, thalidomide, or lenalidomide~~ **approved or investigational treatments for SMM or/and MM (including but not limited to conventional chemotherapies, immunomodulatory drugs (IMiDs), or proteasome inhibitors).**
Rationale: Clarified follow-up phase instructions.	
9.1.4. Follow-up Phase	Added text in bold. Subjects who discontinue before disease progression must continue to have disease evaluations **at Week 5, Week 9, and then** every 8 weeks for the first year, **thereafter** ~~then~~ every 16 weeks according to the Table 1 until confirmed PD, death, the start of a new anticancer therapy, withdrawal of consent, lost to follow-up, or the end of the study. Replaced text in strikethrough with text in bold. Follow-up for subsequent ~~anticancer~~ **multiple myeloma** therapy **(including the response to the first subsequent multiple myeloma therapy)**, second primary malignancies, and survival status will be obtained at least every 6 months.
Rationale: Edited timepoints to perform β2 microglobulin analysis to be consistent with the Time and Events Schedule.	
9.2.1.5. β2 microglobulin	Added text in bold. Blood samples for β2 microglobulin analysis are to be collected at Screening **and upon disease progression**, and will be analyzed by the central laboratory
Rationale: Added flow cytometry as a method for disease characterization of bone marrow at screening.	
9.2.1.6. Bone Marrow Examination, Table 7, Screening, Local Testing	Added text in bold. Disease characterization (morphology and either immunohistochemistry, ~~or~~ immunofluorescence**, or flow cytometry**).
Rationale: Updated section on assessment of bone lesions to improve readability.	
9.2.1.7. Assessment of Bone Lesions	Reorganized section, added subheadings, and incorporated edits throughout, and added text in bold. **PET-CT can be used as an alternative imaging test to replace MRI.**
Rationale: Updated information in the protocol on pharmacokinetic parameters and analyses, as this level of detail is unnecessary for the protocol.	
9.3.2. Analytical Procedures;	Removed information on timing of analysis.
9.3.3. Pharmacokinetic Parameters; 11.4 Pharmacokinetic Analyses	Removed references to calculation of CL and V.

Applicable Section(s)	Description of Change(s)
11.6 Pharmacokinetic/Pharmacodynamic Analyses	Added text in bold: If sufficient data are available, pharmacokinetic/pharmacodynamic modeling will be performed, including exploring the relationship between serum concentrations of daratumumab and endpoints of clinical efficacy **and safety**.
Rationale: Modified language for clarity, and edited the reasons for premature discontinuation of study treatment to allow greater flexibility for the retention of subjects in the Treatment Phase.	
10.3. Premature Discontinuation of Study Treatment	Replaced text in strikethrough with text in bold. A subject's study treatment ~~should~~ **must** be discontinued if: • ~~The subject initiates treatment with a prohibited medication~~ • ~~The subject received concurrent (non-protocol) treatment for SMM~~ • The subject missed **more than** 2 consecutive planned doses **due to** ~~of~~ daratumumab**-related AEs**
Rationale: Clarified the instructions that subjects who withdraw from the study need to have the End-of-Treatment (EOT) Visit assessments performed only if the subject is still in the Treatment Phase, and the assessments had not yet been obtained. Subjects who withdraw from the study during the Follow-up Phase do not need to have the EOT visit assessments repeated	
10.4. Withdrawal From the Study	Added text in bold. If a subject withdraws from the study **before the end of the Treatment Phase**, assessments outlined in the End-of-Treatment Visit should be obtained.
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment-1 (20 January 2015)

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

The overall reason for the amendment: The overall reason for the amendment is to add administration of steroids for 2 days postinfusion, as a safety precaution and in line with other single agent studies of daratumumab.

Applicable Section(s)	Description of Change(s)
Rationale: Additional safety precaution.	
Table 3, Time and Events Schedule	Added a row for post-infusion medication
Synopsis, Overview of Study Design 3.1, Overview of Study Design	Added sentence in bold: Measures to prevent infusion related reactions will include preinfusion medication with methylprednisolone, paracetamol, and an antihistamine before each daratumumab infusion. **Methylprednisolone will also be administered after daratumumab infusions in Cycle 1 to prevent delayed infusion reactions.**

Applicable Section(s)	Description of Change(s)
6.3.2, Postinfusion Medication	Added paragraph to beginning of section: **For the prevention of delayed infusion-related reactions, all subjects will receive corticosteroid orally (20 mg methylprednisolone or equivalent in accordance with local standards) on the 2 days following daratumumab infusions in Cycle 1 (beginning the day after the infusion). In the absence of infusion related AEs after Cycle 1, postinfusion corticosteroids will be administered per investigator discretion.** Added text in bold to first bullet: • Antihistamine (diphenhydramine or equivalent) **on the 2 days following all daratumumab infusions (beginning the day after the infusion).**
Rationale: Correction regarding provision of study medication.	
6.2, Daratumumab Administration	Deleted sentence: Daratumumab (16 mg/kg) will be administered by IV infusion to subjects (1) in Arm A once every week in Cycle 1, every other week in Cycle 2 and Cycle 3, every 4 weeks in Cycle 4 to Cycle 7, and from Cycle 8 to Cycle 20 on Day 1 of each cycle; (2) in Arm B once every week in Cycle 1, and then on Day 1 of each cycle from Cycle 2 to Cycle 20; or (3) in Arm C once every week in Cycle 1 only. This schedule is presented schematically in Figure 3. ~~After the end of the study, the sponsor will ensure that subjects benefiting from treatment with daratumumab will be able to continue treatment~~
Rationale: Clarification of biomarker evaluations in subjects with genetic modifications	
Table 1, Time and Events Table, Bone marrow aspirate/ biopsy	Replaced strikethrough with text in bold: A fresh aspirate is requested for ~~high risk profiling~~ **assessment of genetic modifications**…
Synopsis, Biomarker Evaluations 9.4, Biomarkers	…to determine the clinical benefit (ORR, PFS, and OS) of daratumumab in ~~high risk molecular subtypes~~ **subjects with genetic modifications**…
3.2, Study Design Rationale (DNA and Biomarker Collection) 9.4, Biomarkers	…using **DNA**/RNA sequencing of MM cells to allow for assessment of ~~high risk genomics~~ **genetic modifications** such as…
9.2.1.6, Bone Marrow Examination	Added below Table 6: **A portion of the bone marrow aspirate at baseline and at disease progression when feasible will be utilized for DNA/RNA sequencing to characterize subjects (t(4;14), del17p, t(14;16), UAMS70, etc) and to evaluate potential mechanisms of resistance (CD38 mutations, expression of CD38 and CD59).**
Rationale: Clarification for subjects participating in QTc substudy	
9.5.1, Electrocardiogram, QTc Evaluation Substudy	Replaced text in strikethrough with text in bold: For the first 30 subjects ~~receiving daratumumab~~ **eligible for the QTc substudy** at sites participating in the QTc evaluation substudy…
Synopsis, Sample Size Determination, 11.2, Sample Size Determination	Added test in bold: To ensure 25 subjects are evaluable, the QTc substudy will enroll **approximately** 30 subjects

Applicable Section(s)	Description of Change(s)
Rationale: Adjustments of various study procedures to improve clarity.	
Table 1, Time and Events Schedule	made the following clarifications: • serum and urine IFE should be done at screening, • serum free light chain should be done when CR is suspected or maintained • CMMC blood sample to be obtained at screening, not C1D1 • MRI of spine and pelvis required, whole body MRI per local practice or when clinically indicated
4.3, Prohibitions and Restrictions	Added following sentence to section on blood type and IAT results: **Please refer to SIPPM and IB for details.**
6.3.3, Management of Infusion-related Reactions	deleted phrase in strikethrough: in case of any infusion reactions occurring, and resources necessary for resuscitation (eg, agents such as epinephrine and aerosolized bronchodilator, also medical equipment such as oxygen tanks, ~~tracheostomy equipment~~, and a defibrillator) must be available at the bedside.
9.2.1.7, Assessment of Bone Lesions	Deleted text in strikethrough and added text in bold: An MRI ~~should also~~ **of spine and pelvis** will be regularly performed to assess focal bone lesions; **whole body MRI should be performed per local practice or if clinically indicated.**
9.5.2, Other Safety Evaluations	Added footnote "b" to serum chemistry table, with instruction to calculate creatinine clearance as per Section 9.2.1.3.
10.3, Premature Discontinuation of Study Treatment	deleted phrase in strikethrough: The subject experiences disease progression (please see below). ~~Relapse from CR is not considered as disease progression.~~
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

SYNOPSIS

A Randomized Phase 2 Trial to Evaluate Three Daratumumab Dose Schedules in Smoldering Multiple Myeloma

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

OBJECTIVES AND HYPOTHESIS

Primary Objective

The primary objectives are:

- To evaluate if daratumumab can effectively decrease M protein in subjects with intermediate or high-risk smoldering MM (SMM) as assessed by CR rate
- To determine if daratumumab reduces the progression/death rate in subjects with intermediate or high-risk SMM

Secondary Objectives

The secondary objectives are:

- To evaluate preliminary efficacy, including Overall Response Rate (ORR) and PFS
- To evaluate the MRD negative rate
- To evaluate the pharmacokinetics and immunogenicity of daratumumab
- To assess the safety profile of daratumumab given in 3 different dosing schedules
- To determine if daratumumab has an effect on QT interval

Exploratory Objectives

The exploratory objectives are:

- To explore biomarkers predictive of response to daratumumab
- To evaluate the utility of CMMCs (circulating MM cells) to predict SMM progression to MM

Hypothesis

Two hypotheses will be tested:

1. H_0: CR rate $\leq 15\%$

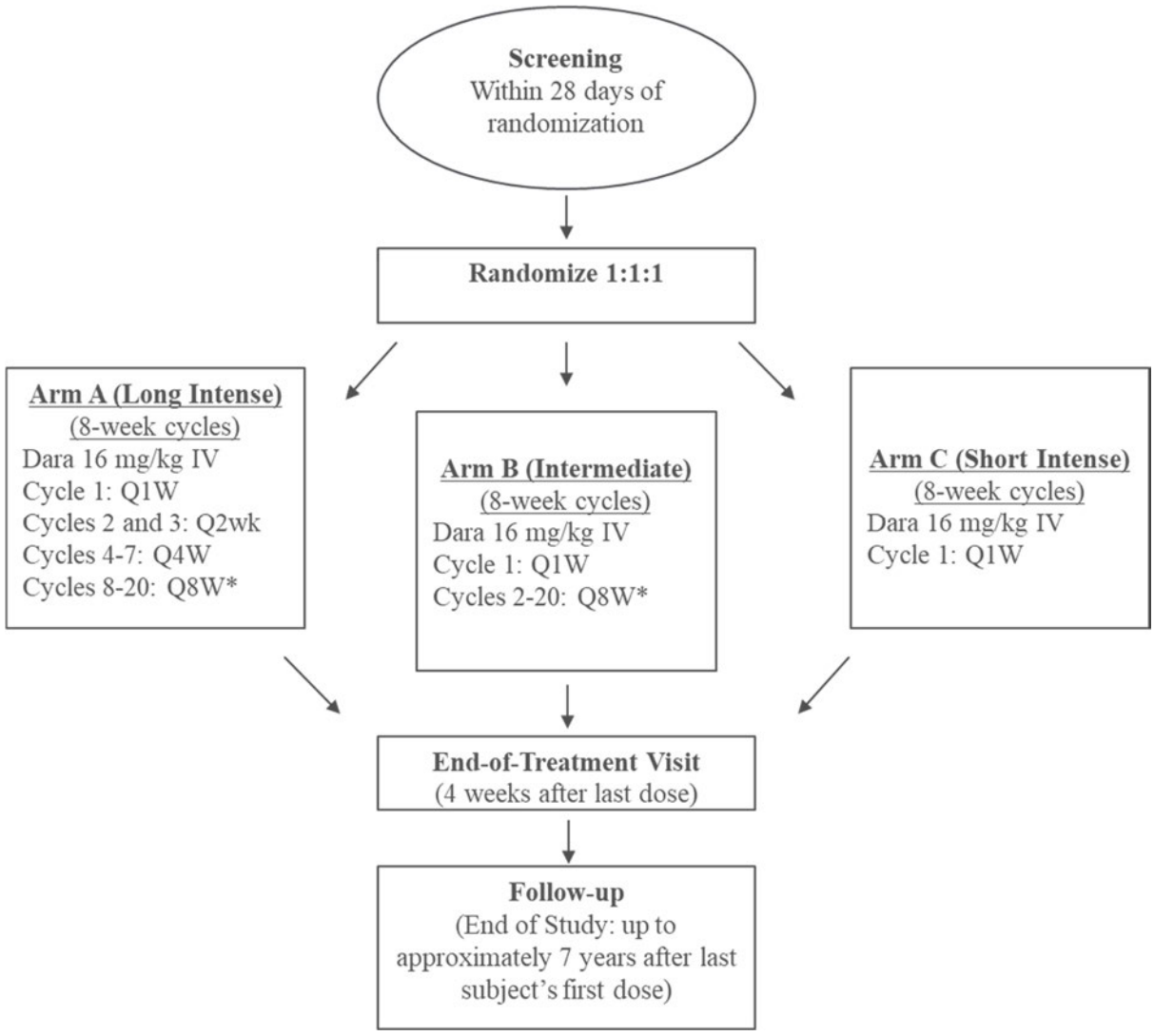
   H_a: CR rate $\geq 35\%$

2. H_0: PD/death rate ≥ 0.346/patient-year (median PFS < 24 months)

   H_a: PD/death rate ≤ 0.185/patient-year (median PFS > 45 months)

OVERVIEW OF STUDY DESIGN

This is a randomized, open-label, 3-arm, multicenter study in subjects at least 18 years old with intermediate or high-risk SMM. Approximately 120 subjects will be enrolled in this study with 40 subjects planned per treatment arm.



* Every 8 weeks (Q8W) beyond Cycle 20 (in case of treatment extension or treatment re-initiation if applicable), as per investigator's discretion. As of Amendment 5, subjects continuing in the Treatment Extension Phase may switch to daratumumab 1800 mg SC Q8W at the discretion of the investigator. Subjects with a known allergy/intolerance to sorbitol will not be eligible to switch to daratumumab SC.

Subject participation will include a Screening Phase, a Treatment Phase, and a Follow-up Phase. The Screening Phase will be up to 28 days before Cycle 1, Day 1. Treatment cycles are 8 weeks in length. For subjects randomized to Arm A or Arm B, the Treatment Phase will extend from Cycle 1 to Cycle 20. In Arm A, daratumumab will be administered weekly in Cycle 1, every other week in Cycle 2 and Cycle 3, every 4 weeks in Cycle 4 to Cycle 7, and from Cycle 8 to Cycle 20 on Day 1 of each cycle. In Arm B, daratumumab will be administered weekly in Cycle 1 and then on Day 1 of each cycle from Cycle 2 to Cycle 20. For subjects in Arm A (long intense) and Arm B (intermediate), there is a possibility to extend treatment with IV daratumumab (Q8W) after the end of Cycle 20 if, as per investigator discretion, there is a positive benefit/risk ratio, absence of Grade ≥3 treatment related toxicity, and at least stable disease has been achieved. In the case of subjects who already completed EOT and end of Cycle 20 occurred <6 months, these subjects can also continue receiving IV daratumumab administrations every 8 weeks.

For subjects randomized to Arm C, the Treatment Phase consists of Cycle 1 only, when daratumumab will be administered weekly. Randomization will be stratified based on the number of risk factors for progression to symptomatic MM (<2 vs ≥2) as described in Section 5.

Measures to prevent infusion-related reactions will include pre-dose medication with methylprednisolone, paracetamol, and an H1-antihistamine before each daratumumab administration. Methylprednisolone will also be administered after daratumumab administration in Cycle 1 to prevent delayed infusion reactions. More information on the guidelines to prevent infusion-related reactions are provided in Section 6.4.

The Follow-up Phase will begin once a subject completes the planned number of cycles, or in the case of treatment extension, the investigator decides to end the treatment and the End-of-Treatment visit at 4 weeks after last dose (±7 days) is completed. Other reasons for premature discontinuation of treatment are listed in Section 10.3. Subjects who discontinue before disease progression must continue to have disease evaluations according to the Time and Events Schedule (As of Amendment 5, refer to the Time and Events Schedule in Attachment 4). The Follow-up Phase will continue until death, lost to follow up, consent withdrawal, or study end, whichever occurs first.

Three data cutoff timepoints are planned:

- The first data cutoff is for an interim analysis 6 months after the last subject is randomized. This will be the basis for the analysis of the primary study endpoint of CR. All available data at the time of this data cutoff may be included in the interim analysis.
- The second data cutoff will occur 12 months after the last subject is randomized. This will be the basis for the analysis of the primary study endpoint of PD/death rate. All available data at the time of this data cutoff will be included in the Clinical Study Report.
- A third data cutoff will occur at the end of the study. The data collected will be reported in a Clinical Study Report.

The end of the study will occur up to approximately 7 years after the last subject's first dose, following a decision by the sponsor to end the study based on data from the smoldering multiple myeloma Phase 3 study (54767414SMM3001 [SMM3001]), or for reasons as outlined in Section 17.9.2, whichever occurs first.

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

SUBJECT POPULATION

Key eligibility criteria include the following: subjects who are ≥18 years of age, have a confirmed diagnosis of intermediate or high-risk SMM, and an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1.

DOSAGE AND ADMINISTRATION

Daratumumab (16 mg/kg) will be administered by IV infusion to subjects (1) in Arm A once every week in Cycle 1, every other week in Cycle 2 and Cycle 3, every 4 weeks in Cycle 4 to Cycle 7, and from Cycle 8 to Cycle 20 on Day 1 of each cycle; (2) in Arm B once every week in Cycle 1, and then on Day 1 of each cycle from Cycle 2 to Cycle 20; or (3) in Arm C once every week in Cycle 1 only. For subjects in Arm A (long intense) and Arm B (intermediate), there is a possibility to extend treatment with IV daratumumab (Q8W) after the end of cycle 20 if, as per investigator discretion, there is a positive benefit/risk ratio, absence of Grade ≥3 treatment related toxicity, and at least stable disease has been achieved. In the case of subjects who already completed EOT and end of Cycle 20 occurred <6 months, these subjects can also continue receiving IV daratumumab administrations every 8 weeks.

To minimize the time subjects spend in the clinic due to the coronavirus (COVID-19) pandemic, subjects who are being treated in the Treatment Extension Phase as of Amendment 5 will be given the option to switch to SC daratumumab dosing (1800 mg dose) at the discretion of the investigator (see Section 6 for details). Subjects with a known allergy/intolerance to sorbitol will not be eligible to switch to daratumumab SC.

Alternatively, for subjects who continue to receive daratumumab IV, the duration of infusion may be shortened to a 90-minute infusion for subjects without a history of an infusion related reaction (IRR) after the third dose, at the discretion of the investigator. More information is provided in the Site Investigational Product Procedures Manual (SIPPM). See Section 6 for more details.

EFFICACY EVALUATIONS/ENDPOINTS

Disease assessments will be performed at Week 5, Week 9, and then every 8 weeks in the first year, thereafter every 16 weeks until disease progression (as of Amendment 5, refer to Attachment 4). A window of ±7 days before the scheduled assessment date is allowed. For subjects with treatment delays, disease assessments should be performed at the time of daratumumab administration, but do not need to be repeated if they were performed within 14 days before the actual treatment date.

There are two co-primary endpoints:

- Complete Response (CR) rate, defined as the proportion of subjects with a CR, as defined in Section 9.2.1.1
- PD/Death rate, defined as the proportion of subjects that have progressed to MM or died per patient-year (number of events (PD or death)/total follow-up for all subjects).

Secondary endpoints are:

- Minimal residual disease negative rate
- Time to next treatment defined as, the time from the date of randomization to the date of the first subsequent MM treatment
- Overall Response Rate defined as CR+PR rate
- PFS, defined as the time from the date of randomization to the date of initial documented PD according to the CRAB criteria, myeloma defining events, or date of death, whichever occurs first. For subjects who are progression-free and are alive at the time of data cutoff for an analysis, PFS will be censored at their last disease assessments on or before initiation of subsequent anti-MM therapy, lost to follow-up, or withdrawal of consent if any of them occurred, or last disease assessments if none of them occurred. PFS will be censored at the date of randomization if there is no postbaseline disease evaluation recorded.
- Incidence of symptomatic MM with adverse prognostic features, which include International Staging System (ISS) Stage III (based on β2-microglobulin and albumin) and adverse cytogenetic characteristics
- Response to first subsequent MM treatment
- Overall survival rate

PHARMACOKINETIC AND IMMUNOGENICITY EVALUATIONS

Samples to assess both the serum concentration (pharmacokinetics) of daratumumab and the generation of antibodies to daratumumab (immunogenicity) will be obtained from all subjects according to Table 1. At specified timepoints, venous blood samples (5 mL per sample) will be collected to determine serum

concentration of daratumumab and the serum will be divided into 3 aliquots (1 aliquot for pharmacokinetic analysis, 1 aliquot for antibodies to daratumumab analysis [when appropriate], and 1 aliquot as a backup).

As of Amendment 5, these samples will not be collected.

BIOMARKER EVALUATIONS

Biomarker assessments will focus on 4 main objectives including evaluating the ability of daratumumab to reduce MRD in SMM subjects who achieve a complete response, to determine the clinical benefit (ORR, PFS, and OS) of daratumumab in subjects with genetic modifications, to evaluate the immunophenotype of SMM patients for potential immune cell contributions to daratumumab response, and to evaluate the contribution of CMMCs to progression of disease. All biomarker assessments will be performed centrally.

Bone marrow aspirates will be collected at screening and following treatment. In addition, blood samples will be obtained for assessment of CMMCs, immunophenotyping and plasma and PBMC biomarker assessments.

As of Amendment 5, these samples will not be collected.

SAFETY EVALUATIONS

Safety will be measured by adverse events, laboratory test results, ECGs, vital sign measurements, physical examination findings, and assessment of ECOG performance status score. A QT substudy will be conducted in 30 subjects at selected sites.

STATISTICAL METHODS

Two hypotheses will be tested:

1. H_0: CR rate $\leq 15\%$

   H_a: CR rate $\geq 35\%$

2. H_0: PD/death rate ≥ 0.346/patient-year (median PFS < 24 months)

   H_a: PD/death rate ≤ 0.185/patient-year (median PFS > 45 months)

This study will enroll 120 subjects (40/arm) in total. With 40 subjects per arm, each arm will have:

- 90% power to show that the true CR rate is 35% at a one-sided level of 0.05
- 80% power to show that the true PD/death rate is 0.185/patient year at a one-sided level of 0.1

If two or more treatment schedules are deemed to be effective, with 40 subjects per arm this study would have:

- 85% probability of identifying the arm with the higher CR
- 80% probability of identifying the arm with the lower PD/death rate

For the QTc substudy, assuming that the intrasubject standard deviation for change from baseline in QTc (ΔQTc) is 20 milliseconds and that the true difference in means is 5 milliseconds, a sample size of 25 evaluable subjects (completers) will have 80% power to show that the upper limit of the two-sided 90% confidence interval (1 sided upper 95% confidence interval) for the difference in mean QTc (ΔQTc) at each timepoint and baseline will be less than 20 milliseconds. To ensure 25 subjects are evaluable, the QTc substudy will enroll approximately 30 subjects.

The first primary efficacy analysis of CR rate will occur 6 months after the last subject has been randomized and will be considered as an interim analysis. The purpose of this analysis is to select an appropriate dose and schedule and enable the sponsor's decision to proceed to Phase 3.

The second primary efficacy analysis of PD/death rate will occur 12 months after the last subject has been randomized. The purpose of this analysis is to make a decision to either proceed to Phase 3 if at the interim analysis there was not enough evidence to do so or to confirm the decision made after the interim analysis to proceed to Phase 3.

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.

Table 1: Time and Events Schedule Overview

As of Amendment 5, refer to Attachment 4 for a description of dose administration and study procedures for subjects who continue in the Treatment Extension Phase or who have discontinued treatment but remain in Follow-up.

	Notes	Screening Phase within 28 days before randomization	Treatment Phase (including treatment extension/re-initiation phase) 8-week cycles	EOT at 28 ± 7 days after last dose	Follow-up
Study treatment should be initiated within 5 days after randomization. The start of each cycle may occur ±5 days of the scheduled day in order to accommodate the schedule of the site or subject. After EOT, subjects in all treatment arms prior to PD will continue to return for disease evaluations. After PD is documented, subjects will be followed for survival; subsequent anticancer therapy, and occurrence of other malignancy. Follow-up visits, unless otherwise specified, are at Week 5, Week 9, and then q8wks during the first year after subject's first dose, then q16wks until PD and q6mos after PD.					
Procedures					
Informed consent	ICF must be signed before any study-related procedures are performed.	X			
Eligibility criteria		X			
Demography/ Medical History		X			
Chest X-ray	Acceptable for screening if performed as part of SOC within 42 days before randomization	X			
FEV1 test	Subjects with COPD	X			
ECOG	Once a subject discontinues or completes therapy prior to PD, ECOG will only be assessed at the End-of-Treatment Visit and additionally when PD is suspected.	X	Week 5, Week 9, and then q8wk in first year, thereafter q16wk during the Treatment Phase	X	
12-lead ECG	Subjects not participating in QTc substudy. Acceptable for screening if performed within 42 days before randomization. See Table 2 for subjects in QTc substudy.	X	Pre-dose C1Wk8	X	
Physical exam	including neurological, height at screening only, clinically significant abnormalities should be reported as AEs	X	symptom and disease directed exam as clinically indicated		
Vital signs, weight	Please see Table 3 for details.	X	Please see Table 3	X	
Blood type and IAT results	Includes ABO, Rh, and IAT results. A wallet card with the subject's blood type will be provided.		C1D1 pre-dose		
Laboratory Assessments					
Pregnancy test	For women of childbearing potential only within 14 days prior to randomization.	X	as clinically indicated		
Hematology		X	Please see Table 3 for details.		
HBV serology [a]	Local testing for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (Anti-HBs), and hepatitis B core antibody (Anti-HBc). Refer to Section 9.5.2.		only when re-initiating treatment		

	Notes	Screening Phase within 28 days before randomization	Treatment Phase (including treatment extension/re-initiation phase) 8-week cycles	EOT at 28 ± 7 days after last dose	Follow-up
HBV DNA test	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. Refer to Section 9.5.2.		Prior to re-initiation, Q12W during treatment, at the End of Treatment Visit, and Q12W for up to 6 months after the last dose of study treatment		
Serum chemistry		X	Please see Table 3 for details.		
Whole blood	Plasma and PBMC biomarker assessments		C1D1, C4D1	X	
Whole blood	Immunophenotyping		C1D1, C2D1, C4D1, C8D1	X	
Daratumumab PK	During treatment phase, 1 sample to be collected before start (window -2 hrs) and 1 sample immediately after end (window +2 hrs) of dara infusion. For subjects in QTc substudy, see Table 2 for collection on C1D1 and C1Wk8. Samples to be sent to central laboratory.		Arm A: C1D1, C1Wk8 (day of Dose #8), C2D1, C3D1, C4D1, C6D1, C8D1 Arm B: C1D1, C1Wk8, C2D1, C3D1, C4D1, C6D1 Arm C: C1D1, C1Wk8	4wks and 8wks after last dara dose	
Daratumumab immunogenicity	No additional sample needed for planned timepoints; will be taken from PK sample. All planned treatment phase timepoints are pre-dose only.		Arm A: C1D1, C2D1, C4D1, C6D1 Arm B: C1D1, C2D1, C4D1, C6D1 Arm C: C1D1, C1Wk8 If an infusion reaction occurs, obtain unscheduled blood sample as soon as possible.	4wks and 8wks after last dara dose	
Disease Evaluations: Subjects in Arm C will continue disease assessments per schedule below after completion of treatment in Cycle 1. For all subjects, every effort should be made to conduct disease evaluations as per schedule (window ±7 days). Refer to Section 9.2 for details					
Serum disease evaluations (SPEP)	Sample to be sent to central laboratory. IFE at screening and when CR is suspected or maintained.	X	Week 5, Week 9, and then every 8 weeks in first year, thereafter every 16 weeks until PD.[b] Not required on C1D1 if screening values were obtained within 14 days of C1D1		
Urine disease evaluations (UPEP)	Sample to be sent to central laboratory. IFE at screening and when CR is suspected or maintained. In subjects with baseline UPEP result below the level of quantification, UPEP analysis will be repeated only (1) at the time of disease progression and (2) to confirm a CR.	X	Week 5, Week 9, and then every 8 weeks in first year, thereafter every 16 weeks until PD. Not required on C1D1 if screening values were obtained within 14 days of C1D1		
Serum free light chain	Sample to be sent to central laboratory	X	Week 5, Week 9, and then every 8 weeks in first year, thereafter every 16 weeks until PD, and when CR is suspected or maintained. Not required on C1D1 if screening values were obtained within 14 days of C1D1		
β2-microglobulin	At screening and at progression. Samples to be sent to central laboratory. At screening, within 14 days of C1D1.	X	When PD is diagnosed, or prior to any subsequent anti-MM therapy		
Calcium, albumin	Samples to be sent to central laboratory.	X	Week 5, Week 9, and then every 8 weeks in the first year, thereafter every 16 weeks until PD. Not required on C1D1 if screening values were obtained within 14 days of C1D1		
Quantitative Ig		X	q16wk for first year, q32wk thereafter until PD		

	Notes	Screening Phase	Treatment Phase (including treatment extension/re-initiation phase)	EOT	Follow-up
		within 28 days before randomization	8-week cycles	at 28 ± 7 days after last dose	
Hemoglobin, creatinine	At screening and during treatment, these tests are included in the local hematology and clinical chemistry tests.		After completion of study treatment, obtain with disease assessments until PD.		
Bone marrow aspirate/biopsy	Acceptable for screening if performed as part of SOC within 56 days before randomization. A fresh aspirate is requested for assessment of genetic modifications, establishment of the MM clone for MRD evaluation, and immunophenotyping (all central lab). If fresh aspirate is not collected, then unstained, non-decalcified diagnostic tissue must be collected (see Section 9.2.1.7 for details). For disease confirmation, archival tissue may be used (may be local lab).	X	At suspected CR and at 12 months and 18 months after first dose for subjects who maintain CR. Only fresh aspirate is needed for biomarker assessment. Core biopsy or aspirate is needed for clinical evaluation of CR/sCR. An additional aspirate, if feasible, will be taken within 2 months of PD diagnosis.		
Blood sample for CMMCs	As of Amendment 4, these samples will no longer be collected.	X	At suspected CR, and at 12 months and 18 months after first dose for subjects who maintain CR	X	
Skeletal radiography, or low-dose CT	Screening assessment may be performed within 56 days before randomization	X	Use same methodology during study as used at screening: Skeletal radiography or low-dose CT q12 months, and at biochemical progression (eg, increase in SPEP >25%) or at suspected PD. For subjects with (1) negative MRI results at baseline, (2) M-protein increase ≤25%, and (3) no other signs of clinical progression, only an MRI needs to be performed. For these subjects, low-dose whole body CT or skeletal survey does not need to be repeated unless focal lesions have been identified by MRI.		
MRI of spine and pelvis	Screening assessment may be performed within 56 days before randomization	X	q6 months for the first 3 years, then q12 months, and at biochemical progression (eg, increase in SPEP >25%) or at suspected PD; whole body MRI per local practice or when clinically indicated.		
Second primary malignancy					X
Subsequent Anti-myeloma Therapy	Record both treatment and response.				X
Survival					X
Ongoing Subject Review					
Adverse Events	See Section 12 for detailed instructions.	continuous from the time of signing of ICF until 30 days after last dose of last study treatment			
Concomitant Medications	See Section 8 for detailed instructions.	continuous from the time of signing of ICF until 30 days after last dose of last study treatment			

Abbreviations: AE=adverse event; C=cycle; CMMCs: circulating multiple myeloma cells; COPD=chronic obstructive pulmonary disease; CR=complete response; ECOG=Eastern Cooperative Oncology Group; D=day; Dara=daratumumab; ECG=electrocardiogram; EOT= End-of-Treatment; FEV= Forced Expiratory Volume (in 1 second); FFPE=formalin-fixed paraffin embedded; FLC=free light chain; IAT= indirect antiglobulin test; ICF=informed consent form; IFE=immunofixation; MRD=minimal residual disease; MRI=magnetic resonance

imaging; PBMC= peripheral blood mononuclear cell ; PK=pharmacokinetics; PD= disease progression; SAE=serious adverse event; SOC=standard of care; SPEP=serum M-protein quantitation by electrophoresis; UPEP=urine M-protein quantitation by electrophoresis; Wk=week

[a] Includes HBsAg, anti-HBs, and anti-HBc. For subjects who enter extension treatment period, HBV serology (HBsAg, anti-HBs, and anti-HBc) testing is to be performed locally prior to re-initiation. HBV serology is not required at re-initiation if this was performed as part of standard of care within 3 months prior to the re-initiation or the start of extension treatment is within 3 months of last daratumumab dose.

[b] If study subject already discontinued study drug and EOT took place < 6 months, treatment can be re-initiated again if there is no disease progression at the time of re-initiation of the treatment. The assessment of disease progression will be based on the last disease evaluation performed. If last disease evaluation was performed ≥5 months at treatment re-initiation, a new disease evaluation is to be performed to make sure that subject has not progressed. Every case of treatment re-initiation is to be discussed with the medical monitor prior to re-initiation.

Table 2: Time and Events Schedule, QTc Substudy

As of Amendment 4, the QTc Substudy was considered complete and the data collection in Table 2 below is not applicable. As of Amendment 5, refer to Attachment 4 for a description of dose administration and study procedures for subjects who continue in the Treatment Extension Phase or who have discontinued treatment but remain in Follow-up.

	Notes	Screening Phase	Treatment Phase	
		Any day from D-14 to D-1	Cycle 1 Dose 1	Cycle 1 Dose 8
Triplicate 12-lead ECGs will be collected from subjects in the QTc substudy. For these subjects, on Cycle 1 Dose 1 and Cycle 1 Dose 8, procedures for obtaining triplicate ECGs will be performed in the following order. All other procedures outlined in Table 1 and Table 3 for Cycle 1 Dose 1 and Cycle 1 Dose 8 will also be performed.				
1. Pre-infusion Medications			Administer according to Table 3	Administer according to Table 3
2. Vital Signs			Pre-dose before ECG	Pre-dose before ECG
3. Triplicate ECGs	Screening serial ECG collection to be collected within 2 weeks prior to first dose of daratumumab (timepoint window +/-5 min).	1:00pm 2:00pm 3:00pm 4:00pm 5:00pm	Pre-dose (window -30 min)	Pre-dose (window -30 min)
4. Daratumumab PK			collect PK sample immediately after ECG assessment	collect PK sample immediately after ECG assessment
5. Daratumumab infusion			after completion of all pre-dose assessments	after completion of all pre-dose assessments
6. Vital Signs			0.5, 1, 1.5, 2, 3.5 hrs after the start of the infusion and at end of infusion	at end of infusion
7. Triplicate ECGs			after end of infusion (window +15 min)	after end of infusion (window +15 min)
8. Daratumumab PK			collect PK sample immediately after ECG assessment	collect PK sample immediately after ECG assessment
9. Vital Signs			0.5,1 hr after end of infusion	N/A
10. Triplicate ECGs			N/A	1 hour after end of infusion (window + 20 min)
11. Daratumumab PK			N/A	collect PK sample immediately after ECG assessment

Table 3: Time and Events Schedule, Dose Administration

As of Amendment 5, refer to Attachment 4 for a description of study drug administration and study procedures for subjects who continue in the Treatment Extension Phase or who have discontinued treatment but remain in Follow-up.

		C1								C2 and C3				C4-C7		C8-C20 (including treatment extension/ re-initiation phase)	EOT
		D1	D8	D15	D22	D29	D36	D43	D50	D1	D15	D29	D43	D1	D29	D1	
Study Drug Administration. Refer to Site investigational Product Procedures Manual for recommendations on daratumumab infusion rate.																	
Arm A		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Arm B		X	X	X	X	X	X	X	X	X				X		X	
Arm C		X	X	X	X	X	X	X	X								
Pre-infusion Medications																	
Methylprednisolone	Methylprednisolone 100 mg for first 2 infusions, 60 mg for all subsequent infusions. Substitutions allowed, see Attachment 3.	approximately 1 hr prior to every infusion of daratumumab															
H1-antihistamine	Diphenhydramine 25-50 mg, cetirizine 10 mg, or equivalent	approximately 1 hr prior to every infusion of daratumumab															
Paracetamol	Paracetamol or acetaminophen 650-1000 mg	approximately 1 hr prior to every infusion of daratumumab															
Monteleukast	Monteleukast 10 mg (optional)	approximately 1 hr prior to every infusion of daratumumab															
Post-infusion Medications																	
Methylprednisolone	Methylprednisolone 20 mg/day orally. Substitutions allowed, see Attachment 3.	for 2 days following daratumumab infusions in Cycle 1 (beginning the day after the infusion)															

		C1	C2 and C3	C4-C7	C8-C20 (including treatment extension/ re-initiation phase)	EOT
Other Study Procedures						
Hematology	For Cycle 1 Day 1, no need to repeat tests if they have been performed within the past 7 days. Testing may be performed up to 2 days before other infusion days. Results of hematology tests must be evaluated before each study drug administration. Perform at additional timepoints, as clinically indicated. To be done by local lab.	At Screening and prior to every infusion of daratumumab: hemoglobin, white blood cell count with absolute neutrophils and lymphocytes, platelet count				X
Clinical Chemistry		At Screening and on Day 1 of each cycle of daratumumab administration: uric acid, total bilirubin, creatinine, blood urea nitrogen, AST, ALT, ALP, LDH At Screening and during Cycle 1 only, before the second through eighth daratumumab infusions: potassium, sodium, magnesium, calcium				X
Weight	If a subject's weight changes by more than 10% from baseline, the dose of study drug will be re-calculated	Day 1 of each cycle of daratumumab administration				
Vital Signs	Vital signs (blood pressure, temperature) measured in sitting position.	On Cycle 1 Day 1 only: immediately before the start of dara infusion; at 0.5, 1, 1.5, 2, 3.5 hrs after the start of the infusion; at end of infusion; and 0.5,1 hr after end of infusion. After Cycle 1 Day 1, immediately before infusion start and at end of each daratumumab infusion.				

ABBREVIATIONS

ADCC	antibody-dependent cell-mediated cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
AE	adverse event
AL amyloidosis	immunoglobulin light chain amyloidosis
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
CDC	complement-dependent cytotoxicity
CL	total systemic clearance
Cmax	maximum observed concentration
Cmin	minimum observed concentration
CMMCs	circulating multiple myeloma cells
COPD	chronic obstructive pulmonary disease
CR	complete response
CT	computed tomography
Ctrough	maximum trough concentrations
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
eDC	electronic data capture
EOT	end of treatment
EU	European Union
FEV	forced expiratory volume
FFPE	formalin fixed paraffin embedded
FLC	free light chain
GCP	Good Clinical Practice
HBV	hepatitis B virus
HIV	human immunodeficiency virus
HR	hazard ratio
IAT	indirect antiglobulin test (also known as indirect Coombs test)
IB	Investigator Brochure
ICF	informed consent form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IFE	immunofixation
Ig	immunoglobulin
IgG1K	immunoglobulin G1 kappa
IMiD	immunomodulatory agent
IMWG	International Myeloma Working Group
IPPI	Investigational Product Preparation Instructions
IRB	Institutional Review Board
IRR	infusion-related reaction
ISS	International Staging System
IV	intravenous
IWRS	interactive web response system
LLN	lower limit of normal
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MGUS	monoclonal gammopathy of undetermined significance
MM	multiple myeloma
MR	minimal response
MRD	minimal residual disease
MRI	magnetic resonance imaging
MTD	maximum tolerated dose

NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next generation sequencing
NK	natural killer
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PC	plasma cell
PD	disease progression
PET-CT	positron emission tomography-computed tomography
PFS	progression free survival
PK	pharmacokinetics
PO	per os
PQC	Product Quality Complaint
PR	partial response
Q8W	every 8 weeks
RBC	red blood cell
rHuPH20	recombinant human hyaluronidase PH20
SAE	serious adverse event
SC	subcutaneous
sCR	stringent complete response
SIPPM	Site Investigational Product Procedures Manual (or equivalent document)
SMM	smoldering multiple myeloma
SPEP	serum M-protein quantitation by electrophoresis
TTP	time to progression
ULN	upper limit of normal
UPEP	urine M-protein quantitation by electrophoresis
US	United States
V	volume of distribution
VGPR	very good partial response
VMP	VELCADE-melphalan-prednisone

1. INTRODUCTION

1.1. Disease Background

Multiple myeloma (MM) is a mostly incurable malignant plasma cell disorder diagnosed annually in approximately 20,000 patients in the US [Weiss 2009][25]. In a majority of patients [Landgren 2009][11], MM evolves from premalignant, asymptomatic plasma cell disorders such as non IgM monoclonal gammopathy of undetermined significance (MGUS) or smoldering multiple myeloma (SMM), which are characterized by monoclonal plasma cell proliferation in the bone marrow and absence of end-organ damage such as renal failure, anemia, and lytic bone lesions [Weiss 2009; Kyle 2009; Kyle 2010][25,8,7]. Smoldering multiple myeloma accounts for 13% to 15% of all myeloma patients [SEER, Kantar Health] and progresses to symptomatic MM at a rate of 10% per year for the first 5 years, decreasing to 3% per year over the following 5 years [ESMO Clinical Practice Guidelines].

Currently there are no approved treatment options for patients with SMM outside of clinical trials and clinical management involves close monitoring until development of symptomatic disease [Landgren 2013][10]. Some early studies that investigated treatment for SMM with various chemotherapy regimens (melphalan-prednisone, thalidomide) or bisphosphonates did not show consistent clinical benefit and were often poorly tolerated [Dispenzieri 2013; Landgren 2013][3,10]. Data from a recent Phase 3 study of lenalidomide and dexamethasone (Len-dex, n=57) compared with observation (n=62) in high-risk SMM patients showed that lenalidomide-based treatment was associated with a significant delay in progression to symptomatic myeloma [Mateos 2013][18]. With a median follow- up of 40 months, the median time to progression (TTP) was significantly longer in the treatment group than in the observation group (median not reached vs. 21 months)(hazard ratio [HR] for progression, 0.18; $p<0.001$). Additionally, lenalidomide plus dexamethasone resulted in response rates of 14% complete response (CR) in the induction phase and 26% CR in the maintenance phase. However, treatment-related toxicities may preclude the long-term use of this regimen in a preventive setting. Therefore, further study in this population is needed to identify novel therapeutic agents that delay or prevent the onset of symptomatic MM, and demonstrate a favorable safety profile over prolonged treatment durations.

1.2. Daratumumab

Daratumumab is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody (mAb) that binds with high affinity to a unique epitope on CD38, a transmembrane glycoprotein. It is a targeted immunotherapy directed towards tumor cells that express high levels of CD38, in a variety of hematological malignancies including MM, leukemia, and non-Hodgkin's lymphoma (NHL).

Daratumumab induces lysis of CD38-expressing tumor cells, 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; Overdijk 2013][2,20].

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

1.2.1. Nonclinical Studies

Preliminary pharmacodynamic studies suggest that daratumumab utilizes multiple effector cell functions, resulting in immune mediated killing of CD38-expressing tumor cells. In ex vivo experiments utilizing human bone marrow stromal cells co-cultured with primary CD38-expressing MM cells, complement-dependent cytotoxicity (CDC) occurs rapidly and demonstrates maximal myeloma cell killing by daratumumab within 1 hour of antibody-mediated activation of the complement proteins (de Weers 2011)[2]. Daratumumab-induced antibody-dependent cell-mediated cytotoxicity (ADCC) is slower in its action, with maximal ADCC by daratumumab observed at 4 hours in vitro (de Weers 2011)[2]. Daratumumab has also been shown to induce antibody-dependent cellular phagocytosis (ADCP) in the presence of macrophages within 4 hours in vitro (Overdijk 2013)[20]. Further, in vitro studies indicated that daratumumab inhibited the cyclase activity of CD38 and stimulated the CD38 hydrolase activity (Study No. GMB 3003-013).

Studies on proliferation of and release of cytokines in human blood cells have indicated that daratumumab does not exert target-specific agonistic activity. The cytokine release observed is mainly caused by the Fc-portion of IgG1 and comparable to that of approved therapeutic antibodies already in clinical use. Specific binding of daratumumab was detected in multiple tissues of both human and chimpanzee origin.

1.2.1.1. Toxicology

Toxicology data have been derived from studies with daratumumab in chimpanzees and with a surrogate anti-CD38 antibody in cynomolgus monkeys. The primary toxicities identified in chimpanzees were infusion-related reactions (IRRs) during the first, but not subsequent, daratumumab infusions and thrombocytopenia. Anemia was observed in cynomolgus monkeys. The binding affinity of daratumumab is significantly higher for chimpanzee platelets than for human platelets, suggesting that thrombocytopenia may be less pronounced in humans. The effect on platelets and red blood cells (RBCs) was reversible.

Depletion of specific lymphocyte phenotypic cell populations, as expected, based on the intended pharmacological effect of daratumumab, was observed in both chimpanzees and cynomolgus monkeys. No genotoxicity, chronic toxicity, carcinogenicity, or reproductive toxicity testing has been conducted.

1.2.2. Clinical Studies

Preliminary data as of 31 July 2014 from 5 ongoing clinical studies are summarized. For further details and the most up-to-date information, please refer to the Daratumumab IB.

As of 31 July 2014, approximately 300 subjects have been treated across 5 ongoing clinical studies of daratumumab in subjects with MM: Studies GEN501, GEN503, 54767414MMY1001, 54767414MMY1002, and 54767414MMY2002 (hereafter referred to as MMY1001, MMY1002, and MMY2002, respectively). Single-agent daratumumab has been administered to 232 subjects in Studies GEN501, MMY1002, and MMY2002; 41 subjects have been treated with daratumumab in combination with lenalidomide and dexamethasone in Study GEN503, and 25 subjects have been treated with daratumumab in combination with VELCADE-containing regimens (VELCADE-dexamethasone [VD], VELCADE-thalidomide-dexamethasone [VTD], VELCADE-melphalan-prednisone [VMP]) and pomalidomide-dexamethasone [Pom-dex] in Study MMY1001. In addition, as of the clinical cutoff date, 16 subjects have been randomized in Study 54767414MMY3003 (MMY3003).

1.2.2.1. Clinical Pharmacokinetics

Pharmacokinetic (PK) data are available from Study GEN501 Part 1. The doses ranged from 0.005 to 24 mg/kg. The PK profile was consistent with target mediated disposition (TMD) with rapid target-related clearance at low doses and slower clearance at higher doses. Following long-term treatment, clearance may decrease as the tumor burden decreases. The preliminary PK data in Studies GEN501 Part 2 and MMY2002 are consistent with the PK profile obtained in GEN501 Part 1. Preliminary PK data from Study GEN503 show that following both the first dose and multiple repeated doses, the PK profile of daratumumab in combination with lenalidomide and dexamethasone is similar to what was observed in Study GEN501 following the same dose and schedule. The data suggest that lenalidomide and dexamethasone do not affect the PK profile of daratumumab.

1.2.2.2. Preliminary Efficacy

Preliminary efficacy data for Study GEN501 Parts 1 and 2 were presented at the 2013 and 2014 American Society of Clinical Oncology (ASCO) Annual Meetings, respectively. As the study is still ongoing, and data reconciliation activities are underway, the data should be considered preliminary. Among 12 subjects treated with daratumumab in Part 1 at doses ≥4 mg/kg, 5 partial responses (PRs) and 3 minimal responses (MRs) were observed. Seven (7) of these subjects had a 50 to 100% concomitant reduction in bone marrow plasma cells. Among 29 subjects treated with 8 mg/kg daratumumab in Part 2, 3 subjects (10%) had a PR; the response rate was 10%. Among 20 subjects treated with 16 mg/kg, 2 subjects (10%) had a CR, 1 subject (5%) had a very good partial response (VGPR), and 4 subjects (20%) had a PR; the response rate was 35%.

1.2.2.3. Safety and Tolerability

In general, daratumumab is tolerated well. Maximum tolerated dose (MTD) has not been reached following intravenous (IV) infusions up to 24 mg/kg monotherapy and 16 mg/kg in combination studies. The most frequently reported adverse events (AEs) across the daratumumab program have been IRRs following single agent therapy. Among all subjects treated in ongoing studies (monotherapy and combination therapy), IRRs have been reported in 49% of subjects; among 151 subjects treated with 16 mg/kg daratumumab monotherapy in Studies GEN501 and MMY2002, the percentage of subjects with a reported IRR was identical (49%) to what was

observed across all treated subjects. The most frequently reported AEs (reported in ≥5% of subjects) reported as IRRs were rhinitis allergic (8%), cough (7%), and nasal congestion (6%). Among subjects treated with 16 mg/kg daratumumab monotherapy, the most commonly reported IRRs were nasal congestion (8%), cough (7%), and rhinitis allergic and throat irritation (5% each). Grade 3 or higher IRRs were reported in 5% of subjects treated with 16 mg/kg daratumumab as monotherapy, with bronchospasm and hypertension being the most frequently reported Grade 3 or higher IRRs (1% each).

Across all ongoing studies, bronchospasm was reported in 10 subjects. Early in daratumumab development, in Study GEN501, 2 cases of bronchospasm were reported 24-48 hours following the second full-dose infusion of daratumumab. With the exception of those 2 cases, which had a delayed onset, all other reported bronchospasm events occurred following the first dose. All of the events occurring during the infusion period resolved quickly after standard treatments were administered. The daratumumab infusion was restarted, and no new onset of bronchospasm occurred. Most of the subjects who experienced bronchospasm had underlying respiratory diseases (asthma, chronic obstructive pulmonary disease [COPD], and others).

Among the 151 subjects treated with 16 mg/kg daratumumab as monotherapy in Studies GEN501 and MMY2002, the most frequently reported AEs (reported in >10% of subjects) were fatigue (29%); anemia (23%); nausea (19%); back pain (18%); cough (17%); thrombocytopenia (16%); decreased appetite (13%); pyrexia, dyspnea, upper respiratory tract infection (12% each); nasal congestion and neutropenia (11% each). Grade 3 and higher AEs were reported in 48% of subjects treated with 16 mg/kg monotherapy daratumumab. The most frequently reported Grade 3 or higher AEs were anemia (13%) and thrombocytopenia (9%). All other Grade 3 and higher AEs were reported in <5% of subjects. No deaths due to daratumumab-related AEs have been reported in any ongoing study.

1.2.2.4. Daratumumab Subcutaneous

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

To minimize the time subjects spend in the clinic during the coronavirus (COVID-19) pandemic, subjects who are being treated in the Treatment Extension Phase as of Amendment 5 will be given the option to switch to SC daratumumab dosing (1800 mg dose, every 8 weeks [Q8W]) at the discretion of the investigator. Subjects with a known allergy/intolerance to sorbitol will not be eligible to switch to daratumumab SC.

This SC formulation of daratumumab has been evaluated in the Phase 3 Study 54767414MMY3012 (MMY3012; COLUMBA), which compared efficacy, PK, and safety of SC vs IV daratumumab in 522 subjects. Adults with relapsed/refractory multiple myeloma were randomized 1:1 to SC (1800 mg; co-formulated with rHuPH20; n=263) or IV (16 mg/kg; n=259)

daratumumab. Randomization was stratified by body weight, prior therapy lines, and myeloma subtype. Primary objectives were to demonstrate non-inferiority of SC vs. IV administration in overall response rate (ORR; at least partial response) and maximum trough concentrations (C_{trough}) (Cycle 3, Day 1).

Co-primary endpoints ORR and C_{trough} met predefined non-inferiority criteria, demonstrating that daratumumab SC is non-inferior to IV. ORR was 41% and 37% with SC and IV daratumumab administration, respectively (relative risk, 1.11; 95% CI, 0.89–1.37). Geometric mean ratio for C_{trough} was 107.93% (90% CI, 95.74–121.67). Median duration of injection was 5 minutes (range 1–18) for the first, second, and subsequent SC administrations vs. 7 hours (1–14), 4.3 hours (3-10.5), and 3.4 hour (2–7.7) for corresponding IV infusions. Infusion-related reactions were reported in 13% of subjects receiving daratumumab SC versus 35% receiving daratumumab IV (odds ratio, 0.28; 95% CI, 0.18–0.44, p<0.0001). Daratumumab SC offers consistent efficacy and exposure to standard IV administration, with significantly shorter infusion times and an improved safety profile.

1.3. Overall Rationale for the Study

Daratumumab is a targeted immunotherapy that binds to tumor cells that overexpress CD38, a transmembrane glycoprotein. Plasma cells in patients with SMM express high levels of CD38, similar to plasma cells in symptomatic MM [Tiedemann 2010][23]. Daratumumab, as a single agent, has shown clinical activity at 16 mg/kg in patients with relapsed/refractory MM who have already failed a number of prior therapies and whose myeloma clones have become resistant to many therapies [Lokhorst 2014][15]. Daratumumab has also demonstrated an acceptable and manageable safety profile.

Patients with SMM are asymptomatic and relatively immunocompetent. In current practice, the standard of care for subjects with SMM is watchful waiting. For high-risk patients, treatment under clinical trials has been recommended [Landgren 2013][10]. As an immunotherapy, daratumumab's immediate and effective cell-mediated (and potentially direct) cytotoxic effects against MM cells may be an ideal mechanism for providing disease interception and early intervention at the SMM stage. Furthermore, the low risk of serious side effects increases the appeal of daratumumab as a treatment option to prevent and/or delay transition to symptomatic MM.

This study is designed to evaluate whether daratumumab as a single agent is effective in delaying the transition from an intermediate or high-risk premalignant condition (SMM) to symptomatic MM, and to find the optimal schedule of treatment administration. Three different treatment schedules will be investigated. An intensive daratumumab treatment schedule, similar to the schedule proposed for Arm A, has demonstrated clinical activity and an acceptable safety profile in subjects with relapsed/refractory MM [Lokhorst 2014][15]. However, in this asymptomatic patient population, a less intensive but still efficacious treatment schedule would be more attractive to patients and providers. In Study 501, subjects with relapsed or refractory MM received 2 pre and 7 full doses of daratumumab over a 9 week treatment period. Even with this abbreviated schedule, clinical activity (5 PRs and 3 MRs) was observed and the response was durable after stopping daratumumab [Lokhorst 2013][16]. These data suggest that 8 weekly infusions of daratumumab (as

proposed for Arm C) might be sufficient to delay the onset of symptomatic MM in this relatively immunocompetent patient population. A third alternative will be tested in Arm B, with an intensive treatment schedule once a week for 8 weeks followed by maintenance infusions once every 8 weeks.

As of Amendment 5, which was implemented to minimize the time subjects spend in the clinic during the coronavirus (COVID-19) pandemic, subjects continuing in the Treatment Extension Phase may switch to daratumumab 1800 mg SC, Q8W, at the discretion of the investigator. The SC formulation of daratumumab has been evaluated in the Phase 3 randomized Study MMY3012 (COLUMBA), which compared efficacy, PK, and safety of SC vs IV daratumumab in 522 subjects which met pre-defined non-inferiority criteria, demonstrating that daratumumab SC is non-inferior to IV.

2. OBJECTIVES AND HYPOTHESIS

2.1. Objectives

Primary Objective

- To evaluate if daratumumab can effectively decrease M protein in subjects with intermediate or high-risk SMM as assessed by CR rate
- To determine if daratumumab reduces the progression/death rate in subjects with intermediate or high-risk SMM

Secondary Objectives

The secondary objectives are:

- To evaluate preliminary efficacy, including ORR and progression-free survival (PFS)
- To evaluate the minimal residual disease (MRD) negative rate
- To evaluate the PK and immunogenicity of daratumumab
- To assess the safety profile of daratumumab given in 3 different dosing schedules
- To determine if daratumumab has an effect on QT interval

Exploratory Objective

- To explore biomarkers predictive of response to daratumumab
- To evaluate the utility of circulating MM cells (CMMCs) to predict SMM progression to MM

2.2. Hypothesis

Two hypotheses will be tested:

1. H_0: CR rate $\leq 15\%$

   H_a: CR rate $\geq 35\%$

2. H_0: PD/death rate ≥ 0.346/patient-year (median PFS < 24 months)

   H_a: PD/death rate ≤ 0.185/patient-year (median PFS > 45 months)

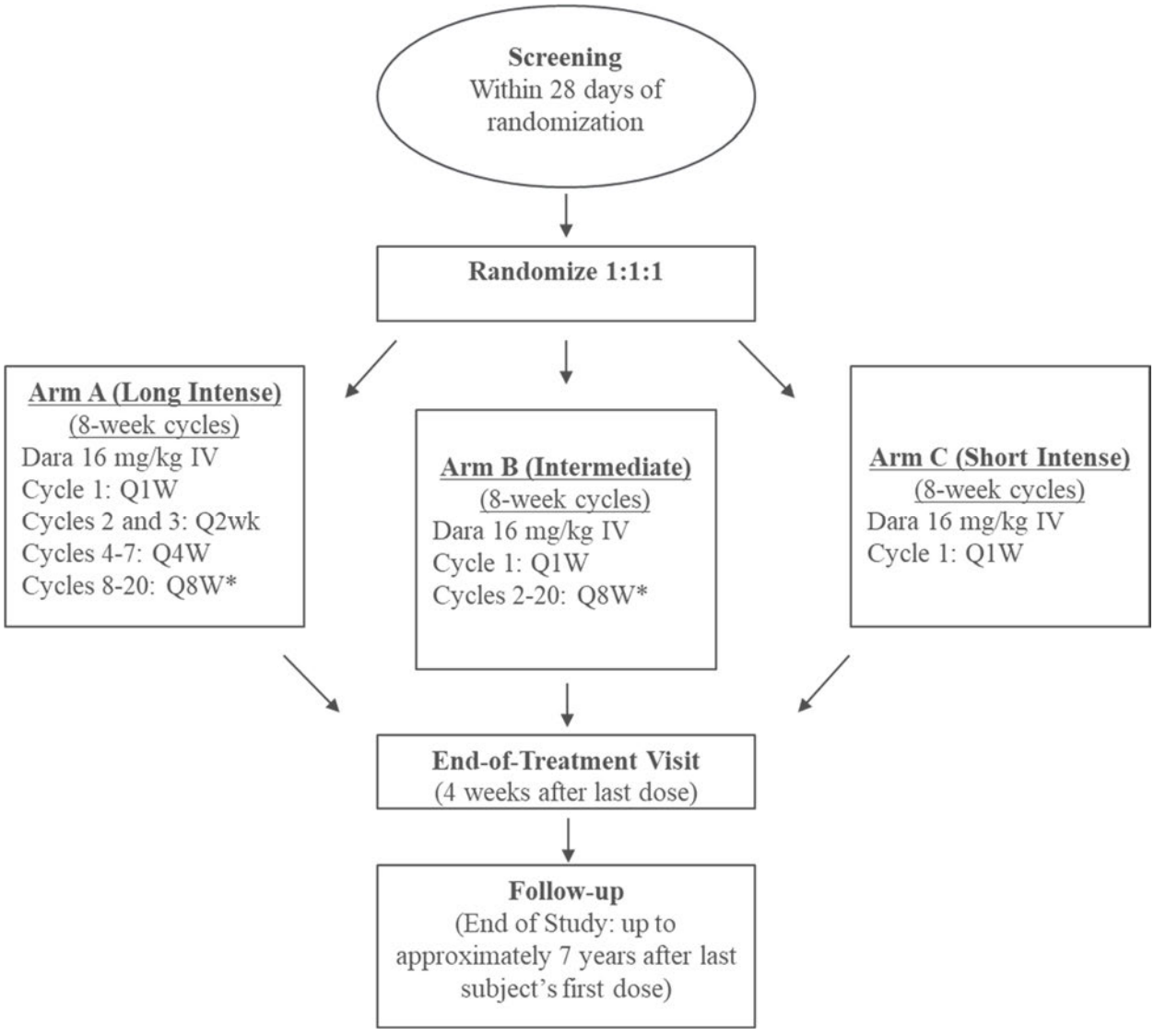
3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a randomized, open-label, 3-arm, multicenter study in subjects at least 18 years old with intermediate or high-risk SMM. Approximately 120 subjects will be enrolled in this study with 40 subjects planned per treatment arm.

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

Figure 1: Schematic Overview of the Study



* Every 8 weeks (Q8W) beyond Cycle 20 (in case of treatment extension or treatment re-initiation if applicable), as per investigator's discretion. As of Amendment 5, subjects continuing in the Treatment Extension Phase may switch to daratumumab 1800 mg SC Q8W at the discretion of the investigator. Subjects with a known allergy/intolerance to sorbitol will not be eligible to switch to daratumumab SC.

Subject participation will include a Screening Phase, a Treatment Phase, and a Follow-up Phase. The Screening Phase will be up to 28 days before Cycle 1, Day 1. Treatment cycles are 8 weeks in length. For subjects randomized to Arm A or Arm B, the Treatment Phase will extend from Cycle 1 to Cycle 20. In Arm A, daratumumab will be administered weekly in Cycle 1, every other week in Cycle 2 and Cycle 3, every 4 weeks in Cycle 4 to Cycle 7, and from Cycle 8 to Cycle 20 on Day 1 of each cycle. In Arm B, daratumumab will be administered weekly in Cycle 1 and then on Day 1 of each cycle from Cycle 2 to Cycle 20. For subjects in Arm A (long intense) and Arm B (intermediate), there is a possibility to extend treatment with IV daratumumab (every 8 weeks [Q8W]) after the end of Cycle 20 if, as per investigator discretion, there is a positive benefit/risk ratio, absence of Grade ≥3 treatment related toxicity, and at least stable disease has been achieved. In the case of subjects who already completed EOT and end of Cycle 20 occurred <6 months, these subjects can also continue receiving IV daratumumab administrations every 8 weeks. Per Amendment 5, subjects continuing in the study will follow the modified Time and Events schedule detailed in Attachment 4.

For subjects randomized to Arm C, the Treatment Phase consists of Cycle 1 only, when daratumumab will be administered weekly. Randomization will be stratified based on the number of risk factors for progression to symptomatic MM (<2 versus ≥2) as described in Section 5.

Measures to prevent IRRs will include pre-dose medication with methylprednisolone, paracetamol, and a H1-antihistamine before each daratumumab administration. Methylprednisolone will also be administered after daratumumab administration in Cycle 1 to prevent delayed infusion reactions. More information on the guidelines to prevent IRRs are provided in Section 6.4.

The Follow-up Phase will begin once a subject completes the planned number of cycles or in case of treatment extension, the investigator decides to end the treatment and the End-of-Treatment visit at 4 weeks after last dose (±7 days) is completed. Reasons for premature discontinuation of treatment are listed in Section 10.3. Subjects who discontinue before disease progression must continue to have disease evaluations according to the Time and Events Schedule (as of Amendment 5, refer to the Time and Events Schedule in Attachment 4). The Follow-up Phase will continue until death, lost to follow up, consent withdrawal, or study end, whichever occurs first.

Three data cutoff timepoints are planned:

- The first data cutoff is for an interim analysis 6 months after the last subject is randomized. This will be the basis for the analysis of the primary study endpoint of CR. All available data at the time of this data cutoff may be included in the interim analysis.
- The second data cutoff will occur 12 months after the last subject is randomized. This will be the basis for the analysis of the primary study endpoint of PD/death rate. All available data at the time of this data cutoff will be included in the Clinical Study Report.
- A third data cutoff will occur at the end of the study. The data collected will be reported in a Clinical Study Report.

- The end of the study will occur up to approximately 7 years after the last subject's first dose, following a decision by the sponsor to end the study based on data from the smoldering multiple myeloma Phase 3 study (SMM3001), or for reasons as outlined in Section 17.9.2, whichever occurs first.

Assessment of tumor response and disease progression will be conducted in accordance with the International Myeloma Working Group (IMWG) response criteria. An assessment of MRD will be conducted on bone marrow aspirate samples. Safety evaluations will include AE monitoring, physical examinations, electrocardiogram (ECG) monitoring, clinical laboratory parameters (hematology and chemistry), vital sign measurements, and Eastern Cooperative Oncology Group (ECOG) performance status. A QTc substudy will be conducted in a subpopulation of subjects at selected sites. Blood samples will be drawn for assessment of PK and biomarker parameters.

3.2. Study Design Rationale

Rationale for Study Design

Randomization in the assignment of subjects to a dosing schedule will allow assessment of preliminary efficacy and safety across all 3 arms. To further minimize imbalance across treatment arms and to allow for important subgroup analyses, subjects will be stratified according to the number of risk factors present at screening (<2 versus ≥2) using the criteria of Dispenzieri (2013)[3]. These risk factors will include: abnormal free light chain (FLC) ratio (<0.126 or >8), serum M-protein ≥3 g/dL, urine M-protein >500 mg/24 hours, IgA subtype, and immunoparesis (at least 1 uninvolved immunoglobulin [IgG, IgA, IgM] decreased more than 25% below lower limit of normal [LLN]). Stratification factors will be based on central laboratory analyses.

The treatment effect, evaluating whether initial response will reduce the rate of progression to symptomatic MM or death in subjects with intermediate or high-risk SMM, will be measured using the endpoint of PFS, defined as the time between randomization and progression to symptomatic MM or death. Given that the median time to progression in the high-risk SMM patient population is about 2 years, assessment of PFS rate approximately 1 year after the last subject is randomized should provide an early indication of treatment effect. However, all subjects will continue to be followed, and in the final study analysis (expected up to approximately 7 years after the last subject's first dose), long-term data on PFS will be analyzed.

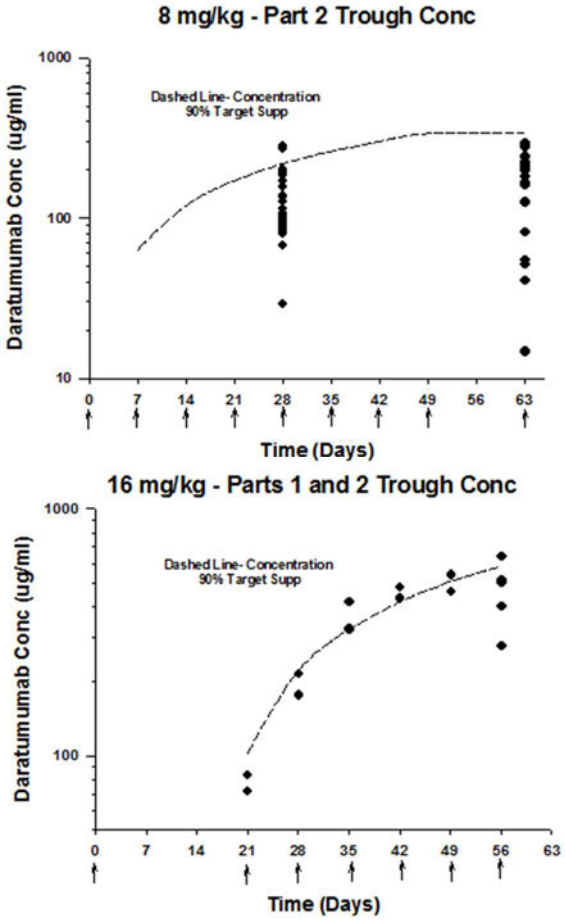
The criteria for efficacy (both response and follow up to progression to symptomatic MM, as defined by the IMWG, are objective and will be measured in all 3 treatment dosing schedules. The CR rate is defined as the proportion of subjects with CR. In a recent Phase 3 study of lenalidomide and dexamethasone in high-risk SMM patients, CR rate in the maintenance phase was 26% [Mateos 2013][18]. A correlation between CR and time to symptomatic MM has been demonstrated in simulation models conducted by the Janssen statistical team. A CR rate of 35% was chosen as the alternative hypothesis for this study, since a CR rate of at least 30% is considered to be most likely to translate into delay of progression to myeloma.

Even if a therapeutic approach is able to delay the progression to symptomatic MM, it will be important to establish whether the delayed symptomatic MM has a similar biology, responsiveness to standard therapy approaches, and outcomes as compared with watchful waiting. Within the constraints of a randomized Phase 2 design, data (including cytogenetics) will be collected on the biologic characteristics of the myeloma, the response to frontline therapy, and overall survival (OS).

Rationale for IV Daratumumab Dose Selection

CD38, the target for daratumumab, is expressed on NK cells and clinical data have shown NK cell suppression to be a marker of on target drug activity. Clinical PK data have shown the 16 mg/kg dose to be the lowest dose that results in nearly complete target suppression at all timepoints. This dose and schedule continuously suppressed NK cells throughout dosing. Daratumumab maximal target suppression is presented in Figure 2.

Figure 2: Daratumumab Maximal Target Suppression



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

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

The ORR appeared higher for the 16 mg/kg dose compared with the 8 mg/kg dose, based on early preliminary data from Part 2 of Study GEN501 and from Study MMY2002 (both ongoing studies) as of a cutoff date of 24 January 2014. In Study GEN501, the ORRs (ie, PR or greater) were 11% and 40% for the 8 mg/kg (n=28) and 16 mg/kg (n=15) dose regimens, respectively. For

Study MMY2002, the unconfirmed ORRs for the 8 mg/kg and 16 mg/kg dose regimens were similar to those observed in GEN501. In addition, VGPRs were observed for 7 of 30 subjects treated with the 16 mg/kg dose in the 2 studies. VGPR had not been observed at lower dose levels. These preliminary data support that full target saturation at the 16 mg/kg dose is needed to achieve higher and deeper response.

Rationale for Daratumumab SC Dose Regimen

The clinical pharmacology assessment of daratumumab SC monotherapy data are available from daratumumab SC-dosed subjects in a Phase 1/1b study (54767414MMY1004 [MMY1004; Part 2]), a Phase 3 study (MMY3012), and population PK and exposure-response analyses.

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

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

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

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

Rationale for QTc Study

In addition to expression on immune cell populations, CD38 is also expressed on cardiomyocytes. Daratumumab inhibits the cyclase activity of CD38, which is involved in the modulation of ER calcium release. The resulting lower intracellular calcium concentrations could potentially affect the function of cardiomyocytes.

In a limited toxicology study in chimpanzees, no ECG findings were noted. No other cardiovascular safety pharmacology data are available, and generation of further nonclinical safety data would be challenging given the lack of suitable animal models other than the chimpanzee,

since daratumumab does not bind to CD38 of species typically used for nonclinical toxicology testing (mouse, rat, rabbit, pig, cynomolgus monkey, or rhesus monkey).

Preliminary clinical data from study GEN501 Part 2 showed that QTc prolongation was observed upon administration of daratumumab at 16 mg/kg; however, these were not time-matched observations. The pre-to-post dosing increase for QTcF was approximately 10 msec. No subject had a post-dose absolute QT above 500 msec and no subject had an increase from baseline that was more than 60 msec. In addition, no infusion-related cardiac arrhythmia was observed.

To further investigate the potential effect of daratumumab on QTc prolongation, a QTc substudy will be included in this study. This study is suitable for evaluation of QTc since daratumumab is given as a single agent in a relatively healthy population of SMM patients.

Rationale for Pharmacokinetic and Immunogenicity Evaluations

The PK data from this study will be used for PK/pharmacodynamic modeling to aid in the selection of a Phase 3 dosing schedule.

The demographic characteristics of the SMM population differ significantly from previously studied daratumumab patient populations and may impact the PK profile. Therefore, samples will be obtained from all subjects to determine the PK profile, and the derived PK parameters will provide information about the determinates of inter subject variability in this population.

Immunogenicity to daratumumab is possible, and the incidence of anti-drug antibody generation in subjects with SMM may be different from previously studied populations because these subjects are expected to be less immune compromised. Therefore, samples to determine the presence of antibodies to daratumumab (immunogenicity) will be collected from all subjects during treatment and after the last dose in the study according to the Time and Events Schedule. As of Amendment 5, refer to Attachment 4 for required assessments.

Rationale for Biomarker Evaluations

MRD assessment:

Minimal Residual Disease (MRD) assessment allows evaluation of the depth of clinical response beyond the standard IMWG CR/sCR response category. There are multiple methods to assess MRD in MM, including next-generation sequencing (NGS)/PCR of immunoglobulin genes in bone marrow or whole blood [Ladetto 2014][9]. Several studies have demonstrated that MRD status is correlated with PFS and OS in MM [Martinez-Lopez 2014][17]. In the present study, we will assess for MRD in bone marrow aspirate when samples are obtained at screening, at confirmation of CR, and at 12 months and 18 months after first dose for subjects who maintain CR. As of Amendment 5, refer to Attachment 4 for required assessments.

DNA and Biomarker Collection:

Biomarker samples will be collected to evaluate the depth of clinical response to daratumumab through evaluation of MRD, using DNA sequencing of immunoglobulin genes, and to determine

response rates in specific molecular subgroups of MM, using DNA/RNA sequencing of MM cells to allow for assessment of genetic modifications such as deletion 17p, t(4;14), t(14;20), t(14;16), deletion13, GEP signatures such as UAMS-70, and mutations in p53, BRAF, FGFR, IGH, PI3K, or other molecular subtypes associated with disease progression. As of Amendment 5, refer to Attachment 4 for required assessments.

Exploratory biomarkers

In previous MM daratumumab studies, NK cell counts were reduced significantly following the first dose of daratumumab and maintained at low levels while patients were on therapy. Other immune cell populations (T and B cells) were not susceptible to decreases and were maintained at levels similar to baseline counts. Given that SMM precedes MM, and MM patients present with deficiencies in humoral and cell mediated immune function [Laubach 2011][12], these immune cell populations will be examined in SMM patients to determine whether a similar response is seen in NK, T, and B cells, and to evaluate the role of immune subpopulations (MDSC, cytotoxic T cells, regulatory T cells) in daratumumab response in this premalignant condition. Bone marrow MM cells may be evaluated for expression of CD38 expression and complement inhibitor proteins (CD46, CD55, CD59) which show association with response in previous clinical studies. Circulating MM cells (CMMCs) appear to be associated with response and can potentially serve as a prognostic marker for SMM patients who will progress to symptomatic MM. Seventy percent of MGUS, SMM and symptomatic MM patients have been reported to present with CMMCs and, furthermore, median TTP for patients with increasing CMMCs was significantly decreased compared to those who had stable counts [Witzig 1994; Kumar 2005; Ghobrial 2012][26,6,5]. In addition, CMMCs may be characterized for other assessments, such as RNA profiling, to compare to MM cells in the bone marrow niche. As of Amendment 5, refer to Attachment 4 for required assessments.

4. SUBJECT POPULATION

Screening for eligible subjects will be performed within 28 days before randomization.

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

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

4.1. Inclusion Criteria

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

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

2. Diagnosis of SMM for <5 years.

3. Criterion modified per Amendment INT-2.

3.1. Diagnosis of intermediate or high-risk SMM. Potential subject must meet both of the following criteria:

- Bone marrow plasma cells ≥10% and
- At least 1 of the following:
  - Serum M-protein ≥3 g/dL [except IgA ≥2 g/dL], or
  - Urine M-protein >500 mg/per 24 hours, or
  - Abnormal FLC ratio (<0.126 or >8) and serum M-protein <3 g/dL but >1 g/dL, or
  - The absolute involved serum free light chain (sFLC) is ≥100 mg/L with abnormal FLC ratio (<0.126 or >8).

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

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

a) absolute neutrophil count (ANC) ≥1.0 x 10^9/L (ie, ≥1000/μL);

b) platelet count ≥75 x 10^9/L (not permissible to transfuse a subject to reach this level);

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

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

e) total bilirubin ≤1.5 x ULN, except in subjects with congenital bilirubinemia, such as Gilbert syndrome (in which case direct bilirubin ≤1.5 x ULN required).

6. Criterion modified per Amendment INT-2.

6.1. Women of childbearing potential must commit to either abstain continuously from heterosexual sexual intercourse or to use 2 methods of reliable birth control simultaneously. This includes one highly effective form of contraception (tubal ligation, intrauterine device [IUD], hormonal [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 prior to dosing and continue until 4 months after the last dose of daratumumab. Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy or bilateral oophorectomy. During the study and for 4 months after receiving the last dose of daratumumab, a woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction.

7. A woman of childbearing potential must have a negative serum or urine pregnancy test within 14 days prior to randomization.

8. A man who is sexually active with a woman of childbearing potential must agree to always use condom during sexual intercourse, and all men must also not donate sperm during the study and for 4 months after receiving the last dose of study drug.

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

4.2. Exclusion Criteria

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

1. Active MM, requiring treatment, defined by any of the following:

    1. Bone lesions (one or more osteolytic lesions on skeletal radiography, computed tomography (CT), or positron-emission tomography [PET]-CT)
    3. Hypercalcemia (serum calcium >0.25 mmol/L (>1 mg/dL) higher than ULN or >2.75 mmol/L (>11 mg/dL)
    2. Renal insufficiency (see Section 9.2.1.4; preferably determined by creatinine clearance <40 mL/min measured or estimated using validated equations [MDRD or CKD-EP formulae recommended], or serum creatinine >177 µmol/L [>2 mg/dL])
    3. Anemia, defined as hemoglobin <10 g/dL and/or >2 g/dL below LLN in the absence of transfusion support or concurrent treatment with erythropoietin stimulating agents (ESAs)
    4. Clonal bone marrow plasma cell percentage ≥60%
    5. Serum free light chain involved:uninvolved ratio ≥100
    6. More than 1 focal lesion by magnetic resonance imaging (MRI)
2. Primary systemic AL (immunoglobulin light chain) amyloidosis

3. Criterion modified per Amendment INT-2.

3.1 Prior or concurrent exposure to any of the following:

- To approved or investigational treatments for SMM or/and MM (including but not limited to conventional chemotherapies, immunomodulatory drugs (IMiDs), or proteasome inhibitors).
- To daratumumab or other anti CD-38 therapies
- To concurrent treatment with corticosteroids with a dose >10 mg prednisone per day or equivalent.
- To concurrent treatment with bone-protecting agents (eg, bisphosphonates, denosumab) for treatment of SMM or MM. The subjects who are on a stable dose of these medications for a nonmalignant condition are allowed in the study.
- Received an investigational drug (including investigational vaccines) or used an invasive investigational medical device within 4 weeks before Cycle 1, Day 1

4. Subject has a history of malignancy (other than SMM) within 3 years before the date of randomization, except for the following if treated and not active: basal cell or nonmetastatic squamous cell carcinoma of the skin, cervical carcinoma in situ, ductal carcinoma in situ of breast, or International Federation of Gynecology and Obstetrics (FIGO) Stage 1 carcinoma of the cervix.

5. a) Subject has known chronic obstructive pulmonary disease (COPD) with a Forced Expiratory Volume in 1 second (FEV1) <50% of predicted normal. Note that FEV1 testing is required for patients suspected of having COPD and subjects must be excluded if FEV1 <50% of predicted normal.

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

6. Criterion modified per Amendment 4.

   6.1 Subject is:

- known to be seropositive for human immunodeficiency virus (HIV).
- known to have a history of hepatitis C.
- seropositive for hepatitis B (defined by a positive test for hepatitis B surface antigen [HBsAg]). Subjects with resolved infection (ie, subjects who are HBsAg negative but positive for antibodies to hepatitis B core antigen [anti-HBc] and/or antibodies to hepatitis B surface antigen [anti-HBs]) must be tested 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 (antiHBs 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.

For subjects who enter extension treatment period, HBV serology (HBsAg, anti-HBs, and anti-HBc) testing is to be performed locally prior to re-initiation. HBV serology is not required at re-initiation if this was performed as part of standard of care within 3 months prior to the re-initiation or the start of extension treatment is within 3 months of last daratumumab dose.

7. Subject has any concurrent medical or psychiatric condition or disease (eg, autoimmune disease, active systemic disease, myelodysplasia) that is likely to interfere with the study procedures or results, or that in the opinion of the investigator, would constitute a hazard for participating in this study.

8. Subject has clinically significant cardiac disease, including significant ischemic coronary disease, congestive heart failure (New York Heart Association [NYHA] Class III or IV), unstable arrhythmias, myocardial infarction or unstable angina within 6 months before randomization, a history of additional risk factors for torsades de pointes (eg, electrolyte abnormalities, family history of Long QT Syndrome), or a family history of sudden cardiac death before age 40.

9. Screening QT interval as corrected by Fridericia's formula (QTcF) >470 msec.

10. Subject has known allergies, hypersensitivity, or intolerance to monoclonal antibodies or human proteins, or their excipients (refer to Daratumumab IB), or known sensitivity to mammalian-derived products.

11. Vaccination with live attenuated vaccines within 4 weeks of first study agent administration

12. Subject is known or suspected of not being able to comply with the study protocol (eg, because of alcoholism, drug dependency, or psychological disorder). Subject has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments. Subject is taking any prohibited medications as per Section 8.2

13. Subject is a woman who is pregnant, or breast-feeding, or planning to become pregnant while enrolled in this study within 4 months after the last dose of daratumumab. Or, subject is a man who plans to father a child while enrolled in this study within 4 months after the last dose of daratumumab.

14. For subjects in the QTc substudy, screening 12-lead ECG based on a central laboratory reading showing any of the following:

    - QTcF >470 msec, based on the mean of 3 tracings
    - QRS interval of ≥110 milliseconds, based on the mean of 3 tracings

- PR interval ≥200 milliseconds, based on the mean of 3 tracings
- Pulse rate <45b pm or >90 bpm

15. Criterion modified per Amendment INT-2.

15.1 For subjects in the QTc substudy, the following additional exclusion criteria apply:

- Skin condition likely to interfere with ECG electrode placement, breast implant, or thoracic surgery likely to cause abnormality in electrical conduction
- Received medications with a known or possible risk of torsades de pointes (see https://www.crediblemeds.org) within 4 weeks prior to ECG screening day

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. Section 17.4, describes the required documentation to support meeting the enrollment criteria. Subjects who fail to meet the inclusion and exclusion criteria (ie, screen failures) may be rescreened once if their condition changes. Rescreening must be discussed with and approved by the sponsor on a case-by-case basis. Subjects who are determined to be eligible for rescreening must sign a new ICF and will then be assigned a new screening number.

5. TREATMENT ALLOCATION AND BLINDING

Treatment Allocation

Eligible subjects will be stratified based on the number of risk factors for progression to symptomatic MM (<2 vs ≥2) using the criteria of Dispenzieri (2013)[3]. These risk factors will include: abnormal FLC ratio (<0.126 or >8), serum M-protein ≥3 g/dL, IgA subtype, urine M-protein >500 mg/24 hours, and immunoparesis (at least 1 uninvolved immunoglobulin [IgG, IgA, IgM] decreased more than 25% below lower limit of normal [LLN]). Stratification factors will be based on central laboratory analyses.

Subjects will then be randomized to treatment in a 1:1:1 ratio to either Treatment Arm A, Treatment Arm B, or Treatment Arm C. The method of randomization is randomly permuted blocks. An interactive web-based randomization system (IWRS) will be used. Each subject will be assigned a unique subject number.

Blinding

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

6. DOSAGE AND ADMINISTRATION

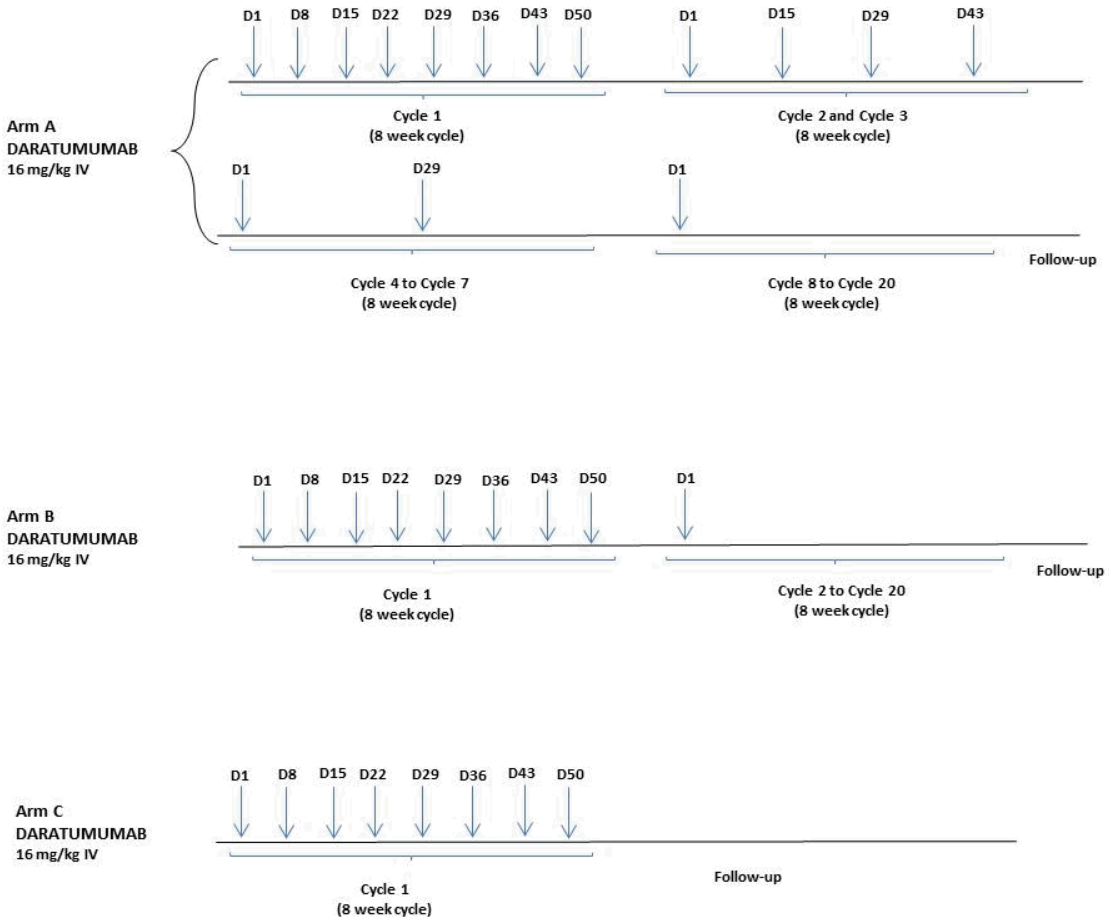
Daratumumab is to be administered as described in Table 3. Each cycle is 8 weeks in length. The start of each cycle may occur ±5 days of the scheduled day in order to accommodate the schedule of the site or subject. The start of each cycle should be scheduled relative to Cycle 1 Day 1 and should not change if visits have shifted within the allowed window. Subjects will continue to

receive daratumumab according to Table 3 until completion of the planned number of cycles. Reasons for early discontinuation of treatment are listed in Section 10.3.

For subjects in Arm A (long intense) and Arm B (intermediate), there is a possibility to extend treatment with IV daratumumab (Q8W) after the end of Cycle 20 if, as per investigator discretion, there is a positive benefit/risk ratio, absence of Grade ≥3 treatment related toxicity, and at least stable disease has been achieved. In the case of subjects who already completed EOT and end of Cycle 20 occurred <6 months, these subjects can also continue receiving IV daratumumab administrations every 8 weeks. As of Amendment 5, subjects continuing in the Treatment Extension Phase may switch to daratumumab 1800 mg SC Q8W at the discretion of the investigator. Subjects with a known allergy/intolerance to sorbitol will not be eligible to switch to daratumumab SC.

A schematic of study treatment administration is provided in Figure 3. For subjects still receiving doses in the Treatment Extension Phase as of Amendment 5, daratumumab 16 mg/kg IV may be switched to daratumumab 1800 mg SC at the discretion of the investigator on the same dosing (Q8W) schedule.

Figure 3: Schematic Overview of Study Treatment Administration



6.1. Daratumumab Preparation

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

6.2. Daratumumab IV Administration

Daratumumab (16 mg/kg) will be administered by IV infusion to subjects (1) in Arm A once every week in Cycle 1, every other week in Cycle 2 and Cycle 3, every 4 weeks in Cycle 4 to Cycle 7, and from Cycle 8 to Cycle 20 on Day 1 of each cycle; (2) in Arm B once every week in Cycle 1, and then on Day 1 of each cycle from Cycle 2 to Cycle 20; or (3) in Arm C once every week in Cycle 1 only. This schedule is presented schematically in Figure 3. As of Amendment 5, IV daratumumab infusion rates have been redefined with added flexibility and may be shortened to a 90-minute infusion for subjects without a history of an infusion-related reaction after the third dose, at the discretion of the investigator. More information is provided in the SIPPM.

For subjects in Arm A (long intense) and Arm B (intermediate), in case treatment will be extended after cycle 20, study drug will be given at the same frequency as during Cycles 8-20, which is at Day 1 of each cycle (Q8W). If a subject has already discontinued study drug and EOT took place <6 months, treatment can be re-initiated if, as per investigator's discretion, there is a positive benefit/risk ratio and at least stable disease has been achieved at the time of EOT without any evidence of disease progression at the time of re-initiation of the treatment. The assessment of disease progression will be based on the last disease evaluation performed. If the last disease evaluation was performed ≥5 months prior to the time of treatment re-initiation, disease evaluation is to be performed to make sure that the subject has not progressed. Every case of treatment re-initiation is to be discussed with the medical monitor prior to re-initiation.

If EOT took place ≥3 months but <6 months before re-initiation, the same instructions on infusion rates are applicable as per the SIPPM, meaning that slower infusion rates are to be applied during the first infusion, with acceleration during the subsequent infusions to avoid the occurrence of IRR.

Each subject's dose will be calculated based on the subject's weight rounded to the nearest kilogram. There is no cap on the absolute dose allowed, as long as the dose does not exceed 16 mg/kg. If a subject's weight changes by more than 10% from baseline, the dose of daratumumab will be re-calculated. For further information on daratumumab administration, please refer to the SIPPM. Subjects will receive pre-dose medications and post-dose medications as outlined in Section 6.4. Every effort should be made to keep subjects on the planned dosing schedule.

As noted in Table 3, vital signs should be monitored extensively on Cycle 1 Day 1 before, during, and after the first administration of daratumumab. For all other administrations, vital signs should be measured immediately before the start of administration and at the end of the administration. If a subject experiences any significant medical event, then the investigator should assess whether the subject should stay overnight for observation.

6.3. Daratumumab SC Administration

If the investigator decides to allow a switch from daratumumab IV to daratumumab SC administration, daratumumab SC will be administered by SC injection at a fixed dose of 1800 mg once Q8W until documented progression, unacceptable toxicity, or study end. Doses will be administered by manual push over 3-5 minutes in the abdominal SC tissue, rotating between the four quadrants. The volume of the SC solution will be 15 mL for the 1800 mg dose. Refer to the IPPI for additional guidance on SC administration of daratumumab SC.

The dose of daratumumab will remain constant throughout the study. For subjects who initially received daratumumab IV and then switch to daratumumab SC following Amendment 5, it is recommended subjects are observed for a period of time deemed appropriate by the investigator following the first daratumumab SC dose and, if necessary, after subsequent injections. Reasons for continued observation on subsequent daratumumab administrations may include, but are not limited to the following: subjects with a higher risk of respiratory complications (eg, subjects with mild asthma or subjects with COPD who have an FEV1 <80% at screening or developed FEV1 <80% during the study without any medical history), subjects with IRR with prior administrations of study drug, or subjects with a decreased condition on day of dosing compared to prior dosing day.

Subjects with a known allergy/intolerance to sorbitol will not be eligible to switch to daratumumab SC.

6.4. Guidelines for Prevention of Infusion Reactions

6.4.1. Pre-dose Medication

Pre-dose medications for subjects receiving daratumumab will be administered as described in Attachment 4. On daratumumab administration days (IV or SC), subjects will receive the following medications prior to dosing:

- Paracetamol (acetaminophen) 650-1000 mg IV or orally (PO) approximately 1 hour prior to daratumumab dose
- An H1-antihistamine (diphenhydramine 25-50 mg IV, PO, cetirizine 10 mg PO, or equivalent) approximately 1 hour prior to daratumumab dose
- Approximately 1 hour prior to daratumumab dose, methylprednisolone IV or PO 100 mg for the first 2 doses, 60 mg for all subsequent doses (in the absence of infusion-related AEs in the first 2 doses). An equivalent intermediate-acting or a long-acting corticosteroid may substitute [see Attachment 3 for conversion table]. IV administration is preferred, but oral steroids may be substituted.
- Montelukast 10 mg approximately 1 hour prior to daratumumab dose; use is optional per investigator discretion.

6.4.2. Post-dose Medication

For the prevention of delayed IRRs, all subjects will receive long- or intermediate-acting corticosteroid orally (20 mg methylprednisolone or equivalent in accordance with local standards) on the 2 days following daratumumab doses in Cycle 1 (beginning the day after the administration). In the absence of infusion-related AEs after Cycle 1, post-dose corticosteroids will be administered per investigator discretion. For subjects previously treated with daratumumab IV who switch to daratumumab SC, post-dose medications may be offered in conjunction with the first and subsequent dose of daratumumab SC, per investigator discretion, or as required due to an IRR experienced previously in the study during Cycle 1.

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

- H1-antihistamine (diphenhydramine, cetirizine, or equivalent) on the 2 days following all daratumumab administrations (beginning the day after the administration)
- Short-acting β2 adrenergic receptor agonist such as salbutamol aerosol
- 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 salbutamol ± inhaled corticosteroids for subjects with COPD)

In addition, these at-risk subjects may be hospitalized for monitoring for up to 2 nights after an administration. If subjects are hospitalized, then their FEV1 should be measured before discharge. If these subjects are not hospitalized, then a follow up telephone call should be made to monitor their condition within 48 hours after all administrations. If the subject has not experienced a significant medical event but is hospitalized overnight only for observation, then the hospitalization should not be reported as a SAE. Investigators may prescribe bronchodilators, H1-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, after 4 full doses, an at-risk subject experiences no major IRRs, then post-dose medications (except Cycle 1 corticosteroids) may be stopped at the investigator's discretion.

6.4.3. Management of Infusion-related Reactions

Infusion-related reactions are systemic reactions related to daratumumab administration (IV or SC). Subjects should be carefully observed during daratumumab administrations. Trained study staff at the clinic should be prepared to intervene in case of any infusion reactions occurring, and resources necessary for resuscitation (eg, agents such as epinephrine and aerosolized bronchodilator, also medical equipment such as oxygen tanks, tracheostomy equipment, and a defibrillator) must be available at the bedside. Attention to staffing should be considered when multiple subjects will be dosed at the same time.

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

- Subjects should be treated with acetaminophen, H1-antihistamine, or corticosteroids. Intravenous saline may be indicated. For bronchospasm, urticaria, or dyspnea, subjects may require H1-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.

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

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

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

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

6.4.3.2. Infusion-Related Reactions of Grade 3 or Higher

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

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

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

6.4.3.3. Injection-Site Reactions

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

6.5. Dose Delays

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

6.5.1. Daratumumab Toxicity Management

Refer to Section 6.4 for details on management of IRRs. If any of the following criteria are met, the daratumumab administration must be held to allow for recovery from toxicity. The criteria for a dose delay are:

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

6.5.2. Daratumumab Delays

Administration of daratumumab may be restarted upon recovery from toxicity to Grade 2 or baseline, with the exception that Grade 2 laryngeal edema or Grade 2 bronchospasm must be fully recovered.

If 2 consecutive planned doses of daratumumab are missed (also in case of treatment extension or treatment re-initiation), this should be brought to the attention of the Sponsor at the earliest possible time; subject continuation can occur if agreed by the Sponsor.

If more than 2 consecutive planned doses of daratumumab are missed (also in case of treatment extension or treatment re-initiation) due to daratumumab-related AEs, treatment should be permanently discontinued.

If a dose delay occurs, then PK and pharmacodynamic assessments should be performed on the actual administration day of daratumumab, not on the original scheduled administration day.

7. TREATMENT COMPLIANCE

Study drug (daratumumab) will be administered by qualified site staff, and the details of each administration will be recorded in the electronic case report form (eCRF). Additional details are provided in the SIPPM or equivalent document.

8. CONCOMITANT THERAPY

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 8.2. 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 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 post-dose systemic reactions, bisphosphonates, and any anticancer therapy (including radiation). Concomitant medications to manage AEs and SAEs will be recorded as per Section 12.3.1.

8.1. Permitted Therapies

Supportive management for infections is strongly recommended, including vaccination with pneumococcal vaccine before beginning treatment with daratumumab. Management of IRRs is also recommended, as discussed in Section 6.4. Other symptoms may be managed according to institutional guidelines provided medications that could potentially prolong the QT interval are not administered (see Section 8.2).

Vaccination is allowed per local guidelines (see Section 8.2 for Prohibited Therapies).

8.2. Prohibited Therapies

For subjects in the QTc substudy, medications with known or possible risk of torsades de pointes (see https://www.crediblemeds.org) are prohibited during Cycle 1. Use of such medications may result in the subject becoming unevaluable for the assessment of potential effects of daratumumab on QT.

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

- Administration of approved or investigational treatments for SMM or/and MM (including but not limited to conventional chemotherapies, immunomodulatory drugs (IMiDs), or proteasome inhibitors).

- Other agents that target CD38

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

8.3. 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 9.5.2.

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

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedule (Table 1) summarizes the frequency and timing of efficacy, PK, immunogenicity, biomarker, and safety measurements applicable to this study. As of Amendment 5, refer to Attachment 4 for a description of study procedures for subjects who continue in the Treatment Extension Phase or who have discontinued treatment but remain in Follow-up.

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

Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.

The maximum blood volume for the study is estimated at approximately 25 mL during screening and 340 mL during the first year. In the Follow-up Phase, subjects prior to PD will continue to have approximately 20 mL blood drawn every 2 months for serum disease evaluations. This includes laboratory assessments associated with safety, efficacy, and PK evaluations, as well as scientific research samples. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1.2. Screening Phase

The signed ICF must be obtained before any study-specific procedures are performed. The Screening Phase begins when the first protocol specified screening assessment is performed (typically signing of the ICF). During the Screening Phase, eligibility criteria will be reviewed and a complete clinical evaluation will be performed as specified in Table 1. Screening procedures will be performed within 28 days before randomization; however, chest x-rays and 12-lead ECGs

performed up to 42 days before randomization and imaging (skeletal radiography, low-dose CT, or MRI) and bone marrow aspirate/biopsy performed up to 56 days before randomization as routine standard of care for the subject's disease can be used.

Eligibility of the subject is based on central laboratory results of screening serum and urine M-protein measurements.

9.1.3. Treatment Phase

Details of the procedures performed during the Treatment Phase (including treatment extension or treatment re-initiation) are outlined in Table 1. As of Amendment 5, refer to Attachment 4 for a description of study procedures for subjects who continue in the Treatment Extension Phase or who have discontinued treatment but remain in Follow-up. Subjects should start study treatment within 5 days after randomization. A window of ±5 days is allowed for visits to the clinic. The start of each cycle should be scheduled relative to Cycle 1 Day 1 and should not change if visits have shifted within the allowed window. Subjects will be closely monitored for AEs, laboratory abnormalities, and clinical response. Clinical evaluations and laboratory studies may be repeated more frequently, if clinically indicated. If disease progression is diagnosed, then the subject will discontinue study treatment, complete the End-of-Treatment Visit, and enter the Follow-up Phase.

For subjects in Arm A (long intense) and Arm B (intermediate), there is a possibility to extend treatment with IV daratumumab (Q8W) after the end of Cycle 20 if, as per investigator discretion, there is a positive benefit/risk ratio, absence of Grade ≥3 treatment related toxicity, and at least stable disease has been achieved. In the case of subjects who already completed EOT and end of Cycle 20 occurred <6 months, these subjects can also continue receiving IV daratumumab administrations every 8 weeks. For subjects continuing in the Treatment Extension Phase as of Amendment 5, daratumumab 16 mg/kg IV may be switched to daratumumab 1800 mg SC at the discretion of the investigator at the same dosing (Q8W) schedule. Subjects with a known allergy/intolerance to sorbitol will not be eligible to switch to daratumumab SC.

End of Treatment Visits

Unless a subject withdraws consent for study participation or is lost to follow up, an End-of-Treatment Visit is to occur at 28 days ± 7 days after the last dose of all study treatments. Every effort should be made to conduct the End-of-Treatment Visit before the subject starts subsequent treatment. If a subject is unable to return to the site for the End-of-Treatment Visit, then the subject should be contacted to collect information on AEs and concomitant medications that occur up to 30 days after the last dose of study treatment. Additional information on reporting of AEs is presented in Section 12. Due to the addition of the treatment extension outlined in Amendment 4 which allowed some subjects to resume daratumumab treatment if within 6 months of last dose of Cycle 20, it is possible for subjects to have 2 EOT visits associated with this study. As of Amendment 5, this additional EOT visit associated with treatment extension should be conducted as specified in Attachment 4.

As such, 2 EOT visit CRFs should be completed as applicable for subjects who continued to treatment extension (End of Treatment CRF and End of Treatment Extension CRF).

9.1.4. Follow-up Phase

The Follow-up Phase will begin once subjects complete the planned number of cycles, and no treatment extension will be given as per investigator's discretion. In case of treatment extension or treatment re-initiation, the same procedures are to be followed as outlined in Section 9.1.3 and Table 1 (as of Amendment 5, refer to Attachment 4). If included in the treatment extension, it is possible that subjects will have 2 Follow-up Phase portions of the study (1 after the planned 20 cycles, and 1 after the last dose in the treatment extension). As of Amendment 5, these additional protocol-specified Follow-up assessments should be conducted as specified in Attachment 4.

Reasons for premature discontinuation of study treatment are listed in Section 10.3. Subjects who discontinue before disease progression must continue to have disease evaluations at Week 5, Week 9, and then every 8 weeks for the first year, thereafter every 16 weeks according to the Table 1 (as of Amendment 5, refer to Attachment 4) until confirmed PD, death, the start of a new anticancer therapy, withdrawal of consent, lost to follow-up, or the end of the study. If subjects have not progressed to symptomatic MM, no other treatment for SMM or MM is allowed during the study. After progressive disease, follow-up for subsequent multiple myeloma therapy (including the response to the first subsequent multiple myeloma therapy), second primary malignancies, and survival status will be obtained at least every 6 months.

If the information is obtained via telephone contact, written documentation of the communication must be available for review in the source documents. If the subject has died, the date and cause of death will be collected and documented in the eCRF.

The end of the study will occur up to approximately 7 years after the last subject's first dose, following a decision by the sponsor to end the study based on data from the smoldering multiple myeloma Phase 3 study (SMM3001), or for reasons outlined in Section 17.9.2, whichever occurs first.

9.2. Efficacy

As of Amendment 5, refer to Attachment 4 for a description of study procedures for subjects who continue in the Treatment Extension Phase or who have discontinued treatment but remain in Follow-up. Disease assessments will be performed at Week 5, Week 9, and then every 8 weeks in the first year, thereafter every 16 weeks (including treatment extension/re-initiation phase) until disease progression. A window of ±7 days before the scheduled assessment date is allowed. For subjects with treatment delays, disease assessments should be performed at the time of daratumumab administration, but do not need to be repeated if they were performed within 14 days before the actual treatment date. Disease progression, if based on laboratory results only, must be confirmed by a consecutive assessment.

Disease assessments will be performed by a central laboratory (unless otherwise specified) according to Table 1. Disease progression to symptomatic MM will be evaluated using the IMWG criteria (Rajkumar 2014)[21]. For subjects who discontinue study drug before disease progression, disease assessments should continue to be performed as scheduled until disease progression, death,

withdrawal of consent for study participation, or the end of the study. Disease assessments scheduled for treatment days should be collected before study drug is administered.

9.2.1. Evaluations

As of Amendment 5, refer to Attachment 4 for a description of study procedures for subjects who continue in the Treatment Extension Phase or who have discontinued treatment but remain in Follow-up. The text that follows in the subsections of 9.2.1 describes the evaluations required prior to Amendment 5.

9.2.1.1. Assessment of Response

Disease evaluations must be performed as outlined in the Time and Events Schedules on the scheduled assessment day (±7 days). Disease evaluations scheduled for treatment days should be collected before study drug is administered. Disease evaluations will be performed by a central laboratory (unless otherwise specified).

This study will use the IMWG consensus recommendations for MM treatment response criteria (Durie 2007; Rajkumar 2011)[4,22] presented in Table 4. For quantitative immunoglobulin at baseline, M-protein, and immunofixation measurements in serum and 24-hour urine, the investigator will use results provided by the central laboratory.

Table 4: 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* • <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%
Stable disease (SD)	• Not meeting criteria for CR, VGPR, PR, or symptomatic MM

FLC = free light chain; PC = plasma cell
All response categories (CR, sCR, VGPR, PR) require 2 consecutive assessments made at any time before the institution of any new therapy and 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.
*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.
[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.

9.2.1.2. Assessment of Disease Progression to Multiple Myeloma

For data analysis and reporting, the sponsor will use a computer algorithm to objectively and consistently implement the IMWG diagnostic criteria for MM requiring systemic therapy. During the study, disease progression will be measured according to the published international uniform diagnostic criteria for MM requiring systemic therapy established by the IMWG (Rajkumar 2014)[21] presented in Table 5.

Table 5: Diagnostic Criteria for Multiple Myeloma Requiring Systemic Therapy

Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma[a] PLUS 1 or more of the following: • Calcium elevation (>0.25 mmol/L [>1 mg/dL] higher than ULN or >2.75 mmol/L [>11 mg/dL]) • Renal insufficiency (creatinine clearance[b] <40mL/min or serum creatinine >177 µmol/L [>2 mg/dL]) • Anemia (hemoglobin <10 g/dL [<6.5 mmol/L] or >2 g/dL [>1.25 mmol/L] lower than LLN • Bone disease (one or more osteolytic lesions on skeletal radiography, CT, or PET-CT[c]) • Clonal bone marrow plasma cell percentage[a] ≥60% • Involved: uninvolved serum free light chain ratio[d] ≥100 • >1 focal lesion[e] on MRI studies

a. Clonality should be established by showing κ/λ light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and the core biopsy, the highest value should be used.
b. Measured or estimated by validated equations.
c. 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. These values are based on the serum Freelite assay (The Binding Site Group, Birmingham UK). The involved free light chain must be ≥100mg/L.
e. Each focal lesion must be 5mm or more in size.

From Rajkumar 2014[21]

Progressive disease must be documented consistently across clinical study sites using the same criteria. Disease progression based on 1 of the laboratory tests alone must be confirmed by at least 1 repeat investigation. It is important that instances of progression be reported to the sponsor as soon as possible.

9.2.1.3. Free Light Chain Ratio

In a subset of subjects, daratumumab disproportionally decreases the uninvolved light chain, thus artificially skewing the FLC ratio. The artificially elevated FLC ratios have led to ambiguous cases in interpretation of disease progression. In cases where the subject's disease progresses solely based on FLC criteria, if the subject continues to benefit from the study treatment based on investigator assessment, the subject is allowed to continue the study treatment if agreed by the sponsor. The investigator or designee must consult with the subject and discuss the considerations for recommending continuation of study treatment. The agreement of the subject to continue treatment with daratumumab must be documented in the medical record. Disease evaluations must continue at a frequency of at least every 8 weeks.

9.2.1.4. CRAB Criteria-Related Laboratory Assessments

The following laboratory tests must be performed at every disease assessment, including during the follow-up period, whenever disease assessments are required:

- Serum calcium corrected for albumin (central lab)
- Creatinine clearance or serum creatinine (local lab)
- Hemoglobin (local lab)

Serum Calcium Corrected for Albumin

Development of hypercalcemia (according to CRAB criteria; corrected serum calcium >11 mg/dL or >2.75 mmol/L) indicates progression to symptomatic MM if it is not attributable to any other cause (see Table 5). 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.

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])

Measurement of free ionized calcium is an acceptable alternative to corrected serum calcium for determining hypercalcemia. Free ionized calcium levels >1.5 mmol/L are considered to be hypercalcemic (according to CRAB criteria) for this study. Calcium and albumin will be analyzed centrally.

Creatinine Clearance

Development of renal insufficiency (according to CRAB criteria: measured or estimated creatinine clearance <40 mL/min using validated equations preferred; or creatinine >2 mg/dL or >177 µmol/L) indicates progression to symptomatic MM if it is not attributable to any other cause. Measured or estimated glomerular filtration rates (according to the modification of diet in renal disease [MDRD, Levey 2006][13] or chronic kidney disease epidemiology collaboration [CKD-EPI, Levey 2009][14] formulae, as per local practice) are preferred over a fixed serum creatinine concentration. For online calculators, please go to https://www.kidney.org/professionals/KDOQI/gfr_calculator. Creatinine clearance or serum creatinine will be analyzed locally as part of the safety laboratory evaluations during treatment. For subjects who discontinue treatment prior to PD, these measurements should continue to be analyzed locally every time disease assessments are performed.

Hemoglobin

Development of anemia (according to CRAB criteria; hemoglobin <10 g/dL or >2 g/dL lower than LLN) indicates progression to symptomatic MM if it is not attributable to any other cause. Before PD is declared on the basis of anemia without other CRAB signs or symptoms, additional diagnostic tests should be carried out to determine that there is no other underlying cause of anemia. Hemoglobin will be analyzed locally as part of the safety laboratory evaluations during treatment. For subjects who discontinue treatment prior to PD, these measurements should continue to be analyzed locally every time disease assessments are performed.

9.2.1.5. Myeloma Protein Measurements in Serum and Urine

Blood and 24-hour urine samples for M-protein measurements will be sent to and analyzed by a central laboratory. Only 1 serum and one 24-hour urine sample per time point are required by the central laboratory to perform the following tests.

- Serum quantitative immunoglobulins (QIgs)
  - All subjects will be evaluated for IgG, IgA, IgM, IgE, and IgD at Screening. During treatment, subjects with IgD or IgE disease will be evaluated for IgG, IgA, IgM, IgE, and IgD and subjects with IgG, IgA, or IgM disease will be evaluated for IgG, IgA, and IgM.
- Serum M-protein quantitation by electrophoresis (SPEP)
- Serum immunofixation at Screening and thereafter when a CR is suspected or maintained. If daratumumab interference is suspected based on SPEP and IFE results, additional reflex IFE testing may be performed.
- Serum free light chain assay
- 24-hour urine M-protein quantitation by electrophoresis (UPEP)
- Urine immunofixation at Screening and thereafter when a CR is suspected or maintained.

Blood and 24-hour urine samples will be collected as specified in Table 1 until the development of confirmed disease progression. In subjects with baseline UPEP result below the level of quantification, UPEP analysis will be repeated only (1) at the time of disease progression and (2) to confirm a CR. Serum/urine immunofixation assays will be performed at screening, and at other times if considered helpful in the interpretation of SPEP and UPEP results.

Daratumumab, as an immunoglobulin, may interfere with clinical SPE/IFE assessments. In cases where daratumumab interference is suspected, a reflex assay (DIRA: Daratumumab-specific Interference Reflex Assay) confirming the presence of daratumumab will be performed. In cases where CR or sCR is suspected and DIRA confirms that daratumumab is present on SPE/IFE, additional clinical assessments will be triggered to confirm the CR/sCR. A subject who meets all other clinical criteria for CR/sCR, and who has daratumumab interference confirmed by the reflex assay, will be considered a CR/sCR.

9.2.1.6. β2-microglobulin

Blood samples for β2 microglobulin analysis are to be collected at Screening and upon disease progression, and will be analyzed by the central laboratory.

9.2.1.7. Bone Marrow Examination

Bone marrow assessments to be performed locally and centrally are summarized in Table 6.

Table 6: Bone Marrow Testing

	Local Testing	Central Testing
Screening	Disease characterization (morphology and either immunohistochemistry, immunofluorescence, or flow cytometry). Cytogenetics by conventional karyotype or FISH.	MRD and molecular subtyping: a portion of bone marrow aspirates collected at screening will be sent to a central laboratory. If a fresh bone marrow aspirate will not be performed at screening because a sample is available within 56 days prior to randomization, then unstained, non-decalcified diagnostic tissue [bone marrow aspirate slides, touch prep from biopsy (rolled biopsy) slides, or clot specimen slides] must be collected for MRD assessment.
CR, sCR	For response confirmation, additional bone marrow aspirates or biopsies (or both) will be performed locally 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.	MRD: a portion of bone marrow aspirates collected during these timepoints will be sent to a central laboratory.
Maintained CR, sCR	Not applicable.	MRD: For subjects who maintain CR, an additional bone marrow aspirate will be obtained 12 and 18 months (+/-1 month) after first dose and sent to central laboratory.
Disease Progression	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; FFPE=formalin-fixed paraffin embedded; FISH=fluorescence in situ hybridization; MRD=minimal residual disease; sCR=stringent complete response

A portion of the bone marrow aspirate at baseline and at disease progression when feasible will be utilized for DNA/RNA sequencing to characterize subjects (t(4;14), del17p, t(14;16), UAMS70, etc) and to evaluate potential mechanisms of resistance (CD38 mutations, expression of CD38 and CD59).

9.2.1.8. Assessment of Bone Lesions

The presence of bone lesions will be evaluated locally per local imaging practice (eg, complete skeletal survey including skull, entire vertebral column, pelvis, chest, humeri, femora, and any other bones for which the investigator suspects involvement by disease radiography). During the Treatment Phase and before disease progression is confirmed, imaging should be performed as indicated in the Time and Event Schedule, to document response or progression.

Skeletal radiography or low-dose whole body CT

Osteolytic lesions will be assessed by radiography, low-dose whole body CT scan, or PET-CT. Bone lesion assessments will be performed at Screening and regularly during the study as indicated in the Time and Events Schedule. The same methodology should be used throughout the study for comparison purposes.

For subjects with (1) negative MRI results at baseline, (2) M-protein increase ≤25%, and (3) no other signs of clinical progression, only an MRI needs to be performed. For these subjects, low-dose whole body CT or skeletal survey does not need to be repeated unless focal lesions have been identified by MRI.

MRI

An MRI (spine and pelvis or whole body) will be performed to assess focal lesions at Screening, every 6 months for the first 3 years, and then yearly, and at biochemical progression (eg, increase of SPEP >25%) or at suspected PD. Whole body MRI should be performed per local practice or if clinically indicated. PET-CT can be used as an alternative imaging test to replace MRI.

Disease Progression

Sometimes subjects present with disease progression manifested by symptoms of pain or vertebral compression fractures due to bone changes. Therefore, disease progression may be documented, in these cases, by additional images such as CT or PET-CT to clarify if the changes are related to myeloma. One or more sites of osteolytic bone destruction (≥ 5 mm in size) seen on CT (including low-dose whole-body CT) or PET-CT does fulfil the criteria for bone lesion in MM and should be regarded as meeting the CRAB requirement irrespective of whether they can be visualized on skeletal radiography or not. Increased uptake on PET-CT alone is not adequate for the diagnosis of osteolytic bone lesion; evidence of underlying osteolytic bone destruction is needed on the CT portion of the examination. However, PET-CT can be used as alternative imaging test to replace MRI for identification of focal lesions. If the diagnosis of disease progression is obvious by imaging investigations (skeletal radiography, low-dose whole-body CT, PET CT, or MRI), then no repeat confirmatory imaging is necessary. In instances where changes may be more subtle, repeat imaging may be performed in 1 to 3 months per investigator discretion.

9.2.1.9. Best Response to First Subsequent Anti-myeloma Therapy

Best response to first subsequent anti-myeloma therapy will be assessed by physician report at 6-month intervals. IMWG response criteria for MM will be used for these assessments.

9.2.2. Endpoints

9.2.2.1. Primary Endpoint

There are two co-primary endpoints:

- Complete Response (CR) rate, defined as the proportion of subjects with a CR, as defined in Section 9.2.1.1

- PD/Death rate, defined as the proportion of subjects that have progressed to MM or died per patient-year (number of events (PD or death)/total follow-up for all subjects).

9.2.2.2. Major Secondary Endpoints

- Minimal residual disease negative rate
- Time to next treatment defined as, the time from the date of randomization to the date of the first subsequent MM treatment
- Overall Response Rate defined as CR+PR rate
- PFS, defined as the time from the date of randomization to the date of initial documented PD according to the CRAB criteria, myeloma defining events, or date of death, whichever occurs first. For subjects who are progression-free and are alive at the time of data cutoff for an analysis, PFS will be censored at their last disease assessments on or before initiation of subsequent anti-MM therapy, lost to follow-up, or withdrawal of consent if any of them occurred, or last disease assessments if none of them occurred. PFS will be censored at the date of randomization if there is no postbaseline disease evaluation recorded.
- Incidence of symptomatic MM with adverse prognostic features, which include International Staging System (ISS) Stage III (based on β2-microglobulin and albumin) and adverse cytogenetic characteristics
- Response to first subsequent MM treatment
- Overall survival rate

9.2.2.3. Exploratory Endpoints

Exploratory endpoints include:

- To explore biomarkers predictive of response to daratumumab
- To evaluate the utility of CMMCs to predict SMM progression to MM

9.3. Pharmacokinetics and Immunogenicity

As of Amendment 5, samples for the evaluation of PK and immunogenicity described below in the subsections of 9.3 will not be collected. Refer to Attachment 4 for a description of study procedures for subjects who continue in the Treatment Extension Phase or who have discontinued treatment but remain in Follow-up.

9.3.1. Evaluations

Samples to assess both the serum concentration (PK) of daratumumab and the generation of antibodies to daratumumab (immunogenicity) will be obtained from all subjects according to Table 1. At specified timepoints, venous blood samples (5 mL per sample) will be collected to determine serum concentration of daratumumab and the serum will be divided into 3 aliquots (1 aliquot for PK analysis, 1 aliquot for antibodies to daratumumab analysis [when appropriate], and 1 aliquot as a backup). Samples collected for determining serum concentrations of daratumumab in this study may be retained to address questions about drug characteristics that may arise at a later time point.

The exact dates and times of blood sampling must be recorded. Refer to the Laboratory Manual or equivalent document for sample collection requirements. Collected samples must be stored under the specified and controlled conditions for the temperatures indicated in the laboratory manual.

9.3.2. Analytical Procedures

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

For the 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.

9.3.3. Pharmacokinetic Parameters

The PK parameters are defined as:

C_{max}	Maximum observed concentration
C_{min}	Minimum observed concentration

For daratumumab, the PK evaluations include C_{min} and C_{max}. If sufficient data are available, other PK parameters may be calculated. The Cmax will be determined based on visual inspection of the serum concentration profile. If there are sufficient data, population PK analysis of serum concentration-time data of daratumumab may be performed using nonlinear mixed-effects modeling and used to estimate the CL and V. If the population PK analysis is conducted it will include data from other clinical studies. Details will be provided in a population PK 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 antibodies to daratumumab (immunogenicity) according to Table 1. Daratumumab concentration is also evaluated at all immunogenicity time points to ensure appropriate interpretation of immunogenicity data. When both serum concentration and immunogenicity analyses are specified, they are performed on aliquots from the same blood draw and no additional sampling is required. Procedures for sample collection, preparation, identification, storage, and shipment will be provided in the Laboratory Manual or equivalent document.

A blood sample should be drawn, if possible, for determination of antibodies to daratumumab any time an infusion reaction is observed or reported during the study. Daratumumab serum concentration will also be determined from the same infusion reaction sample for the purpose of interpreting immunogenicity data. These samples will be stored and evaluated if deemed necessary. If the infusion reaction results in treatment discontinuation, then subjects should undergo all scheduled safety and efficacy evaluations. Samples collected for the analysis of daratumumab immunogenicity/serum concentration may additionally be used to evaluate safety or

efficacy aspects that address concerns arising during or after the study period or for the evaluation of relevant biomarkers by the sponsor or sponsor's designee.

9.4. Biomarkers

As of Amendment 5, samples for the evaluation of biomarkers described below will not be collected. Refer to Attachment 4 for a description of study procedures for subjects who continue in the Treatment Extension Phase or who have discontinued treatment but remain in Follow-up.

Biomarker assessments will focus on 4 main objectives including evaluating the ability of daratumumab to reduce MRD in SMM subjects who achieve a complete response, to determine the clinical benefit (ORR, PFS, and OS) of daratumumab in subjects with genetic modifications, to evaluate the immunophenotype of SMM patients for potential immune cell contributions to daratumumab response, and to evaluate the contribution of CMMCs to progression of disease. All biomarker assessments will be performed centrally.

Bone marrow aspirates will be collected at screening and following treatment as outlined in the Time and Events Schedule. Baseline bone marrow aspirates will be subjected to DNA sequencing in order to establish the myeloma clone for MRD monitoring. A fresh bone marrow aspirate at Screening is required if at all possible, for MRD assessment. If bone marrow aspirate is not available, unstained, non-decalcified diagnostic tissue [bone marrow aspirate slides, touch prep from biopsy (rolled biopsy) slides, or clot specimen slides] must be supplied for MRD assessment instead. For subjects who achieve a CR or sCR, additional bone marrow aspirate will be utilized for assessment of MRD by next-generation sequencing (NGS) of immunoglobulin heavy and light chains (Vij 2014)[24]. For subjects who maintain a CR, MRD will also be assessed at 12 and 18 months after first dose in bone marrow aspirate. If this methodology is unavailable, or determined to be scientifically inferior, then alternative methods for MRD assessment may be utilized. In cases where daratumumab is suspected of interfering with serum IFE and preventing clinical CR response calls, subjects with VGPR may also be evaluated for MRD by NGS.

In addition to MRD evaluations, bone marrow aspirates will be utilized for whole exome DNA/RNA sequencing in subjects with genetic modifications (t(4;14), t(14;16), del17p, UAMS-70, etc) and to monitor for potential predictive biomarkers of response and/or resistance, including changes in CD38 and CD59 expression. In addition, changes in expression patterns of genes associated with ADCC, CDC, or other mechanisms of action of daratumumab may be evaluated.

A whole blood sample will be drawn at time points indicated in the Time and Events Table 1 to evaluate immune cell populations by flow cytometry and/or CyTOF, and to reserve plasma for potential proteomic evaluations. These samples may be used to evaluate specific subsets of immune cells such as cytotoxic T cells, regulatory T cells, MDSCs, B cells, and NK cells. Cells may also be used for additional phenotypic and functional profiling. Proteomic analysis may also be used to evaluate changes in cytokines, complement proteins, soluble CD38, IFNγ, granzyme, perforin, and other proteins associated with ADCC/CDC/ADCP and to evaluate potential biomarkers of response and resistance.

Additional whole blood samples will be drawn to evaluate patients for CMMCs when feasible. Use of the CellSearch® or other adequate CTC discovery platforms may be used to enumerate circulating cells and subsequently conduct phenotypic and/or genotypic analysis. As of Amendment 4, these samples will no longer be collected.

Biomarker analyses are dependent upon the availability of appropriate biomarker assays and may be deferred or not performed if during or at the end of the study it becomes clear that the analysis will have no scientific value, or if there are not enough samples or not enough responders to allow for adequate biomarker evaluation. In the event the study is terminated early or shows poor clinical efficacy, completion of biomarker assessments is based on justification and intended utility of the data. Samples for biomarker evaluations will be collected as specified in the Time and Events Schedule.

9.5. Safety Evaluations

9.5.1. Electrocardiogram (ECG)

For subjects not participating in the QTc evaluation substudy, a 12-lead ECG will be performed at screening, Cycle 1 dose 8, and at End-of-Treatment.

QTc Evaluation Substudy

For subjects participating in the QTc evaluation substudy, the QTc endpoint will be the change in QTc interval (at each measured timepoint) from time matched baseline, where baseline is the QTc measurement before any administration of daratumumab.

For the first 30 subjects eligible for the QTc substudy at sites participating in the QTc evaluation substudy, 12-lead ECGs will be obtained at the following timepoints (see Time and Events Schedule for allowable windows):

- Screening (one day from the range Day -14 to Day -1): 1:00 PM, 2:00 PM, 3:00 PM, 4:00 PM, 5:00 PM
- Cycle 1, Dose 1: pre-dose and after the end of infusion
- Cycle 1, Dose 8: pre-dose, after the end of infusion, and 1 hour after the end of infusion

ECGs must be performed with the subject in the same comfortable supine resting position for at least 10 minutes before the ECG tracings. Pre-dose ECGs will be obtained in the time period following administration of preinfusion medications but before the daratumumab infusion. The 12 lead ECGs will be done in triplicate (three 10 second digital ECGs within 5 minutes). It is important to note that the actual test time should be consistent with a timepoint for both the screening and on-study ECGs, to minimize variability in the results obtained. Similarly, for subjects participating in ECG data collection, daratumumab infusions should be administered beginning at approximately the same time of day for Doses 1 and 8 in Cycle 1.

Vital signs, ECGs, and PK samples must be collected according to the timepoints and windows specified in Table 2. On days when triplicate ECGs are scheduled, pre-dose assessments should be performed in the following order:

1. Administer preinfusion medications.
2. Measure vital signs.
3. Obtain triplicate ECGs.
4. Draw blood samples for PK.
5. Administer daratumumab infusion.

Twelve-lead ECGs will be recorded at a paper speed of 25 mm per second until 4 regular consecutive complexes are available. Computer-generated interpretations of ECGs should be reviewed for data integrity and reasonableness by the treating physician. All digital ECG tracings will be sent to a third-party central ECG laboratory for measurement of intervals, diagnostics of abnormalities and review of ECG waveform morphology. For the triplicate ECGs collected at each time point, the mean of 3 measurements for each ECG parameter will be considered for all listing and statistical analyses. Refer to the ECG Manual for details.

9.5.2. Other Safety Evaluations

Safety will be measured by adverse events, laboratory test results, ECGs, vital sign measurements, physical examination findings, and assessment of ECOG performance status score. All toxicities will be graded according to the NCI-CTCAE Version 4. 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. A QTc substudy will be conducted in a subpopulation of subjects at selected sites.

Based on the previous human experience with daratumumab, in vitro studies, and animal toxicological findings, IRRs/allergic reactions, infection, hemolysis, and thrombocytopenia will be closely monitored. As a biologic agent, immunogenicity also will be monitored. Any of the safety monitoring assessments may be performed more frequently, and AEs should be evaluated by the investigator according to the standard practice, if clinically indicated.

Adverse Events

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

Clinical Laboratory Tests

As of Amendment 5, refer to Attachment 4 for a description of study procedures for subjects who continue in the Treatment Extension Phase or who have discontinued treatment but remain in Follow-up.

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

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

- Hematology Panel

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

- Serum Chemistry Panel

  -uric acid
  -total bilirubin [a]
  -creatinine [b]
  -blood urea nitrogen (BUN)
  -aspartate aminotransferase (AST)
  -alanine aminotransferase (ALT)
  -alkaline phosphatase
  -lactate dehydrogenase (LDH)

  At Screening and during Cycle 1 only, before the second through eighth infusions of daratumumab
  -potassium
  -sodium
  -magnesium
  -calcium

  a. direct bilirubin if Gilbert's disease
  b. calculate creatinine clearance; please refer to Section 9.2.1.4.

HBV serology

For subjects who enter extension treatment period, HBV serology (HBsAg, anti-HBs, and anti-HBc) testing is to be performed locally prior to re-initiation. HBV serology is not required at re-initiation if this was performed as part of standard of care within 3 months prior to the re-initiation or the start of extension treatment is within 3 months of last daratumumab dose. For subjects with evidence of positive HBV serology, monitor for clinical and laboratory signs of HBV reactivation during treatment (Q12W), and for at least 6 months (Q12W) following the end of study treatment.

HBV DNA test

Subjects who are positive for Anti-HBc or Anti-HBs will undergo testing for hepatitis B DNA by PCR. Subjects with serologic findings suggestive of HBV vaccination (Anti-HBs positivity as the only serologic marker) and a known history of prior HBV vaccination do not need to be tested for HBV DNA by PCR. During and following study treatment, subjects who have history of HBV infection will be closely monitored for clinical and laboratory signs of reactivation of HBV as specified in the Time and Events Schedule (Table 1). Where required by local law, the results of HBV testing may be reported to the local health authorities.

Serum or urine pregnancy testing

For women of childbearing potential only, serum or urine pregnancy test at screening and as clinically indicated.

Calcium and albumin adjusted calcium:

These parameters will be part of the efficacy evaluations as specified in Section 9.2.1.4 and will be analyzed by the central laboratory. Measurement of calcium and albumin should follow the schedule for disease assessments.

Hemoglobin and creatinine

These parameters will be part of the efficacy evaluations as specified in Section 9.2.1.4 and will be analyzed by the local laboratory. At screening and during treatment, these parameters are part of the safety laboratory assessments. After end of treatment, subjects who stopped before PD will continue to have these parameters evaluated locally with each disease assessment.

β-2 microglobulin

β-2 microglobulin will be assessed at screening and upon disease progression, as part of efficacy evaluations. Sample will be analyzed by the central laboratory.

Daratumumab Interference with Indirect Antiglobulin Test (IAT) results

Daratumumab interferes with the Indirect Antiglobulin Test (IAT), which is a routine pre-transfusion test performed to identify a patient's antibodies to minor antigens so that suitable donor blood can be given for transfusion. Daratumumab does not interfere with ABO/RhD typing. CD38 is expressed at very low levels on erythrocytes. Daratumumab binds to the CD38 on erythrocytes, which results in a positive IAT (Indirect Coombs Test). This positive result masks the detection of antibodies to minor antigens and may prevent or delay blood banks from issuing donor blood for transfusion. This effect occurs during daratumumab treatment and for up to 6 months after treatment ends. Subjects will receive a patient identification wallet card for the study that includes the blood profile (ABO, Rh, and IAT) determined before the first infusion of daratumumab along with information on the IAT interference for healthcare providers/blood banks. Subjects are to carry this card throughout the treatment period and for at least 6 months after treatment ends. Blood banks can eliminate the daratumumab IAT interference by treating reagent RBCs with dithiothreitol (DTT) [Chapuy 2015][1].

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

a) Providing ABO/RhD compatible, phenotypically or genotypically matched units

b) Providing ABO/RhD compatible, K-negative units after ruling out or identifying alloantibodies using DTT-treated reagent RBCs

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

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

Pulmonary Function Test

Subjects with known or suspected COPD must have a FEV1 test during screening. Refer to Section 6.4.2 for details on subjects with higher risk of respiratory complications

Vital Signs

Vital signs (pulse, temperature, and blood pressure) will be performed as specified in Table 3. It is recommended that blood pressure (sitting) and pulse measurements be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones). Only vital signs associated with an AE will be entered in the eCRF; all measurements will be recorded in the source documents.

Physical Examination and ECOG Performance Status

A complete physical examination (including neurological examination) should be performed during the Screening Phase. Thereafter, only a symptom and disease directed physical examination is required. Height will be measured at screening only; weight will be measured regularly as specified in Table 3. Abnormalities will be recorded in the appropriate sections of the eCRF. ECOG Performance Status (Attachment 1) will be used to evaluate the impact of the disease status on the activities of daily living. When scheduled, ECOG assessments should be obtained prior to any other study procedures planned for the same day.

9.6. Sample Collection and Handling

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

For samples collected from the central laboratory, sample dates and times must be recorded on the laboratory requisition form. Further instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual.

10. SUBJECT COMPLETION/WITHDRAWAL

10.1. Completion of Treatment

A subject will be considered to have completed study treatment if he or she has finished all planned doses of daratumumab in the treatment arm to which they were randomized.

For subjects in Arm A (long intense) and Arm B (intermediate), there is a possibility to extend treatment with IV daratumumab (Q8W) after the end of Cycle 20 if, as per investigator discretion, there is a positive benefit/risk ratio, absence of Grade ≥3 treatment related toxicity, and at least stable disease has been achieved. In the case of subjects who already completed EOT and end of Cycle 20 occurred <6 months, these subjects can also continue receiving IV daratumumab administrations every 8 weeks.

For subjects who are treated in the Treatment Extension Phase as of Amendment 5, daratumumab 16 mg/kg IV may be switched to daratumumab 1800 mg SC at the discretion of the investigator at the same dosing (Q8W) schedule. Subjects with a known allergy/intolerance to sorbitol will not be eligible to switch to daratumumab SC.

10.2. Completion of Study

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

10.3. Premature Discontinuation of Study Treatment

If a subject's study treatment must be discontinued before the end of the planned number of cycles or during treatment extension/re-initiation, **this will not result in automatic withdrawal of the subject from the study**. After treatment discontinuation, the subject will move into the Follow-up Phase. The End-of-Treatment Visit should be performed, and Follow-up visit assessments should continue as specified in Table 1 (as of Amendment 5, refer to Attachment 4). If study treatment is discontinued for a reason other than disease progression, then disease evaluations will continue to be performed as specified in Table 1 (as of Amendment 5, refer to Attachment 4).

A subject's study treatment must be discontinued if:

- The investigator believes that for safety reasons (eg, AE) it is in the best interest of the subject to discontinue study treatment
- The subject becomes pregnant
- The subject (or the subject's legally acceptable representative) withdraws consent for administration of study treatment
- The subject experiences unacceptable toxicity, including IRRs described in Section 6.4.3
- The subject missed more than 2 consecutive planned doses due to daratumumab-related AEs

- The subject experiences disease progression (please see below).

A subject who experiences a second primary malignancy that cannot be treated by surgery alone must be withdrawn from the study. However, a subject who develops a malignancy that can be cured surgically may continue to receive the assigned study treatment and should continue to be followed for subsequent progression of MM.

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

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

10.4. Withdrawal from the Study

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

- Lost to follow-up
- Withdrawal of consent for study participation
- Death
- The study investigator or Sponsor, for any reason, stops the study or stops the subject's participation in the study

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

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

Withdrawal from the Use of Samples in Future Research

The subject may withdraw consent for use of samples for future research (refer to Section 16.2.5). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF.

11. STATISTICAL METHODS

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

11.1. Subject Information

The main analysis populations are:

- ITT population, defined as randomized subjects
- Safety population, defined as randomized subjects who received at least 1 dose of study agent

The ITT population will be used to summarize the study population and characteristics and efficacy; and the safety population will be used to summarize the safety data.

11.2. Sample Size Determination

Two hypotheses will be tested:

1. H_0: CR rate $\leq$ 15%
   H_a: CR rate $\geq$ 35%
2. H_0: PD/death rate $\geq$ 0.346/patient-year (median PFS < 24 months)
   H_a: PD/death rate $\leq$ 0.185/patient-year (median PFS > 45 months)

This study will enroll 120 subjects (40/arm) in total. With 40 subjects per arm, each arm will have:

- 90% power to show that the true CR rate is 35% at a one-sided level of 0.05
- 80% power to show that the true PD/death rate is 0.185/patient year at a one-sided level of 0.1

If two or more treatment schedules are deemed to be effective, with 40 subjects per arm this study would have:

- 85% probability of identifying the arm with the higher CR
- 80% probability of identifying the arm with the lower PD/death rate

For the QTc substudy, assuming that the intrasubject standard deviation for change from baseline in QTc (ΔQTc) is 20 milliseconds and that the true difference in means is 5 milliseconds, a sample size of 25 evaluable subjects (completers) will have 80% power to show that the upper limit of the two-sided 90% confidence interval (1 sided upper 95% confidence interval) for the difference in mean QTc (ΔQTc) at each timepoint and baseline will be less than 20 milliseconds. To ensure 25 subjects are evaluable, the QTc substudy will enroll approximately 30 subjects.

11.3. Efficacy Analyses

The first primary efficacy analysis of CR rate will occur 6 months after the last subject has been randomized and will be considered as an interim analysis. The purpose of this analysis is to select an appropriate dose and schedule and enable the sponsor's decision to proceed to Phase 3.

The second primary efficacy analysis of PD/death rate will occur 12 months after the last subject has been randomized. The purpose of this analysis is to make a decision to either proceed to Phase 3 if at the interim analysis there was not enough evidence to do so or to confirm the decision made after the interim analysis to proceed to Phase 3.

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.

11.3.1. Primary Efficacy Endpoint

The primary efficacy endpoints are:

1. CR rate: The number and proportion of subjects who achieve a CR in each arm will be summarized. An exact 90% confidence interval and an exact p-value for rejecting the null hypothesis that the CR rate is 15% will be calculated.
2. PD/death rate: The ratio of subjects with an event (PD or death) to the total follow-up for all subjects will be summarized. A 90% confidence interval and a p-value for rejecting the null hypothesis that the PD/death rate is 0.346 will be calculated.

11.3.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

1. Minimal residual disease (MRD) rate: The number and proportion of subjects who have a negative MRD will be summarized for each treatment arm. An exact 90% confidence interval will also be calculated
2. Time to next treatment: The median TNT in each treatment arm will be estimated using the Kaplan-Meier method. A 90% confidence interval will also be calculated
3. Overall Response Rate defined as CR+PR rate: The number and proportion of subjects who achieve a CR or PR in each arm will be summarized. An exact 90% confidence interval will also be calculated.
4. PFS: The median PFS in each treatment arm will be estimated using the Kaplan-Meier method. A 90% confidence interval will also be calculated
5. Incidence of symptomatic MM with adverse prognostic features, which include International Staging System (ISS) Stage III (based on β2-microglobulin and albumin) and adverse cytogenetic characteristics: The number and proportion of subjects with an incidence of symptomatic MM with adverse prognostic features will be summarized for each treatment arm. An exact 90% confidence interval will also be calculated
6. Response to first subsequent MM treatment will be summarized descriptively.
7. Overall survival rate

11.4. Pharmacokinetic Analyses

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

All serum concentrations below the lowest quantifiable concentration in a sample or missing data will be labeled as such in the concentration data listings. Concentrations below the lowest

quantifiable concentration in a sample 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 timepoint and PK parameters of daratumumab: Cmin and Cmax. Other PK parameters, when available, will also be summarized.

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

11.5. Immunogenicity Analyses

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

11.6. Pharmacokinetic/Pharmacodynamic Analyses

Pharmacokinetic/pharmacodynamic modeling of the relationship between serum concentrations of daratumumab and change from baseline in QTc interval will be performed. If sufficient data are available, PK/pharmacodynamic modeling will be performed, including exploring the relationship between serum concentrations of daratumumab and endpoints of clinical efficacy and safety. Details and results of the analysis will be presented in a separate report.

11.7. Biomarker Analyses

Biomarker studies are designed to identify markers predictive of response (or resistance) to daratumumab. Analyses will be stratified by clinical covariates or molecular subgroups using the appropriate statistical methods (eg, parametric or non-parametric, univariate or multivariate, analysis of variance [ANOVA], 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 dose schedule or clinical response. As this is an open-label study without a control treatment, statistical analyses will be done to aid in the understanding of the results.

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. Safety Analyses

Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The severity assessment for an AE or SAE should be completed using the NCI-CTCAE Version 4. All reported AEs with onset during the treatment phase (ie, treatment-emergent AEs, and AEs that have worsened since baseline) will be included in the analysis. For each AE, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group.

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

Clinical Laboratory Tests

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

Parameters with predefined NCI-CTCAE toxicity grades will be summarized. Change from baseline to the worst toxicity grade experienced by the subject during the study will be provided as shift tables. Worst toxicity grade during treatment will be presented, according to NCI-CTCAE (version 4). Clinically relevant changes (ie, causing a treatment intervention and/or need for concomitant therapy) will be also recorded on the AE eCRF. All other lab abnormalities need not be recorded as AEs.

Vital Signs

Descriptive statistics of temperature and blood pressure (systolic and diastolic) values and changes from baseline will be summarized. The percentage of subjects with values beyond clinically important limits will be summarized.

ECG Analysis

QT interval corrected for heart rate using Fridericia's (QTcF) and Bazett's (QTcB) formulae will be calculated. Descriptive statistics of QTc intervals and changes from baseline will be summarized at each scheduled timepoint. A mixed effects analysis of variance (ANOVA) model will be fit with QTc as the dependent variable, scheduled timepoint of measurement as the fixed effect, and subject as a random effect. Using the means and intrasubject variance obtained from this model, 2 sided 90% confidence intervals will be calculated for the difference in the mean QTc

from baseline at each scheduled timepoint. An effect on QTc will be ruled out if the upper bound of the 90% confidence interval for the difference in means between the postbaseline QTc (at each timepoint) and baseline QTc is less than 20 milliseconds.

The proportion of subjects with a post-dose QTc interval >450 milliseconds and >480 milliseconds will be summarized, as will the proportion of subjects with QTc interval increases from baseline >30 milliseconds or >60 milliseconds. A listing of subjects with a QTc interval >500 milliseconds will also be provided.

The proportion of subjects with post-dose PR interval >200 milliseconds, QRS >110 milliseconds, and heart rate >100 bpm and <50 bpm will be reported. The proportion of subjects with ST segment and T and U wave abnormalities will be reported.

All important abnormalities in ECG waveform that are changes from the baseline readings will be reported (eg, changes in T-wave morphology or the occurrence of U waves.

11.9. Interim Analysis

There will be one interim analysis for efficacy. This analysis will occur 6 months after the last subject has been randomized. The purpose of this analysis is to make a decision to go forward into Phase 3 based on the analysis of the primary endpoint of CR.

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 on Harmonisation [ICH])

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

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

Serious Adverse Event

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

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

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

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

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For daratumumab, the expectedness of an adverse event will be determined by whether or not it is listed within the Reference Safety Information included in the Investigator's Brochure.

Adverse Event Associated with the Use of the Drug

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

12.1.2. Attribution Definitions

Not Related

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

Doubtful

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

Possible

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

Probable

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

Very Likely

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

12.1.3. Severity Criteria

The severity assessment for an adverse event or serious adverse event should be completed using the NCI-CTCAE Version 4.

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

12.2. Special Reporting Situations

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

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

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

12.3. Procedures

12.3.1. All Adverse Events

All adverse events and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until 30 days after the last dose of study treatment, unless the subject withdraws consent for study participation, or starts subsequent anticancer therapy. For subjects who have received subsequent treatment with therapeutic intent for MM during the adverse event reporting period, only adverse events that are considered to be possibly, probably, or definitely related to daratumumab need to be reported. Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study treatment, must be reported using the Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

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

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

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

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

- Study number
- Statement, in the local language(s), that the subject is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical staff only)
- Site number
- Subject number
- Blood type and IAT (as described in Section 9.5.2)

12.3.2. Serious Adverse Events

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

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

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

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

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

- If the subject has not experienced a significant medical event but is hospitalized overnight only for observation following administration of daratumumab, then the hospitalization should not be reported as a serious adverse event.

- Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the eCRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.

12.3.3. Pregnancy

All initial reports of pregnancy must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, stillbirth, and congenital anomaly) are considered serious adverse events and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must promptly discontinue further study treatment.

Because the effect of the study drug on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form.

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

12.4. Contacting Sponsor Regarding Safety

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

13. PRODUCT QUALITY COMPLAINT HANDLING

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

13.1. Procedures

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

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

13.2. Contacting Sponsor Regarding Product Quality

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

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drug

Daratumumab IV

The daratumumab supplied for IV infusion is a colorless to yellow liquid and sterile concentrate of 20 mg/mL in a 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. Refer to the current Investigator's Brochure for a list of excipients.

Daratumumab SC

The daratumumab supplied for SC injection is a colorless to yellow liquid and sterile concentrate of 120 mg/mL daratumumab + 2000 U/mL rHuPH20 in a 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 current Investigator's Brochure for a list of excipients.

14.2. Packaging

Daratumumab IV

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

Daratumumab SC

Daratumumab 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.

14.3. Labeling

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

14.4. Preparation, Handling, and Storage

Daratumumab IV

Vials 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. Daratumumab IV must not be utilized after the expiry date printed on the label. The product must be protected from light and must not be frozen. Daratumumab IV does not contain preservatives; therefore, any unused portion remaining in the vial must be discarded.

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

Daratumumab SC

Daratumumab 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. Daratumumab SC must not be utilized after the expiry date printed on the label. Daratumumab 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 IPPI and SIPPM for additional guidance on study drug preparation, handling, and storage.

14.5. Drug Accountability

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

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

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

Study drug should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. Study drug may not be relabeled or reassigned for use by other

subjects. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Investigator Brochure for daratumumab
- Site Investigational Product Procedures Manual
- Laboratory manual
- eCRF completion guidelines
- Sample ICF
- Subject wallet card indicating blood type and IAT
- Other manuals and guidance documents as needed

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

The primary safety profile of daratumumab is consistent with IRRs; see Section 6.4 for prevention details. Based on the mode of action of daratumumab, a potential risk could be infection; therefore, the protocol requires the review of hematological laboratory results prior to daratumumab administration. CD38 is distributed in erythrocytes and platelets. A significant reduction of platelets was reported in an animal study. In a human clinical study (Study GEN501), thrombocytopenia was also reported. However, safety laboratory monitoring did not show a clinically meaningful reduction of platelets. Anemia was also reported in Study GEN501. Free hemoglobin was mildly elevated, but other parameters did not support hemolysis. No bleeding events were observed. Routine safety laboratory measurement of RBCs and platelets will be closely monitored in this study.

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

The maximum blood volume for the study is estimated at approximately 25 mL during screening and 340 mL during the first year. In the Follow-up Phase, subjects 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 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
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IEC/IRB requests to fulfill its obligation

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

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

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor

- Revisions to compensation for study-related injuries
- New edition(s) of the Investigator's Brochure and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of adverse events that are serious, unlisted/unexpected, and associated with the study drug
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

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

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

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

16.2.3. Informed Consent

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

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential subjects or their legally acceptable representatives the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of his or her

disease. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject or legally acceptable representative is authorizing such access, including permission to obtain information about his or her survival status, and agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, if needed, and subsequent disease-related treatments, or to obtain information about his or her survival status.

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

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

16.2.4. Privacy of Personal Data

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

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

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

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

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

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

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand daratumumab, to understand MM, to understand differential drug responders, and to develop tests/assays related to daratumumab and MM. 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 10.4, Withdrawal from the Study (Withdrawal from the Use of Samples in Future Research).

16.2.6. Country Selection

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

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

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

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

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

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

17.2.2. Required Prestudy Documentation

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

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

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

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

17.3. Subject Identification, Enrollment, and Screening Logs

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

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

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

17.4. Source Documentation

At a minimum, source documentation must be available for the following to confirm data collected in the eCRF: subject identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; concomitant medication; drug receipt/dispensing/return records; study treatment administration information; and date of study completion and reason for early discontinuation of study treatment or withdrawal from the study, if applicable.

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

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

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

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

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

17.5. Case Report Form Completion

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

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

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

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

All eCRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel. If necessary, queries will be generated in the eDC tool. The investigator or study-site personnel must adjust the eCRF (if applicable) and complete the query.

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

- Study site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Study site manager can generate a query for resolution by the study-site personnel.
- Clinical data manager can generate a query for resolution by the study-site personnel.

17.6. Data Quality Assurance/Quality Control

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

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

17.7. Record Retention

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

investigator/institution will take measures to prevent accidental or premature destruction of these documents.

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

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

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

17.8. Monitoring

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

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

17.9. Study Completion/Termination

17.9.1. Study Completion

The study is considered completed up to approximately 7 years after the last subject's first dose, following a decision by the sponsor to end the study based on data from the smoldering multiple

myeloma Phase 3 study (SMM3001), or for reasons outlined in Section 17.9.2, whichever occurs first. The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject at that study site in the time frame specified in the Clinical Trial Agreement.

17.9.2. Study Termination

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

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

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

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

17.10. On-Site Audits

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

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

17.11. Use of Information and Publication

All information, including but not limited to information regarding daratumumab or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including exploratory biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to

accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

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

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

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of Clinical Studies and Disclosure of Results

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

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Attachment 1: ECOG Performance Status Scale

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

Reference: Oken 1982[19]

Attachment 2: 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 onany day	Daily			Several time per day		
	Interference with normal activity	None			Minor limitation			Some limitation			Extremely limited		
Normal FEV1/FVC : 8-19 yr 85% 20-39 yr 80% 40-59 yr 75% 60-80 yr 70%	Lung function FEV1 FEV1/FVC	N/A	Normal FEV_1 between exacerbations > 80% > 85%	Normal FEV_1 between exacerbations > 80% Normal	N/A	> 80% > 80%	> 80% Normal	N/A	60-80% 75-80%	60-80% Reduced 5%	N/A	< 60% < 75%	< 60% Reduced 5%
Risk	Exacerbations requiring oral systemic corticosteroids	0-1/year			≥ 2 exacerbations in 6 months requiring oral steroids or >4 wheezing episodes/1 year lasting >1 day and risk factors for persistent asthma	≥ 2/year Relative annual risk may be related to FEV_1.	≥ 2/year Relative annual risk may be related to FEV_1.	≥ 2 exacerbations in 6 months requiring oral steroids or >4 wheezing episodes/1 year lasting >1 day and risk factors for persistent asthma	≥ 2/year Relative annual risk may be related to FEV_1.	≥ 2/year Relative annual risk may be related to FEV_1.	≥ 2 exacerbations in 6 months requiring oral steroids or >4 wheezing episodes/1 year lasting >1 day and risk factors for persistent asthma	≥ 2/year Relative annual risk may be related to FEV_1.	≥ 2/year Relative annual risk may be related to FEV_1.
		Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category.											
Recommended Step for Initiating Treatment		Step 1			Step 2			Step 3 and consider short course of oral steroids	Step 3: medium dose ICS and consider short course of oral steroids	Step 3 and consider short course of oral steroids	Step 3 and consider short course of oral steroids	Step 3: medium dose ICS OR Step 4 and consider short course of oral steroids	Step 4 or 5 and consider short course of oral steroids
		In 2-6 weeks, evaluate level of asthma control that is achieved. 0-4 years: If no clear benefit is observed in 4-6 weeks, stop treatment and consider alternate diagnosis or adjusting therapy. 5-11 and 12+ years: adjust therapy accordingly.											

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

Attachment 3: 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 4: As of Protocol Amendment 5, Study Drug Administration and Required Study Evaluations for Subjects Remaining in Treatment Extension or Follow-up

Note: All assessments are to be performed locally. As of Amendment 5, central laboratory evaluations are not applicable.

	Notes	Treatment Extension Phase	EOT	Follow-up
Study Drug Administration. Refer to Site investigational Product Procedures Manual and appropriate Investigational Product Preparation Instructions for recommendations on daratumumab administration details (including IV infusion rate, SC dose duration).				
Subjects in Treatment Extension Phase	Includes daratumumab IV and daratumumab SC dosing	X (Day 1 of each cycle)		
Pre-dose Medications				
Methylprednisolone	Methylprednisolone 100 mg for first 2 doses, 60 mg for all subsequent doses (in the absence of infusion-related AEs in the first 2 doses). Substitutions allowed, see Attachment 3.	approximately 1 hr prior to every dose of daratumumab		
H1-antihistamine	Diphenhydramine 25-50 mg, cetirizine 10 mg, or equivalent	approximately 1 hr prior to every dose of daratumumab		
Paracetamol	Paracetamol or acetaminophen 650-1000 mg	approximately 1 hr prior to every dose of daratumumab		
Monteleukast	Monteleukast 10 mg (optional)	approximately 1 hr prior to every dose of daratumumab		
Post-Dose Medications				
Methylprednisolone	Methylprednisolone 20 mg/day orally. Substitutions allowed, see Attachment 3.	Required after all doses for subjects in Treatment Extension Phase who experienced an IRR during Cycle 1 (exception made for steroid intolerance); may be offered in conjunction with the first dose and subsequent doses of daratumumab SC for subjects who switch dosing routes; per investigator discretion for all other subjects/cycles.		

Attachment 4: Dosing Administration and Required Study Evaluations as of Protocol Amendment 5 for Subjects Remaining in Treatment Extension or Follow Up (Continued).

	Notes	Treatment Extension Phase	EOT	Follow-up
Other Study Procedures				
Hematology	To be performed by local lab and reported in the CRF	Prior to every dose of daratumumab: hemoglobin, white blood cell count with absolute neutrophils and lymphocytes, platelet count.	X	After completion of study treatment, obtain with disease assessments until PD.
Clinical Chemistry		Day 1 of each cycle of daratumumab administration: uric acid, total bilirubin, creatinine, blood urea nitrogen, AST, ALT, ALP, LDH	X	Creatinine only: After completion of study treatment, obtain with disease assessments until PD.
Weight	If a subject's weight changes by more than 10% from baseline, the dose of study drug will be re-calculated for subjects receiving daratumumab IV	Day 1 of each cycle of daratumumab IV administration		
Vital Signs	Vital signs (blood pressure, temperature) measured in sitting position for subjects receiving daratumumab IV	Day 1 of each cycle of daratumumab IV administration immediately before administration start and at end of each daratumumab administration		
The start of each cycle may occur ±5 days of the scheduled day in order to accommodate the schedule of the site or subject. After EOT, subjects in all treatment arms prior to PD will continue to return for local disease evaluations per Standard of Care. After PD is documented, subjects will be followed only for survival; subsequent anticancer therapy, and occurrence of other malignancies every 6 months.				

Attachment 4: Dosing Administration and Required Study Evaluations as of Protocol Amendment 5 for Subjects Remaining in Treatment Extension or Follow Up (Continued).

	Notes	Treatment Extension Phase	EOT	Follow-up
Procedures				
ECOG	Once a subject discontinues or completes therapy prior to PD, ECOG will only be assessed at the End-of-Treatment Visit and additionally when PD is suspected.	Q16W during the Treatment Extension Phase	X	
12-lead ECG			X	
Physical exam	clinically significant abnormalities should be reported as AEs	symptom and disease directed exam as clinically indicated		
Laboratory Assessments				
Pregnancy test		as clinically indicated		
HBV DNA test	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. Refer to Section 9.5.2.	Q12W during treatment, at the End of Treatment / EOT Extension Visit, and Q12W for up to 6 months after the last dose of study treatment		
Disease Evaluations	To be performed locally per Standard of Care. Progressive disease as determined by the Investigator must be reported to the Sponsor. Local SPEP/UPEP/FLC data are not to be recorded in the CRF. Evaluation of response is to be recorded in the CRF.	until progressive disease is determined		

Attachment 4: Dosing Administration and Required Study Evaluations as of Protocol Amendment 5 for Subjects Remaining in Treatment Extension or Follow Up (Continued).

	Notes	Treatment Extension Phase	EOT	Follow-up
Bone marrow aspirate		For subjects with suspected PD, bone marrow aspirate should be assessed locally per standard of care for percentage of plasma cells and reported in the CRF. After PD, no additional collections are required.		
Skeletal radiography, or low-dose CT		Use same methodology during study as used at screening and report results in the CRF: Skeletal radiography or low-dose CT q12 months, and at biochemical progression (eg, increase in SPEP >25%) or at suspected PD. For subjects with (1) negative MRI results at baseline, (2) M-protein increase ≤25%, and (3) no other signs of clinical progression, only an MRI needs to be performed. For these subjects, low-dose whole body CT or skeletal survey does not need to be repeated unless focal lesions have been identified by MRI. After PD, no additional assessments are required.		
MRI of spine and pelvis		q6 months for the first 3 years, then q12 months, and at biochemical progression (eg, increase in SPEP >25%) or at suspected PD; whole body MRI per local practice or when clinically indicated. Results should be entered in the CRF. After PD, no additional assessments are required.		
Second primary malignancy				X
Subsequent Anti- myeloma Therapy	Record both treatment and response.			X
Survival				X
Ongoing Subject Review				
Adverse Events	See Section 12 for detailed instructions.	continuous from the time of signing of ICF until 30 days after last dose of last study treatment		
Concomitant Medications	See Section 8 for detailed instructions.	continuous from the time of signing of ICF until 30 days after last dose of last study treatment		

Abbreviations: AE=adverse event; ALP= alkaline phosphatase; ALT= alanine aminotransferase; anti-HB= anti- hepatitis B antigen; anti-HBc= hepatitis B core antigen; AST= aspartate aminotransferase; CRF=case report form; CT= computed tomography; ECOG=Eastern Cooperative Oncology Group; ECG=electrocardiogram; EOT=End-of-Treatment; FLC=free light chain; HBV= hepatitis B virus; ICF=informed consent form; IRR= infusion-related reaction; IV=intravenous; LDH=lactate dehydrogenase; MRI=magnetic resonance imaging; PCR=polymerase chain reaction; PD= disease progression; SC=subcutaneous; SPEP=serum M-protein quantitation by electrophoresis; UPEP=urine M-protein quantitation by electrophoresis;W=week

INVESTIGATOR AGREEMENT

JNJ-54767414 Daratumumab
Clinical Protocol 54767414SMM2001 Amendment 6

INVESTIGATOR AGREEMENT

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

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

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD MD, PhD

Institution: Janssen Research & Development

Signature: PPD Date: _____

(Day Month Year)

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

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Status: Approved, Date: 29 March 2021