Janssen Research & Development*

Clinical Protocol

An Open label, International, Multicenter, Dose Escalating Phase 1/2 Trial Investigating the Safety of Daratumumab in Combination with Lenalidomide and Dexamethasone in Patients with Relapsed or Relapsed and Refractory Multiple Myeloma

Protocol GEN503; Phase 1/2
AMENDMENT 8

(Short Title: Daratumumab in Combination with Lenalidomide and Dexamethasone in Relapsed and in Relapsed-Refractory Multiple Myeloma)

JNJ-54767414 daratumumab

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

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PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	16 December 2011
Amendment 1	03 February 2012
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Amendment 3	06 July 2012
Amendment 4	25 February 2013
Amendment 5	26 February 2014
Amendment 6	12 January 2015
Amendment 7	06 October 2015
Amendment 8	29 September 2016

Amendments are listed beginning with the most recent amendment.

Amendment 8 (29 September 2016)

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

The overall reason for the amendment: The final analysis of this study has been achieved (all subjects in Phase 1 or 2 have either received more than 24 months of study drug or discontinued), therefore the study is being amended to allow ongoing subjects to continue receiving study drug and limiting data collection to safety follow-up only (serious adverse events [SAEs] and second primary malignancies [SPMs]). Daratumumab will be provided until it is approved in combination with lenalidomide and dexamethasone and commercially available to patients with relapsed/ refractory multiple myeloma in the participating countries.

Applicable Section(s)	Description of Change(s)
Rationale: A description of the circumstances under which commercial supplies of daratumumab will be provided to study subjects was added.	
Synopsis. Overview of Study Design	Added the following text: Daratumumab will be provided until it is approved for use in combination with lenalidomide and dexamethasone and is commercially available for patients with relapsed/refractory multiple myeloma in the countries where subjects are still receiving combination treatment. Subjects still receiving treatment will be transitioned from study drug to commercial product once commercial product is available in their region (or when daratumumab can be accessed from another source). In these circumstances, the Sponsor and investigator will support transition of the subject to ensure that treatment continues and remains uninterrupted. Subjects who are unable to switch to commercial supplies will continue to remain on study. All subjects will be followed for 3 years after the last dose of lenalidomide, to enable collection of secondary primary malignancy (SPM). Table 4. Time and Events Schedule as of Amendment 8 and Attachment 9 Limited Schedule of Events for Subjects Continuing Daratumumab as of Amendment 8 were added.

Applicable Section(s)	Description of Change(s)
Rationale: A description of the data collection methods to be used and the duration of data collection following the switch to commercial supply of daratumumab were added.	
Synopsis. Statistical Methods	Added the following text: NOTE: As of Amendment 8, the final analysis will have been achieved. All subjects in the study have either received at least 24 months of study drug or have discontinued study drug. Ongoing subjects may continue treatment with study drug. Disease assessments/response evaluations will be performed per local institutional practice. Safety information will be limited to collection of data regarding SAEs and SPMs. All subjects will be followed for 3 years after the last dose of lenalidomide, to enable collection of SPMs. The study will end when daratumumab is approved for use in combination with lenalidomide and dexamethasone and is commercially available. Subjects still receiving treatment will be transitioned from study drug to commercial product once commercial product is available in their region (or when daratumumab can be accessed from another source) and will be withdrawn from this study at that time. In these circumstances, the sponsor and investigator will support transition of the subject to ensure that treatment continues uninterrupted. All subjects will be followed for 3 years after the last dose of lenalidomide, to enable collection of SPMs.
Rationale: Description of the data cutoffs was added.	
3.1. Overview of Study Design	Added the following text: The study will have 3 data cutoff time points: • The first data cutoff will be for the interim safety analysis, which is estimated to be performed approximately 6 months after the last subject in the study receives the first dose of daratumumab. All available data at the time of this data cutoff will be included in the abbreviated Clinical Study Report (CSR). • The second data cutoff will be for the primary safety analysis, which is estimated to be performed approximately 12 months after the last subject in the study received the first dose of daratumumab. All available data at the time of this data cutoff will be included in the abbreviated CSR. As of Amendment 8, the following data cutoff is yet to be completed. • The third and final data cutoff will be for the updated safety analysis, which is estimated to be performed approximately 24 months after the last subject in the study receives the first dose of daratumumab. All available data at the time of this data cutoff will be included in a final CSR addendum.
Rationale: The allowed and prohibited medications and therapies were revised.	
8. Concomitant Medications	Deleted the following text: ~~During the Follow up Period and at the End of Trial (EOT) Visit, only therapies that are or may be active against multiple myeloma, erythropoietin, and medications for skeletal disease must be recorded.~~ ~~The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.~~
8.2. Prohibited Medication	Revised the following text: Local radiotherapy for bone pain ~~may be~~is allowed.~~ after completion of Cycle 2 upon approval by the sponsor's medical officer.~~

Applicable Section(s)	Description of Change(s)
Rationale: Evaluations were revised to indicate the procedures relevant to the use of commercial daratumumab.	
9.1.3.1. Treatment Follow-up as per Amendment 8	Added the following text: As per Amendment 8, subjects will continue to be dosed as per Amendment 8 schedule (1 cycle is 28 days) and Table 4. Data collection will be limited to SAEs and SPMs, see details in Section 12 and Attachment 9. Daratumumab will be provided by the sponsor until it is approved for use in combination with lenalidomide and dexamethasone for patients with relapsed refractory multiple myeloma and is commercially available or can be accessed from another source. Subjects receiving treatment will be transitioned from study drug to commercial product once commercial product is available in their region (or when daratumumab can be accessed from another source). In these circumstances, the sponsor and investigator will support transition of the subject to ensure that treatment continues and remains uninterrupted. Subjects who are unable to switch to commercial supplies will continue to remain in the study. Limited data will be collected for 3 years after the last dose of lenalidomide, to enable collection of SPMs. Deleted the following sections: Follow-up Period and End of Trial Visit
9.1.4. Safety Follow-up Period	Deleted the following text: After their last dose of lenalidomide, subjects will be followed for 3 years ~~(at 6-month intervals)~~ to assess ~~survival,~~ occurrence of new cancers~~, and new antimyeloma treatment~~. Investigators will be asked to contact the subjects every **3-**6 months to collect this information. Deleted Unscheduled Visits
9.2. Assessments Following the Final Analysis	Added the following text: Data collection will only include SAEs and SPMs; see details in Section 12 and Attachment 9. Deleted all text regarding collection of any other adverse event data.
9.2.4. Pharmacokinetics and Immunogenicity	Added the following text: As of Amendment 8, blood sample collection will stop and not be performed after the last dose of daratumumab. One final sample should be taken before the start of the last infusion per Amendment 7. Deleted all text regarding collection of blood samples as per Amendment 7.
Rationale: The descriptions of subject and study completion were updated to reflect the changes necessitated by use of the commercial source of daratumumab.	
10. Subject Completion/ Withdrawal	Deleted the following text: ~~A subject will be considered as having completed the study if he or she has completed all visits through the EOT Visit and the posttreatment Week 8 immunogenicity sampling. Subjects who are withdrawn from the study for any reason before completion of this visit will not be considered to have completed.~~ Added the following text: Subjects will be considered as having completed the study if he/she has consented to Amendment 8.
10.1 Discontinuation of Study Treatment	Deleted the following text: ~~If a subject's study treatment must be discontinued before the end of the treatment regimen, this will not result in automatic withdrawal of the subject from the study.~~
10.2 Withdrawal	Added the following bullet and text: • Treatment is delayed for more than 3 weeks and no approval to continue is given by the sponsor If a subject discontinues study treatment or is transferred to commercial supplies, as per Amendment 8, follow-up for the occurrence of SPMs will continue for up to 3 years after the last dose of lenalidomide. Deleted all text describing procedures for withdrawal from the study prior to Amendment 8.

Applicable Section(s)	Description of Change(s)
Rationale: The reporting situations and procedures were revised to indicate changes necessitated by limits to the data collection.	
12.5. Special Reporting Situations	Occurrence of SPM was added.
12.6. Procedures	Added the following text: As per Amendment 8, only SAEs and SPMs will be collected (see Table 4 and Attachment 9). The SAE and SPM data should be entered in the subject file/notes. Any SPM that occurs during a subject's participation in the study or for 3 years after the last dose of lenalidomide is considered an immediately reportable event. It must be reported to the sponsor within 24 hours after the investigator has gained knowledge of it by using the SPM form attached to the regular SAE form.
Rationale: The handling and storage of daratumumab were revised.	
14.4. Preparation, Handling, and Storage	Preparation of infusion bags should be done on the day of the planned infusion, and the time of the dilution should be written on the infusion bag. ~~After preparation, the infusion should be kept at room temperature. If the study drug must be stored for longer than 3 hours after it has been diluted in 0.9% NaCl before initiation of the infusion, it must be kept at 2°C to 8°C. The prepared infusion bags should be kept at room temperature for approximately 1 hour before infusion. The infusion should be completed no later than 24 hours after preparation.~~ Daratumumab must be administered as an IV infusion. The infusion should be given through a well-functioning IV catheter by using an infusion pump. The study drug must be filtered by using an inline filter (0.2 μm) during the infusion.
Rationale: The reporting situations and procedures were revised to indicate changes necessitated by limits to the data collection	
17.8. Monitoring	Added the following text: As per Amendment 8, on site v~~V~~isits are usually made at intervals of at least ~~4 to 12~~24 weeks. A phone call will be done in between (at 12 weeks). At these visits, the monitor will monitor the adequate reporting and follow-up of SAEs, SPMs, drug receipt/dispensing/return records and ensure subjects who showed progressive disease stopped the study treatment. Deleted all text regarding data collection as per study protocol prior to Amendment 8.
17.9. Close-out of Extended Safety Follow-up	Added the following text: The extended safety follow-up will be completed 3 years after the last subject took the last lenalidomide dose and completed follow-up for the occurrence of SPMs. Deleted Study Completion: ~~Per the study design, the study is considered completed after the last subject participating in the study is administered study drug per schedule withdraws consent, dies, is lost to follow up, completes safety follow up, or the study is terminated by the sponsor.~~
Rationale: Minor errors were noted and updates provided	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made. The following abbreviations were added CSR, RBC, SPM.
15 Study Specific Materials	The following items were deleted as they were no longer necessary: Access to the eCRFs (usernames, passwords, and training for personnel designated to perform data entry); Clinical laboratory supplies; Laboratory manual; eDC Manual, and Investigator Brochure.

Amendment 7 (06 October 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 primary analysis of this study has been achieved (all subjects in Phase 1 or 2 have either received more than 12 months of study drug or discontinued), therefore the study is being amended to allow ongoing subjects to continue receiving study drug with a limited schedule of assessments.

Applicable Section(s)	Description of Change(s)
Rationale: Following the primary analysis, ongoing subjects will follow a limited schedule of assessments.	
Synopsis Added a note following the Statistical Methods section; 9.2. Assessments Following the Primary Analysis	Added the following text: NOTE: As of Study 54767414GEN503 Protocol Amendment 7, the primary analysis will be achieved. All subjects in the study have either received at least 12 months of study drug or have discontinued. Ongoing subjects may continue treatment with study drug with a limited schedule of assessments. Disease assessments/response evaluations will be performed per local institutional practice. Safety information will be limited to study drug administration, serious adverse events (SAEs, including secondary malignancies), concomitant medications associated with SAEs, and pregnancy testing. No additional PK blood sampling will be performed, samples will be collected only for immunogenicity and the same samples will be used for determination of the associated daratumumab serum concentrations. Follow up will include collection of survival information, best response and new antimyeloma therapies, and secondary malignancies every 6 months for 3 years after the last dose of study drug or termination of the study by the sponsor, whichever occurs first. Revised the heading for Section 9.2
Attachment 8 and Table 3	Attachment 8 was added, which includes details for the limited assessment schedule as of this amendment. Table 3 provides the modified Time and Events Schedule.
9.1.1 Overview;	Added text regarding changes with Amendment 7.
9.2.2 Clinical Laboratory Assessments; 9.2.2.4 Pregnancy Test; 9.2.3 Myeloma-related Laboratory Efficacy Assessments	Modification with this amendment that clinical laboratory assessments (efficacy and safety) will now be performed by local laboratories with timing based on local institutional practice. Pregnancy tests will continue as scheduled and analyzed by local laboratories.
9.2.4 Pharmacokinetics and Immunogenicity Assessments; Table 3; Attachment 8	As of Amendment 7, immunogenicity samples will be taken at Weeks 4 and 8 after the last dose of study. The same sample will be used to determine the associated daratumumab concentration. Revised heading 9.2.4 and removed heading 9.2.4.1
12.6.1 All Adverse Events	As of Amendment 7, only SAEs will be collected and the SAEs should be reported in the subject file/source notes.
Rationale: Error noted in Section 6.1 stating that daratumumab treatment would be limited to 18 cycles maximum. Treatment with daratumumab can continue until unacceptable toxicity or disease progression, whichever occurs first.	
6.1 Daratumumab	Removed “for 18 cycles or”

Applicable Section(s)	Description of Change(s)
Rationale: Additional information provided about daratumumab interference with indirect antiglobulin test.	
9.2.2.2 Hemoglobin	Additional information provided regarding daratumumab interference with indirect antiglobulin test including possible methods for blood banks to provide safe red blood cells for subjects receiving daratumumab.
Rationale: Modified the subject completion statement to include the immunogenicity sample (8 weeks after last dose of study drug)	
10.1 Subject Completion	Revised the text: A subject will be considered as having completed the study if he or she has completed all visits through the EOT Visit and the posttreatment Week 8 immunogenicity sampling.
Rationale: As of Amendment 7, there is no longer a Follow-up Period before the EOT visit. Ongoing subjects were unlikely to discontinue daratumumab and continue another 2 cycles with lenalidomide/dexamethasone alone	
10.3 Withdrawal from the Study	Before Amendment 7 if the subject was withdrawn or discontinued treatment before disease progression, the subjects entered a Follow-up Period until disease progression. With Amendment 7, there is no longer a Follow-up Period before the EOT visit. Removed the following: A subject may be withdrawn from daratumumab and continue treatment with Len/Dex alone for a maximum of 2 additional cycles and then enter the Follow-up Period. If a subject must discontinue lenalidomide treatment for any reason, he or she will be withdrawn from the Treatment Period and will enter the Follow-up Period.
Rationale: The IDMC will no longer evaluate safety after the primary analysis.	
11.13 Data Monitoring Committee	Added the following statement: The IDMC will no longer be evaluating safety data after the primary analysis.
Rationale: The IDMC is no longer evaluating safety after the primary analysis, therefore the definition of study completion is no longer applicable.	
17.9.1 Study Completion	New definition of study completion: Per the study design, the study is considered completed after the last subject participating in the study is administered study drug per schedule, withdraws consent, dies, is lost to follow up, completes safety follow up, or the study is terminated by the sponsor.
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 6 (12 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 remove the Phase 1 Time and Events Schedule, and to modify the requirements for bone marrow sample collection to allow for differences across countries in local clinical practice.

Applicable Section(s)	Description of Change(s)
Rationale: Subjects enrolled in Phase 1 have met all the predefined assessments of Phase 1, have been on study treatment for more than 12 months, and are no longer required to follow the Phase 1 schedule of safety and pharmacokinetic (PK) assessments, given the data currently available regarding use of the dara/len/dex combination.	
Synopsis, Statistical Methods; Table 1 (Phase 1 Time and Events Schedule); 9.2 Assessments; Table 8	Text added to explain that subjects enrolled in Phase 1 will now follow the Phase 2 Time and Event Schedule.
9.2.4.1. Daratumumab Concentration in Serum	Text revised to explain that subjects in Phase 1 will now follow the Phase 2 Time and Event Schedule for timings of PK assessments.
Rationale: To provide specific details regarding why the blood type is needed and how it should be executed.	
9.2.2.2. Hematology	Added text regarding the reason for the blood type testing. Text was deleted: Direct and indirect Coombs tests will be performed at all daratumumab infusion visits (before infusion and 2 hours after the end of infusion) and all follow up visits until no antibodies are detected. In addition, these tests will be performed at the EOT Visit for all subjects, including those who withdraw from the study.
Rationale: To provide more specific detail regarding recalculation of the daratumumab dose based on weight change.	
Table 2 (Phase 2 Time and Events Schedule); 6.1. Daratumumab	Added a statement that the dose of daratumumab does not need to be recalculated for weight changes <10% from baseline. Footnote "q" added to T&E table.
Rationale: Infusion of daratumumab via syringe pump is not permitted.	
14.4. Preparation, Handling, and Storage	Modified text in to indicate that infusion of daratumumab via syringe pump is not permitted.
Rationale: For safety reasons and for consistency across daratumumab studies.	
6.4. Delaying or Skipping Treatment	Added text that specifies that ONLY if any of the criteria in this section are met and the event cannot be ascribed to lenalidomide, the daratumumab infusion must be held to allow for recovery from toxicity. Modified the criteria for a dose delay to include febrile neutropenia of any grade, and to include neutropenia with infection of any grade.
Rationale: To allow for the use of alternate methods of calculation for creatinine clearance.	
6.2.1.4. Renal Impairment (Table 7); References; Attachment 7	Revised text to state that in addition to the Cockcroft-Gault formula, the Modification of Diet in Renal Disease (MDRD) or Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formulas may also be used for creatinine clearance calculation.

Rationale: To address questions from investigative sites.	
6.6. Management of Infusion-related Reactions	Clarified the definition of subjects with a higher risk of respiratory complications as subjects with COPD who have an FEV1<80%, or subjects with mild asthma.
Rationale: Lenalidomide does not need to be taken at the same time as the premedications. The recommendation for timing of daratumumab infusion in relation to lenalidomide is no longer applicable.	
6.2. Lenalidomide	Modified the text to say that lenalidomide **may** be administered **prior to or** at the same time (preferred) as the premedications. Removed the statement that the daratumumab infusion should begin approximately 1 hour after the lenalidomide administration.
Rationale: Lenalidomide is commonly associated with tiredness.	
6.2. Lenalidomide	Specified that for days on which daratumumab is not administered, lenalidomide may be taken in the evening.
Rationale: To add more detail about prohibited medications.	
8.2. Prohibited Medications	Added text to specify that in addition to concomitant administration of medications for any other anti-neoplastic therapy for the intention of treating multiple myeloma, medications that target CD38 are prohibited, as well as medications for other indications that have antimyeloma properties (eg, interferon and clarithromycin).
Rationale: For consistency and alignment across daratumumab protocols with respect to analyses on serum samples.	
9.2.4.1. Daratumumab Concentration in Serum	Text deleted: 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. Genetic analyses will not be performed on these samples, and subject confidentiality will be maintained.
9.2.5. Analytic Procedures	Text added: Adjustments to bioanalysis timing may be made if it is later determined that the timing for data needed to facilitate crucial decision-making differs from these two planned efforts. However, data from each round of bioanalysis will be considered final and samples will not be reanalyzed in any subsequent efforts.
11.5. Pharmacokinetic Analyses	Text added: 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.
11.6 Pharmacokinetic/Pharmacodynamic Analyses	Section 11.6 added: If sufficient data are available, pharmacokinetic/pharmacodynamic modeling may be performed, including exploring the relationship between serum concentrations of daratumumab and endpoints of clinical efficacy. If performed, details and results of the analysis will be presented in a separate report.

Rationale: Placement of text regarding efficacy assessments during the follow-up period was placed in the incorrect section of protocol. Follow-up period applies to all Cycles, not just Cycles 1-6.	
9.1.4. Follow-up Period; 9.1.6. Safety Follow-Up Period	Text regarding follow-up procedures for efficacy assessments (If a subject completes or discontinues treatment without progression, the subject will be assessed at 8 week intervals till disease progression or until he or she starts new antimyeloma treatment) was moved from Section 9.1.6 (Safety Follow-up Period) to Section 9.1.4 (Follow-up Period) where it correctly belongs. Text deleted from Section 9.1.4 header: (Cycles 1-6).
Rationale: Subjects can continue in study until progressive disease or new antimyeloma treatment.	
Table 2 (Phase 2 Time and Event Schedule); 9.1.4. Follow-up Period; 9.1.6. Safety Follow-up Period	Footnote "r" added to clarify that these assessments are performed on subjects without disease progression. Additional rows added to Table 2 to account for assessment of survival and new antimyeloma treatment during the Safety Follow-up Period. Text regarding follow-up assessments was revised to specify that subjects will be assessed **at 8** week intervals **until death or lost to follow up**. Text revised to clarify that survival and new antimyeloma treatment use will be assessed during Safety Follow-up Period.
Rationale: Change made based on a health authority request that annual IEC/IRB approval is not applicable in all countries.	
Section 16.2.2. Independent Ethics Committee or Institutional Review Board	Replaced the statement that the IEC/IRB must review and reapprove the study at least once a year with a statement indicating that where required, progress reports/written summaries of the study status will be submitted to the IEC/IRB annually, or more frequently if requested.
Rationale: Clarification regarding start of study cycle.	
Synopsis Dosage and Administration; 6. Dosage and Administration	Provided definition of start of study cycle.
Rationale: Clarification that bone marrow assessment can include aspirate or biopsy.	
Table 2 (Phase 2 Time and Event Schedule); 9.2.3.1. Bone Marrow Assessment	Text added: Bone marrow **aspirate/bone marrow biopsy.** Text revised to specify bone marrow biopsy and**/ or** aspirate
Rationale: A lack of sufficient baseline samples are available to perform posttreatment minimal residual disease (MRD) assessment.	
Synopsis Biomarker Evaluations; Table 2 (Phase 2 Time and Event Schedule); 9.2.3.1. Bone Marrow Assessments; 9.2.6.2.2 Phase 2 Biomarker Analyses; 9.2.6.2.3. Phase 2 Pharmacogenomics	Text deleted about MRD assessment. Text deleted in footnote "g" about MRD assessment.
Rationale: Recent data suggest that treatment with Len/Dex should continue until progressive disease or unacceptable toxicity rather than at a fixed timepoint.	
Table 2 (Phase 2 Time and Events Schedule)	Column for "Daratumumab continuation only" assessment deleted. Footnote "p" associated with this column deletion.
Rationale: Clarification regarding PK assessment.	
Table 2 (Phase 2 Time and Event Schedule)	Text added to footnote "l" to clarify one sample is collected before the daratumumab infusion and another sample after the end of the daratumumab infusion.

Rationale: For consistency throughout the protocol.	
6.3. Dexamethasone	Text added: Dexamethasone will be administered until the subject experiences disease progression or unacceptable toxicity, **whichever comes first**.
Rationale: Electrocardiograms will no longer be sent to the central laboratory; local ECG tracing collection is now acceptable based on data collected to date.	
9.2.1.4. Electrocardiogram	Text deleted: Digital ECGs will be transmitted from the sites electronically to a central laboratory (eResearch Technology, Inc) for a treatment-blinded measurement of the cardiac rhythm and assessment of morphology by a central cardiologist.
Rationale: Alignment with other daratumumab protocols.	
12.6.1. All Adverse Events	Text revised to state that adverse events will be collected **within** 30 days of the last dose of **any component of the treatment regimen.**
Rationale: Subjects may continue daratumumab treatment beyond 24 cycles.	
Table 2 (Phase 2 Time and Event Schedule)	Changed range of Study visits column header from "7-24" to "7+**"**.
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 5 (26 February 2014)

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

The overall reason for the amendment: This amendment included defining the change in sponsor to Janssen Research & Development (JRD) and converting to the JRD protocol template. Additionally 10 of the approximately 30 subjects enrolled on Phase 2 will have shortened infusion times for the first daratumumab infusion to evaluate the safety and incidence of infusion related reactions when infusion time is shortened. Eligibility criteria have also been modified to remove the cap placed on prior lines of therapy to allow a broader population to be studied in Phase 2.

Applicable Section(s)	Description of Change(s)
Rationale: JRD has taken over responsibility of this study from Genmab A/S in a partnership effort to develop daratumumab.	
Global	Changed sponsor name from Genmab A/S to Janssen Research & Development
Rationale: The Time and Event Schedules were revised to reflect the changes made in the assessments for the study and to provide more detail and clarity by adding separate tables for assessment in Phase 1 and Phase 2.	
Table 1 and Table 2 Time and Event Schedules	Revised Table 1 (Time and Event Schedule) to reflect changes in the protocol. Added Table 2 (Time and Event Schedule for Phase 2 which includes pharmacokinetic/immunogenicity and exploratory biomarker assessments) for clarity
Rationale: A secondary objective was added to evaluate immunogenicity using JRD analysis methods.	
Synopsis, Section 2.1 Objectives	Added secondary objective for immunogenicity.
Synopsis, T&E	HAHA immunogenicity was removed from Phase 1, as all immunogenicity samples will now be analyzed using the JRD methods.

Sections 9.2.4 Pharmacokinetics and Immunogenicity Assessments, Sections 9.2.5 Analytical Procedures, 9.2.6.1 Immunogenicity Assessments, 11.8 Immunogenicity Analyses	Immunogenicity assessments clarified for Phase 1 and Phase 2. Additional details for sample collection, handling, and storage were added. Details of analysis procedures were added.
Rationale: Preclinical and clinical text shortened and link added to Investigator's Brochure (IB).	
Sections 1.1.3 Preclinical Pharmacology and Pharmacokinetics; 1.1.4 Preclinical Safety; 1.1.5 Clinical Experience	Text was removed and link to IB added.
Section 1.2 Combination Therapy of Daratumumab, Lenalidomide, and Dexamethasone	Text regarding the most commonly reported AEs in GEN 501 was removed as it is no longer relevant.
Rationale: The study hypothesis was added to clarify no formal statistical hypothesis will be tested and to conform to the JRD template.	
Synopsis, Section 2.2 Hypothesis	Added hypothesis
Rationale: The number of subjects to be enrolled into Phase 2 was revised to approximately 30 subjects and clarified 3+3 rules for dose escalation.	
Synopsis, Sections 3.1 Overview of Study Design, 3.2.2 Rationale for Study Design, 11.2 Sample Size Determination;	Added text "the standard "3 + 3" rules for dose escalation will be applied, However, if the study sites have identified 4 eligible subjects to start a new dose level, all 4 subjects may be enrolled." Revised the number of subjects to be enrolled in Phase 2 to approximately 30 subjects; updated the sample size determination with the revised number of subjects and revised the rationale for the sample size to reflect the historical overall response rate and the estimated power of the study.
Synopsis, Sections 4.1 General Considerations, 11.2 Sample Size Determinations	The total number of subjects and screen failure rate has been updated. The number of subjects for Phase 2 was changed from 32 to approximately 30 subjects.
Rationale: Subjects may continue daratumumab treatment beyond 24 cycles.	
Synopsis, Sections 3.1 Overview of Study Design, 9.1.3 Treatment Period (Cycle X Visit X), 17.9.1 Study Completion	"Up to 24 cycles" has been removed throughout the document as treatment may continue until the subjects' experiences disease progression or unacceptable toxicity. In addition, daratumumab may continue until investigator's or sponsor's recommendation of discontinuation, subject's decision to discontinue, or disease progression
Rationale: In Phase 2, the 2 separate cohorts were removed to form 1 cohort.	
Sections 3.2.1 Rationale for Subject Population, 3.2.2 Rationale for Study Design, 5.1 Subject Allocation Procedures	Text regarding 2 cohorts and prior therapies was removed. Subject population also clarified.
Rationale: Based upon emerging safety data and further understanding of the occurrence of infusion related reaction, the pre-dose infusion is no longer required. Pre and post medications and dose interruptions of daratumumab in ongoing single agent and combination studies have provided adequate intervention.	
Sections 3.1 Overview of Study Design, 3.2.3 Dose Rationale, 6.1 Daratumumab	Phase 2 pre-dose was removed

Rationale: Serum samples will be analyzed for PK for both Phase 1 and Phase 2 of this protocol. In addition, GEN501 PK data presented also was analyzed in serum not plasma.	
Synopsis, Sections 3.2.3.1 Phase 1 Dose Escalation; 9.3 Endpoints	Plasma was removed due to typographical error and replaced with serum throughout the protocol.
Rationale: Daratumumab RP2D Rationale Section added	
Section 3.2.3.2 Daratumumab RP2D Rationale	Section added based on new data from Study GEN501 and MMY2002
Rationale: The inclusion and exclusion criteria were revised to better define the patient population and the JRD template. In addition, eligibility criteria have also been modified to remove the cap placed on prior lines of therapy to ensure a broader relapsed/refractory population is study in Phase 2.	
Sections 4.2 Phase 2 Inclusion Criterion	Revised: Phase 2 inclusion #1 to include: - Subjects must have received at least 1 prior line of therapy for multiple myeloma (refer to Attachment 2). - Subject must have achieved a response (PR or better) to at least one prior regimen. - Subject must have documented evidence of progressive disease (PD) as defined by the IMWG criteria on or after their last regimen. Attachment 2 added.
Section 4.3 Exclusion Criteria #3, #4 (removed), #6 (removed) #5 (modified), #12, #14, #18, #20 (renumbered)	#3: Antimyeloma treatment changed to within 2 weeks instead of 3 weeks #5: modified to #4: "Have discontinued lenalidomide due to any treatment-related adverse event or be refractory to any dose of lenalidomide. Refractory to lenalidomide is defined as either: - Subjects whose disease progresses within 60 days of lenalidomide, or - Subjects whose disease is nonresponsive while on any dose of lenalidomide. Nonresponsive disease is defined as either failure to achieve at least an MR or development of PD while on lenalidomide." #12: Persistent asthma added #14: Clarified/added HIV, Hepatitis B and C text #18: Added "or have known allergies, hypersensitivity, or intolerance to monoclonal antibodies or human proteins, or their excipients (refer to Investigator Brochure 2013), or have known sensitivity to mammalian-derived products." For clarity #20: added "or other anti-CD38 therapies"
Rationale: Dosage and administration for Phase 1 and Phase 2 was clarified.	
Section 6.1 Daratumumab	Dosage and administration for Phase 2 was added
Rationale: Based on the infusion rate data from the Phase 2 daratumumab single agent, Study 501, demonstrated safe and well tolerated infusion at median duration of 4 hours.	
Section 6.1 Daratumumab	The infusion rates for Phase 2 have been adjusted. New Table 4 for Phase 2 is added.
Rationale: Dexamethasone modifications were added to ensure that appropriate dosing of dexamethasone is addressed for smaller patients as well as the elderly, both of whom would not require as large a dose of dexamethasone.	
Section 6.3 Dexamethasone	Dexamethasone dose adjustment for elderly or underweight subjects added
Section 6.3.1 Dose adjustments of Dexamethasone	Section added

Rationale: Text added regarding delaying or skipping treatment.	
Section 6.4 Delaying or Skipping Treatment	Section added
Rationale: DLT text needed regarding hemolysis, neutropenic fever, and transfusion of platelets based on GEN501 study.	
Section 6.5 Dose-Limiting Toxicities	DLT section moved based on JRD template.
Rationale: Management of infusion-related reactions for patients with respiratory complications needed.	
Section 6.6 Management of Infusion-Related Reactions	Former Section 6.1.2 moved here. New text was added for the management of infusion-related reactions for patients at a higher risk of respiratory complications.
Section 6.6.1 Infusion-related Reactions of Grade 1 or 2 Section 6.6.2 Infusion-related Reactions of Grade 3 or Higher	Sections headers and text added for clarity on infusion reactions of Grade 1 and 2 and Grade 3 and higher.
Rationale: Text clarified regarding use of bisphosphonates	
Section 8.1 Recommended Concomitant Medications	Zoledrolic acid removed and dose removed
Rationale: Changes and clarifications for study evaluations/assessments needed.	
Section 9.1.2 Screening Period	Rescreening text removed and Phase 2 screening assessments added
Section 9.1.3 Treatment Period (Cycle X Visit X)	Clarified dosing in Treatment Periods for Phase 1 and Phase 2
Section 9.1.6 Safety Follow-up Period	Safety Follow-up period clarified assessments every 8 weeks
Section 9.2.1.4 Electrocardiogram	Clarified electrocardiograms assessment times for Phase 1 and Phase 2; removed “at least 10 minutes apart”
Section 9.2.2.2 Hematology	Clarified assessment times for Coomb’s tests in Phase 1 and Phase 2
Section 9.2.2.3 Serology for HIV, Hepatitis B and Cytomegalovirus Serology	Clarified that these assessments are for Phase 1 only.

Rationale: At the sponsor's request, sections were added and revised as needed to include and clarify biomarker and pharmacogenomic assessments and analysis.	
Synopsis, Sections 9.2.3 Myeloma-related laboratory efficacy assessments, 9.2.3.1 Bone Marrow Assessments, 9.2.3.2 Serum Immunoglobulin A,M, and G, 9.2.3.4 Serum Free Light Chain Ratio, 9.2.6.2.2 Complement, 9.2.6.2.2.1 Leveling of Circulating NK Cells, B, and T Cells (Flow Cytometry), 9.2.6.2 Biomarker Assessments, 9.2.6.2.3 Pharmacogenomics, 9.2.6.2.2 Phase 2 Biomarker Analyses added; 11.9 Biomarker and Pharmacogenomic Analyses	• Added the rationale for evaluating biomarkers during Phase 2 • Added an introduction to the biomarker evaluations and sections for evaluation of FcgR polymorphisms, antibody-dependent cell-mediated cytotoxicity, infusion reaction biomarkers, MRD, and circulating multiple myeloma cells; revised the section on serum biomarkers for Phase 1 and Phase 2 • Added a section to describe the analyses to be performed on biomarker data • Added a section on pharmacogenomic samples, research, and storage.
Rationale: The section describing pharmacokinetic and immunogenicity assessments was revised to clarify procedures and to reflect the sponsor's requests.	
Sections 9.2.4 Pharmacokinetics and Immunogenicity Assessments, 9.2.5 Analytical Procedures, 9.2.6 Pharmacokinetic Parameters, 9.2.6.1 Immunogenicity Assessments, 11.5 Pharmacokinetic Analyses	Revised the pharmacokinetic and immunogenicity assessments to be performed and clarified the timing of sample collection and analysis
Rationale: The section termed "variables" was changed to "endpoints" and updated to reflect changes in the study design.	
Section 9.3 Endpoints	Moved section to conform to JRD template.
Rationale: The reasons for discontinuation of treatment and withdrawal from the study were revised to reflect the sponsor's requests and JRD template.	
Sections 10.2 Discontinuation of Treatment and 10.3 Withdrawal	Revised for discontinuation of treatment.
Rationale: Statistical methods clarified for Phase 1 and Phase 2	
Sections 11.1 Subject Information (added), 11.2 Sample Size Determination, 11.3 Analysis sets, 11.5 Pharmacokinetic Analyses, 11.8 Immunogenicity Analyses, 11.9 Biomarker and Pharmacogenomic Analyses.11.10 Safety Analyses, 11.12 Data Monitoring Committee	• "No formal statistical hypothesis" deleted • Statistical methods for Phase 1 and Phase 2 separated for clarity. New statistical methods added for Phase 2, including change of number of subjects to 20. Removed Figure 5. • Clarified Phase 1 and Phase 2 analysis set • PK analyses clarified • JRD template text added • IDMC text clarified
Rationale: The procedures and contact information for reporting of serious adverse events were revised to reflect the changes made because of the change in sponsors.	
Section 12.6.2. Serious Adverse Events, 12.6.3 Pregnancy	Revised procedures for reporting serious adverse events and pregnancy and changed contact from Chiltern International, Ltd to sponsor.
Rationale: The drug accountability section was revised to reflect the sponsor's procedures.	
Section 14.5 Drug Accountability	Revised to reflect sponsor's procedures and conform to the JRD template

Rationale: Sections were added, deleted, revised, or reordered to reflect JRD standard procedures and to match the JRD protocol template better.	
• Title page • Approval page, Sponsor Contact page, Investigator Agreement page Section 10.2 Discontinuation of Study Treatment, 10.3 Withdrawal • Section 11.1 Subject Information • Throughout the protocol and Section 11.10 Safety Analyses • Section 12 Adverse Event Reporting, Section 13 Product Quality Complaint Handling, Section 15 Study-Specific Materials, Section 16 Ethical Aspects, 16.1. Study-specific Design Considerations, 16.2.4 Privacy of Personal Data, Section 16.2.6 Country Selection, Section 17 Administrative Requirements, Sections 17.1 Protocol Modifications, Section 17.2.1 Regulatory Approval/Notification, Section 17.2.2 Required Prestudy Documentation, 17.3 Subject Identification, Enrollment, and Screening Logs, 17.4 Source Documentation, 17.5 Case Report Form Completion, 17.6 Data Quality Assurance/Quality Control, 17.7 Record Retention, 17.8 Monitoring, 17.9.1 Study Completion, 17.9.2 Termination, 17.11 Use of Information and Publication	• Reformatted and revised to conform to the JRD template • Removed INC Research and Genmab approval page and sponsor contact information because these pages are not required in the JRD template • Reformatted and revised the synopsis to reflect the changes in the protocol and to conform to the JRD template • Changed references to the Safety Committee to sponsor • Revised to match JRD procedures and template • Added/Revised or updated to match JRD procedures and template
• Section 15.5.2 and 15.5.3 of Genmab template has been deleted	
Rationale: Minor grammatical, formatting, and spelling changes were made.	
Throughout the protocol	"Trial" changed to "Study". Part 1 and Part 2 changed to Phase 1 and Phase 2. "Visit 0"changed to "before the first infusion".

Amendment 4 (25 February 2013)

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: This amendment includes the change of sponsor from Genmab A/S to Janssen Research & Development; update of contract research organization (CRO) personnel approving the protocol; addition of more flexible choice of dose for Phase 2, premedication and dosing guidelines, and infusion rates; change in dexamethasone administration; clarification of screening assessments and an exclusion criterion; change in trial drug preparation and storage; removal of glucocorticoid administration after infusion; and minor editorial changes.

Applicable Section(s)	Description of Change(s)
Rationale: Change of sponsor from Genmab A/S to Janssen Research & Development	
Title page, Signature Page, Investigator Agreement, Synopsis, Section 1.4, Section 12.6, Section 13, Section 14.3, and Section 15.10	Genmab will be undertaking the conduct of the GEN503 trial of daratumumab with Janssen Research & Development as sponsor. Therefore, the protocol was updated to reflect this collaboration by including Janssen on the title page, adding an approval signatory from Janssen, and clarifying that Genmab and/or Janssen (as "sponsor") would have responsibility for certain aspects of the trial.
Rationale: Update of CRO personnel approving the protocol	
Signature Page	The approving medical monitor and biostatistician were updated to reflect personnel changes at the CRO.
Rationale: Addition of more flexible choice of dose for Phase 2	
Synopsis, Section 1.4.2, Section 3, Figure 4, Section 11.7, Section 13, and List of Abbreviations	To provide the sponsor with more flexibility in the choice of Phase 2 dose, the maximum tolerated dose originally planned to be determined during Phase 1 was changed to a recommended Phase II dose (RP2D), which could be the MTD or any dose evaluated in the range of 4 to 16 mg/kg of daratumumab. It was noted that the RP2D could be selected before escalation to or completion of the 16 mg/kg cohort.
Rationale: Addition of more flexible premedication and dosing guidelines	
Section 6.1	In the event that data from the ongoing GEN501 trial provides information that might necessitate a change, wording was added to indicate that the sponsor or Independent Data Monitoring Committee (IDMC) may modify predose infusions, infusion rates, or premedications.
Rationale: Addition of more flexible infusion rates	
Table 2	Table 2 was revised to indicate that infusions after the first full-dose infusion may be started and continued at a higher infusion rate at the discretion of the investigator if the subject experienced no infusion reactions during the last full-dose infusion.
Rationale: Change in dexamethasone administration	
Synopsis, Section 6.3, and Section 8.1.3	The administration of dexamethasone was changed from 2 doses of 20 mg each on the day of infusion (20 mg intravenously [IV] before infusion and 20 mg orally [PO] after the end of infusion) to 1 dose of 20 mg IV before infusion and 20 mg PO the day after the infusion.

Rationale: Clarification of screening assessments	
Synopsis and Section 8.1.2	Text was added to the description of the screening period assessment to clarify that vital sign and electrocardiogram (ECG) measurements were to be performed during the Screening Visit and should be done within 21 days before trial entry (Cycle 1 Visit 1).
Rationale: Clarification of an exclusion criterion	
Synopsis and Section 4.3	Exclusion criterion #3 was clarified to include radiotherapy within 3 weeks before the first infusion as an excluded treatment. This exclusion was added based on an adverse event seen in the ongoing GEN501 trial where a subject had received radiotherapy within 3 weeks before the first infusion of daratumumab and then experienced an allergic reaction including severe throat edema and breathing difficulties.
Rationale: Change in trial drug preparation and storage	
Section 12.4	Preparation of the trial drug was revised to indicate that the infusion should be kept at room temperature after preparation, unless it was to be stored longer than 3 hours after dilution and before initiation of the infusion in which case it was to be stored at 2°C to 8°C.
Rationale: Removal of glucocorticoid administration after infusion	
Section 6.1.2	The administration of methylprednisolone on the first and second days after all full-dose infusion was removed because the dose of dexamethasone on the day after full-dose infusions is believed to cover the subjects adequately.
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 3 (06 July 2012)

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: This amendment includes the addition of long-term monitoring for new onset of cancer and more extensive pregnancy testing, as well as clarifications of the screening process, inclusion and exclusion criteria, recommended concomitant medications, timing of the Coomb's tests, urinalysis assessments for M-component, planned flow cytometry testing, and timing of the bone marrow biopsies.

Applicable Section(s)	Description of Change(s)
Rationale: Addition of long-term monitoring for new onset of cancer	
Synopsis, Table 1, Section 8.1.6, Section 9.3.2, Section 9.3.3, and Section 13	The French Competent Authorities (Agence nationale de sécurité du médicament et des produits de santé) requested that the sponsor collect information regarding all cases of cancer that might occur in all participants of this trial for 3 years after the last dose of lenalidomide. In response to this request, the sponsor is amending the protocol to include a Safety Follow-up Period during which investigators will contact subjects every 6 months after their last dose of lenalidomide to collect information on any new cancers. This information will be entered on a questionnaire provided by the sponsor for this purpose. Data from these questionnaires will be entered into the Clinical Drug Safety database. In addition, the agency requested that any cases of new cancer be reported as unexpected serious adverse events (SAEs) (Sections 9.3.2 and 9.3.3) and that the Independent Data Monitoring Committee (IDMC) make recommendations at least every 6 months regarding whether the trial should continue based on the occurrence of new cancers and the reported benefits of daratumumab treatment (Section 13).
Rationale: Addition of more extensive pregnancy testing	
Table 1 and Section 8.2.2.4)	The French Competent Authority requested that more extensive pregnancy testing be added to the protocol to bring it more into accordance with the Summary of Product Characteristics (warnings and precaution for use) for lenalidomide. In addition to pregnancy testing at the Screening and End of Treatment (EOT) Visits, testing will be done every 4 weeks during the treatment and follow-up periods. Serum samples will be tested by the central laboratory.
Rationale: Clarification of screening process	
Synopsis and Section 8.1.2)	To respond to inquiries from investigators, the sponsor clarified the screening process by stating that subjects may be rescreened after failing to meet the inclusion and exclusion criteria if their condition changes. Rescreening is allowed only after discussion with and approval by the sponsor.
Rationale: Inclusion Criterion #1 for Phase 2	
Synopsis and Section 4.2	The requirement for subjects to be naive to lenalidomide treatment has been removed because it conflicted with statements made elsewhere in the protocol.

Rationale: Exclusion Criterion #30 and Pregnancy	
Synopsis and Section 4.3 Section 9.1.6	The French Competent Authority requested that clarification on the length of time subjects must have used adequate contraception before study drug administration be added to the protocol to bring it more into accordance with the Summary of Product Characteristics (warnings and precaution for use) for lenalidomide. Therefore, this criterion has been clarified to include the requirement for adequate contraception for 4 weeks before the first infusion of daratumumab. The section on pregnancy as an adverse event has also been updated to include this requirement.
Rationale: Recommended Concomitant Medications	
Section 7.1	Recommended treatment for tumor lysis syndrome has been added to clarify that such treatment is allowed and should be performed according to local standards.
Rationale: Hematology	
Table 1 and Section 8.2.2.2	To ensure that a final assessment is performed for subjects who withdraw from the trial, additional direct and indirect Coomb's tests have been added to the EOT Visit for all subjects, including those who withdraw from the trial.
Rationale: Urinalysis for M-component	
Table 1 and Section 8.2.3.3)	The urinalysis for total protein at the Screening Visit has been clarified to include analysis of albumin. In addition, quantitation of total protein (including albumin) and creatinine clearance has been added to the urinalysis on the first day of each cycle and at all follow-up visits.
Rationale: Levels of Circulating B and T Cells (Flow Cytometry)	
Section 8.2.4.4	Analysis of CD3-CD56+ has been added to the blood sample assessment by flow cytometry. In addition, a statement that other subgroups may be analyzed for exploratory purposes has been added. These additions will allow for further characterization of the plasma cells and other cells in the blood.
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 2 (23 February 2012)

This amendment is considered to be nonsubstantial 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, in that it does not significantly impact the safety or physical/mental integrity of subjects, nor the scientific value of the study.

The overall reason for the amendment: This amendment includes a correction to the reasons for withdrawal of subjects from treatment.

Applicable Section(s)	Description of Change(s)
Rationale: Withdrawal	
Section 10.2	During review of the protocol, the Medicines and Healthcare products Regulatory Agency noted that subjects must be withdrawn from treatment due to pregnancy. Further review of the protocol by the sponsor indicated that Section 10.2 stated that subjects may be withdrawn from treatment for the reasons listed (including pregnancy). This amendment corrects that statement to clarify that subjects will be withdrawn from treatment for any of the reasons listed.

Amendment 1 (03 February 2012)

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: This amendment includes clarification of an exclusion criterion, and changes to an inclusion criterion, vital sign assessments, the laboratory analyzing electrocardiograms, bone marrow assessments, the definition of dose-limiting toxicities, and informed consent. Details of and reasons for the changes are presented below.

Applicable Section(s)	Description of Change(s)
Rationale: Inclusion Criterion #2	
Synopsis and Section 4.2	Key opinion leaders have advised Genmab to include only patients with measurable M-component in blood or urine. Patients who have involved free light chain levels but no measurable M-component are difficult to evaluate. It is, therefore, the opinion of Genmab and key opinion leaders that including this population could distort evaluation of both safety and efficacy assessments in this small trial and result in ambiguous conclusions. To avoid any unclear and misleading results of GEN503, Genmab has opted to exclude these patients from the trial.
Rationale: Exclusion Criterion #16	
Synopsis, Table 1, Section 4.3, and Section 8.2.2.3	No HIV testing will be performed during the assessment of subject eligibility for enrollment in this trial. Subjects with a history of a positive HIV test will be excluded.
Rationale: Electrocardiogram	
	The central laboratory that will analyze the electrocardiograms performed during this study was incorrectly referred to as BARC and has been corrected to eResearch Technology.
Rationale: Timing of Vital Sign Measurements	
Table 1 and Section 8.2.1.5	The timing of the preinfusion measurement of vital signs was changed to just before the planned infusion start time to provide more relevant information.
Rationale: Addition of Analyses for Bone Marrow Assessments	
Section 8.2.3.1	Three analyses were added to the bone marrow aspirate assessment by flow cytometry: CD19, CD28, and CD117. These additions will allow further characterization of the plasma cells and other cells in the marrow.
Rationale: Addition to the Informed Consent Process	
Section 8.2.3.5	Because of its exploratory nature, subjects will be asked to sign a separate informed consent form for the analysis of prognostic factors.
Rationale: Correction of Definition of Dose-limiting Toxicities	
Section 8.2.3.1	Three analyses were added to the bone marrow aspirate assessment by flow cytometry: CD19, CD28, and CD117. These additions will allow further characterization of the plasma cells and other cells in the marrow.
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

SYNOPSIS

An Open label, International, Multicenter, Dose Escalating Phase 1/2 Trial Investigating the Safety of Daratumumab in Combination with Lenalidomide and Dexamethasone in Patients with Relapsed or Relapsed and Refractory Multiple Myeloma

Description of Compound

Daratumumab is an IgG1κ human monoclonal antibody that specifically recognizes the CD38 epitope. It has demonstrated antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) in multiple myeloma cells, efficacy in multiple myeloma patient cells as well as in vivo antitumor activity in xenograft models.

OBJECTIVES AND HYPOTHESIS

Primary Objective

To establish the safety profile of daratumumab when given in combination with Len/Dex in subjects with relapsed or relapsed and refractory multiple myeloma.

Secondary Objectives

- To evaluate the efficacy of daratumumab when given in combination with Len/Dex in subjects with relapsed or relapsed and refractory multiple myeloma.
- To evaluate the PK profile of daratumumab when given in combination with Len/Dex in subjects with relapsed or relapsed and refractory multiple myeloma.
- To assess the immunogenicity of daratumumab.

Hypothesis

No formal statistical hypotheses are planned to be tested.

OVERVIEW OF STUDY DESIGN

This is an open-label, dose-escalation, multicenter, Phase 1/2 safety study of daratumumab in combination with lenalidomide and dexamethasone (Len/Dex) in the treatment of subjects with relapsed or relapsed and refractory multiple myeloma. The dose escalation portion of the study (Phase 1) will be a standard 3 + 3 design and will evaluate daratumumab, at doses from 2 mg/kg up to a maximum of 16 mg/kg, in combination with Len/Dex in 28-day treatment cycles. The maximum tolerated dose (MTD) will be defined as the highest dose of the combination regimen at which less than 33% of subject's experience dose-limiting toxicity (DLT). A recommended Phase 2 dose (RP2D) will be determined during Phase 1. The MTD or any dose evaluated in the range of 2 to 16 mg/kg of daratumumab may be considered as the RP2D based on available safety, pharmacokinetic (PK)/pharmacodynamic, and efficacy data from Phase 1. The RP2D could be selected before escalation to or completion of the 16 mg/kg cohort. Once the RP2D is determined, the expansion (Phase 2) will open to further explore the safety and efficacy of the RP2D in approximately 30 subjects.

For Phase 1 and Phase 2 portions of the study, the first 2 treatment cycles will consist of weekly daratumumab infusions, totaling 4 infusions during each 28-day cycle. Cycles 3 through 6 will consist of daratumumab infusions administered every other week; Cycle 7 and all subsequent cycles will consist of monthly daratumumab infusions. The combination treatment may continue until the subject experiences disease progression or unacceptable toxicity, whichever comes first. Daratumumab may be continued until investigator's or sponsor's recommendation of discontinuation, the subject's decision to discontinue for any reason, or disease progression. In Phase 1 and Phase 2, if the subject must stop one component of the combination treatment (either daratumumab, lenalidomide or dexamethasone), the subject may

continue the other components until progression or commencing a new regimen for the treatment of multiple myeloma. However, subjects will still receive dexamethasone as premedication to daratumumab.

In Phase 1, to minimize the risk of cytokine release syndrome, the first infusion of the first cycle will be preceded by a predose infusion the day before the scheduled full-dose infusion. The predose infusion will be 10% of the full dose, but will never be more than 10 mg in total dose. Further measures to prevent cytokine release syndrome will include premedication with antihistamines, acetaminophen, and dexamethasone before each daratumumab infusion (both predose and full dose).

Lenalidomide will be administered at a dose of 25 mg orally (PO) on Days 1 through 21 of each 28-day cycle, and dexamethasone will be administered at a total dose of 40 mg weekly. Further details on the administration of dexamethasone are provided in the Test Product, Dose and Mode of Administration section of this synopsis.

During Phase 1, decisions to escalate the dose of daratumumab for the next cohort will be based on the safety data obtained from the 3 (+ 3) subjects in the previous cohort during their first treatment cycle (28 days). The Independent Data Monitoring Committee (IDMC) will evaluate all safety data (including serious adverse events [SAEs], adverse events [AEs], and laboratory data) after each cohort completes Cycle 1. The third subject in the cohort must have received all 4 full doses of daratumumab, and data from an observation period of 6 days after the last infusion must be available for the IDMC to review. Based on the results presented in these safety profiles, the IDMC will recommend to the sponsor if it appears safe to escalate the dose. The recommendation will be discussed and confirmed by the sponsor, who will ultimately decide if dose escalation will occur. Subjects who discontinue the study during the first cycle for reasons other than a DLT will be replaced.

The RP2D dose selected is 16 mg/kg based upon marked M-protein reduction with an acceptable safety profile in doses up to 16 mg/kg, the highest dose of Phase 1. In addition, the following data from Phase 1 of this combination study and data at 16 mg/kg in ongoing monotherapy studies is supportive of the RP2D dose.

- Clinical pharmacokinetic data have shown the 16 mg/kg dose to be the lowest dose that results in complete target suppression at all time points. This dose and schedule continuously suppressed NK cells throughout dosing.
- 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) as of a cutoff date of 24 January 2014.
  - In Study GEN501, the ORRs (ie, partial response [PR] or greater) were 11% and 40% for the 8-mg/kg (n=28) and 16-mg/kg (n=15) dose regimens, respectively.
  - For the 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 those 2 studies. VGPR was not observed at lower dose levels. These preliminary data support that full target saturation at the 16-mg/kg dose is needed to achieve higher and deeper response rates.
- The 16-mg/kg dose and schedule was shown to have an acceptable and manageable safety profile for the approximately 30 subjects for whom preliminary data were available in Studies GEN501 and MMY2002. In Phase 1 of this study, no additive toxicity was observed when comparing the 16 mg/kg combination with the lower dose cohorts

Daratumumab will be provided until it is approved for use in combination with lenalidomide and dexamethasone and is commercially available for patients with relapsed/refractory multiple myeloma in the countries where subjects are still receiving combination treatment. Subjects still receiving treatment will be transitioned from study drug to commercial product once commercial product is available in their

region (or when daratumumab can be accessed from another source). In these circumstances, the Sponsor and investigator will support transition of the subject to ensure that treatment continues and remains uninterrupted. Subjects who are unable to switch to commercial supplies will continue to remain on study. All subjects will be followed for 3 years after the last dose of lenalidomide, to enable collection of second primary malignancy (SPM).

SUBJECT POPULATION

The study population for Phase 1 will consist of adults who have relapsed/refractory multiple myeloma after receiving a minimum of 2 and a maximum of 4 prior lines of therapy and be eligible for treatment with Len/Dex. The study population for Phase 2 will consist of approximately 30 adults with a diagnosis of multiple myeloma who have received at least 1 prior therapy, are not refractory to lenalidomide, and meet all other criteria.

Between 42 and 58 subjects will be enrolled in this study, depending on the number of dose levels included during dose escalation in Phase 1. It is estimated that the screen failure rate will be 25% and that between 56 and 78 subjects will be screened in order to enroll the expected number.

DOSAGE AND ADMINISTRATION

The start of a cycle is defined as the start of any of the study treatments (ie, daratumumab or Len/Dex). If all treatments are held, then it should be reported as a cycle delay.

Daratumumab will be administered by intravenous (IV) infusion in a 28-day cycle, in combination with Len/Dex. For the first 2 cycles (8 weeks), administration of daratumumab will be weekly. In Cycles 3 through 6 (16 weeks), daratumumab will be administered every other week. After Cycle 6, daratumumab will be administered monthly (every 4 weeks). In Phase 1 only, a predose infusion will be given on Day 0.

Lenalidomide will be administered on Days 1 through 21 of each 28-day cycle at a dose of 25 mg/day PO. Lenalidomide will be administered until the subject experiences disease progression or unacceptable toxicity, whichever comes first. All investigators must follow the guidelines of the lenalidomide RevAssist® program in the United States (US) and Pregnancy Prevention Programme in the European Union (EU).

Dexamethasone will be administered at a total dose of 40 mg/week (except for the first week of Cycle 1; see below). As of Amendment 5, subjects older than 75 years or underweight (body mass index [BMI] <18.5), the dexamethasone dose may be administered at a dose of 20 mg weekly. On weeks when daratumumab is administered the 20 mg dose should be administered as the premedication per protocol. During daratumumab infusion weeks, dexamethasone will be administered on the day of daratumumab infusion as 20 mg IV before the infusion and 20 mg PO the day after the infusion. During weeks when no daratumumab infusion is planned, dexamethasone will be administered at a dose of 40 mg/week PO. After the completion of Cycle 6, the administration of dexamethasone may be adjusted at the discretion of the investigator; however, dexamethasone should always be administered at a dose of 20 mg IV on daratumumab infusion days. Dexamethasone will be administered until the subject experiences disease progression or unacceptable toxicity, whichever comes first.

EFFICACY EVALUATIONS/ENDPOINTS

Efficacy endpoints are the rate of response according to the International Uniform Response Criteria, time to progression, duration of response, and progression-free survival.

PHARMACOKINETIC/PHARMACODYNAMIC EVALUATIONS

PK variables are the area under the concentration-time curve (AUC), maximum concentration in serum (C_{max}), minimum (or trough) concentration in serum (C_{min}), time to C_{max} (T_{max}), apparent clearance (CL), volume of distribution (V), and elimination half-life ($t_{1/2}$).

IMMUNOGENICITY EVALUATIONS

Samples drawn from all subjects will be assessed for the generation of antibodies to daratumumab.

BIOMARKER EVALUATIONS

Phase 1: Biomarkers assessments may include evaluation of complement proteins, soluble CD38 levels, and levels of circulating NK Cells, B, and T Cells by flow cytometry.

Phase 2: Biomarker assessments may include further understanding the MOA (ADCC/CDC/ADCP) of daratumumab in combination with lenalidomide and dexamethasone, immunophenotyping, evaluation of complement proteins, soluble CD38, and multiple myeloma cell profiling (including CD38/CD46/CD55/CD59 expression). In addition, exploratory proteomics and SNP analysis may be performed. 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.

PHARMACOGENOMIC (DNA) EVALUATIONS

A pharmacogenomic blood sample will be collected to allow for pharmacogenomic research, as necessary (where local regulations permit). Subject participation in the pharmacogenomic research is optional.

SAFETY EVALUATIONS

Safety variables are the incidence of AEs, physical examination findings, electrocardiogram results, vital sign measurements, ECOG performance status, laboratory test results, and immunogenicity assessments.

Dose-limiting Toxicity:

Dose-limiting toxicities are defined as any of the following events that occur during the first treatment cycle (28 days):

- Nonhematologic toxicity considered to be a serious adverse event (SAE) of grade 3 or higher and related to daratumumab with the exception of:
  - Any nonhematologic reaction of grade 3 or higher that has an onset after the start of infusion on an infusion day, responds to symptomatic therapy, and resolves within 6 hours from onset
- Adverse reactions that prevent the infusion from being resumed regardless of the length of the reaction
- Hematologic toxicity, considered related to daratumumab, defined as
  - Thrombocytopenia (platelet count < 20,000 cells/μL)
  - Asymptomatic grade 4 neutropenia for more than 3 days
  - Neutropenic fever (defined as grade 3 or 4 neutropenia and temperature > 38.5°C) for more than 3 days
- Inability to receive the Day 1 infusion of Cycle 2 because of any toxicity related to daratumumab

STATISTICAL METHODS

The 2 phases of this study will be analyzed separately. When appropriate, all subjects who are treated with daratumumab may be combined together for comprehensive safety assessment. The latest available measurements before study drug administration will serve as baseline values.

Phase 1 follows a standard 3+3 design. For Phase 2, it is assumed that lenalidomide + dexamethasone would achieve an ORR of 50% in the targeted population. With a two-sided alpha of 0.10 and assuming that the addition of daratumumab improves the ORR to 75%, a sample size of approximately 30 subjects would achieve 89% power to detect such a difference. If the addition of daratumumab can improve the ORR to 80%, this sample size would achieve 97% power to detect such a difference. The proportion of subjects with response to treatment (stringent CR [sCR], CR, very good PR [VGPR], and PR) will be estimated. The quality of response (also including subjects who achieve MR) will be summarized. The proportions will be presented with corresponding exact 2-sided 95% confidence intervals. Duration of response, time to progression, and PFS will be estimated using Kaplan-Meier techniques.

Subject information variables will be estimated by using descriptive statistics. Continuous variables will be summarized by using the number of observations (n), mean, standard deviation, median, minimum, and maximum, where n denotes the number of subjects with available data. Categorical variables will be summarized by using n and percentages, where the calculation of the percentages will be based on the number of subjects in the population (N) and the number of subjects with available data (n). Results will be presented by cohort as well as by all subjects combined.

NOTE: As of Amendment 7, the primary analysis will be achieved. All subjects in the study have either received at least 12 months of study drug or have discontinued. Ongoing subjects may continue treatment with study drug with a limited schedule of assessments. Disease assessments/response evaluations will be performed per local institutional practice. Safety information will be limited to study drug administration, serious adverse events (SAEs, including secondary malignancies), concomitant medications associated with SAEs, and pregnancy testing. No additional PK blood sampling will be performed, samples will be collected only for immunogenicity and the same samples will be used for determination of the associated daratumumab serum concentrations. Follow up will include collection of survival information, best response and new antimyeloma therapies, and secondary malignancies every 6 months for 3 years after the last dose of study drug or termination of the study by the sponsor, whichever occurs first.

NOTE: As of Amendment 8, the final analysis will have been achieved. All subjects in the study have either received at least 24 months of study drug or have discontinued study drug. Ongoing subjects may continue treatment with study drug. Disease assessments/response evaluations will be performed per local institutional practice. Safety information will be limited to collection of data regarding SAEs and SPMs. All subjects will be followed for 3 years after the last dose of lenalidomide, to enable collection of SPMs.

The study will end when daratumumab is approved for use in combination with lenalidomide and dexamethasone and is commercially available. Subjects still receiving treatment will be transitioned from study drug to commercial product once commercial product is available in their region (or when daratumumab can be accessed from another source) and will be withdrawn from this study at that time. In these circumstances, the sponsor and investigator will support transition of the subject to ensure that treatment continues uninterrupted. All subjects will be followed for 3 years after the last dose of lenalidomide, to enable collection of SPMs.

Table 1: Phase 1 Time and Events Schedule

Note: As of Amendment 8, all subjects are to follow the Time and Events Schedule in Table 4 (see Attachment 9 for additional details)

	Study Visits															
Assessments	**Screening**	**Cycle 1**					**Cycle 2[a]**				**Cycle 3-6[a]**		**Cycle 7-24[a]**	**FU**	**EOT**	**Safety FU**
Visit Number	**0**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**1**	**2**	**1**	**1-6**	**—**	**—**
Day/Week/Month	**≤21 days before Cycle 1 Visit 1**	**0d**	**1d**	**1w**	**2w**	**3w**	**1d**	**1w**	**2w**	**3w**	**1d**	**2w**	**1d**	**Monthly**	**—**	**—**
Visit Window	**—**	**—**	**—**	**±1d**	**±1d**	**±1d**	**±4d**	**±1d**	**±1d**	**±1d**	**±4d**	**±1d**	**±4d**	**±7d**	**±2d**	**±7d**
Clinical Assessments																
Informed consent	X[b]															
Eligibility criteria	X															
Demographics	X															
Medical history[c]	X															
Height and body weight	X														X	
Physical examination	X	X													X	
Vital sign measurements[d]	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Electrocardiogram[e]	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
X-ray or CT scan	X[f]						X[g]				X[g]		X[g]		X	
ECOG performance status	X	X					X				X		X		X	
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Administration of daratumumab (predose)		X														
Administration of daratumumab			X	X	X	X	X	X	X	X	X	X	X			
Administration of lenalidomide		X (Days 1-21)					X (Days 1-21)				X (Days 1-21)		X (Days 1-21)			
Administration of dexamethasone		X	X	X	X	X	X	X	X	X	X (4 weekly)		X (4 weekly)			
Laboratory Assessments[h]																
Biochemistry[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hematology[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Flow cytometry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy test[k]	X	X					X				X		X	X	X	
Immunogenicity	X						X				X		X	X	X	
Hepatitis B, cytomegalovirus	X															
Complement (CH50)[l]	X						X				X		X		X	
Serum daratumumab level[m]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Blood type assessment	X															
Direct & indirect Coombs tests[n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Table 1: Phase 1 Time and Events Schedule

Note: As of Amendment 8, all subjects are to follow the Time and Events Schedule in Table 4 (see Attachment 9 for additional details)

	Study Visits															
Assessments	**Screening**	**Cycle 1**					**Cycle 2[a]**				**Cycle 3-6[a]**		**Cycle 7-24[a]**	**FU**	**EOT**	**Safety FU**
Visit Number	**0**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**1**	**2**	**1**	**1-6**	—	—
Day/Week/Month	**≤21 days before Cycle 1 Visit 1**	**0d**	**1d**	**1w**	**2w**	**3w**	**1d**	**1w**	**2w**	**3w**	**1d**	**2w**	**1d**	**Monthly**	—	—
Visit Window	—	—	—	**±1d**	**±1d**	**±1d**	**±4d**	**±1d**	**±1d**	**±1d**	**±4d**	**±1d**	**±4d**	**±7d**	**±2d**	**±7d**
Prognostic factors	X															
Soluble CD38	X			X									X			
Response Assessments																
Bone marrow	X[f]						X[g]				X[g]				X[g]	
IgA, IgM, IgG (M-component serum)	X	X			X		X				X		X	X	X	
M-component (24-hour urine sample)[o]	X	X			X		X				X		X	X	X	
Free light chain kappa, lambda, and ratio (serum)	X	X			X		X				X		X	X	X	
New cancer assessment[p]																X

Key: CT = computed tomography; d = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = End of Trial; FU = Follow-up; Ig = immunoglobulin; w = week

[a] All cycles are 28-day cycles: the first visit of a cycle should be 4 weeks after the start of the previous cycle.

[b] Informed consent may be obtained outside of the Screening Visit window, ie, before the Screening Visit date.

[c] Signs and symptoms (nonserious adverse events) occurring between the Screening Visit (before the first infusion) and the first study drug treatment at Cycle 1 Visit 1 should be recorded as medical history.

[d] Vital signs, defined as blood pressure, pulse, and temperature will be measured at the following time points on days when daratumumab infusions are given: just before the planned infusion start time; at 15-minute intervals during the first 2 hours of the infusion; at 60-minute intervals after the first 2 hours during the infusion; at the end of the infusion; and after the infusion at 10 minutes, 30 minutes, 1 hour, and 2 hours.

[e] Electrocardiograms (ECGs) will be performed at the Screening Visit (before the first infusion), before and after each daratumumab infusion, and at the EOT Visit. Three baseline ECGs should be performed before the first infusion of study drug. Before the ECGs are recorded, the subjects must be resting in a horizontal position for at least 20 minutes.

[f] The computed tomography scan and bone marrow biopsy/aspirate may have been performed within 6 weeks before Cycle 1 Visit 1.

[g] To be completed as indicated to confirm response at the subsequent bone marrow biopsy visit or to investigate new symptoms, and at physician discretion.

[h] Unless otherwise stated, all blood and urine samples must be taken before administration of daratumumab.

[i] Blood samples drawn for biochemistry assessments will be analyzed for the following: sodium, potassium, blood urea nitrogen, creatine, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, bone-specific alkaline phosphatase, albumin, calcium, glucose, total creatinine kinase, total bilirubin, lactic dehydrogenase, uric acid, β_2-microglobulin, and C-reactive protein.

[j] Blood samples drawn for hematology assessments will be analyzed for the following: red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, white blood cell count with differential, platelet count, and reticulocyte count.

Table 1: Phase 1 Time and Events Schedule

Note: As of Amendment 8, all subjects are to follow the Time and Events Schedule in Table 4 (see Attachment 9 for additional details)

[k] Blood samples for serum pregnancy tests will be collected at the Screening Visit (before the first infusion), every 4 weeks during the treatment and follow-up periods, and at the EOT Visit.

[l] Blood samples for analysis of complement (CH50) must be drawn 2 hours after the end of infusions.

[m] Blood samples will be collected for pharmacokinetic assessments at the following time points: before infusion and at the end of infusion on all daratumumab infusion days; at 2, 5, and 12 hours after the end of infusion at Cycle 1 Visit 2 (first full-dose daratumumab infusion); at 2 hours after the end of infusion at Cycle 2 Visit 4; at each Follow-up Visit; and at the EOT Visit.

[n] Direct and indirect Coombs tests will be performed at all daratumumab infusion visits (before infusion and 2 hours after the end of infusion) and all follow-up visits until no antibodies are detected. These tests will also be performed at the EOT Visit for all subjects, including those who withdraw from the study.

[o] In addition to quantitation of M-component, urinalysis for total protein (including albumin) and creatinine clearance will be performed.

[p] Subjects will be contacted and asked about the occurrence of new cancers every 6 months for 3 years after their last dose of lenalidomide.

Table 2: Phase 2 Time and Events Schedule

Note: As of Amendment 8, all subjects are to follow the Time and Events Schedule in Table 4 (see Attachment 9 for additional details)

		Study Visits														
Assessments	**Screening**	**Cycle 1**					**Cycle 2[a]**				**Cycle 3-6[a]**		**Cycle 7+**	**FU[r]**	**EOT**	**Safety FU**
Visit Number	**0**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**1**	**2**	**1**		**—**	**—**
Day/Week/Month	**≤21 days before Cycle 1 Visit 1**	**0d Phase 1 only**	**1d**	**1w**	**2w**	**3w**	**1d**	**1w**	**2w**	**3w**	**1d**	**2w**	**1d**	**Q8w**	**—**	**—**
Visit Window	**—**	**—**	**—**	**±1d**	**±1d**	**±1d**	**±4d**	**±1d**	**±1d**	**±1d**	**±4d**	**±1d**	**±4d**	**±7d**	**±2d**	**±7d**
Clinical Assessments																
Informed consent	X[b]															
Eligibility criteria	X															
Demographics	X															
Medical history[c]	X															
Height and body weight	X														X	
Physical examination	X														X	
Vital sign measurements[d]	X		X	X	X	X	X	X	X	X	X	X	X		X	
Electrocardiogram[e]	X		X				X				X		X		X	
X-ray or CT scan	X[f,g]						X[g]				X[g]		X[g]	X	X	
ECOG performance status	X						X				X		X		X	
Adverse events	X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medications	X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Administration of daratumumab[q]			X	X	X	X	X	X	X	X	X	X	X			
Administration of lenalidomide		X (Days 1-21)					X (Days 1-21)				X (Days 1-21)		X (Days 1-21)			
Administration of dexamethasone			X	X	X	X	X	X	X	X	X (4 weekly)		X (4 weekly)			
Laboratory Assessments[h]																
Biochemistry[i]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Hematology[j]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy test[k]	X		X				X				X		X	X	X	

Table 2: Phase 2 Time and Events Schedule

Note: As of Amendment 8, all subjects are to follow the Time and Events Schedule in Table 4 (see Attachment 9 for additional details)

		Study Visits														
Assessments	**Screening**	**Cycle 1**					**Cycle 2[a]**				**Cycle 3-6[a]**		**Cycle 7+**	**FU[r]**	**EOT**	**Safety FU**
Visit Number	**0**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**1**	**2**	**1**		**—**	**—**
Day/Week/Month	**≤21 days before Cycle 1 Visit 1**	**0d Phase 1 only**	**1d**	**1w**	**2w**	**3w**	**1d**	**1w**	**2w**	**3w**	**1d**	**2w**	**1d**	**Q8w**	**—**	**—**
Visit Window	**—**	**—**	**—**	**±1d**	**±1d**	**±1d**	**±4d**	**±1d**	**±1d**	**±1d**	**±4d**	**±1d**	**±4d**	**±7d**	**±2d**	**±7d**
Hepatitis B, C, HIV, and cytomegalovirus	X															
Serum daratumumab level[l]			X								Cycles 3 and 6 only		C12 only	Weeks 4 and 8 after last dose		
Immunogenicity[p]		**No additional sample required; taken from PK sample (see Section 9.2.4)**														
			X											Week 4 and 8 after last dose		
Blood type assessment	X															
Direct & indirect Coombs tests	X															
Flow cytometry			X	X	X	X	X	X	X	X	X		X	X	X	
CDC and other serum-based markers			X	X	X		X								X	
ADCC			X	X			X									
Biomarkers: Whole blood draw (PBMC and plasma for CD38)			X								C3 only				X	
Pharmacogenomics	X															

Table 2: Phase 2 Time and Events Schedule

Note: As of Amendment 8, all subjects are to follow the Time and Events Schedule in Table 4 (see Attachment 9 for additional details)

		Study Visits														
Assessments	**Screening**	**Cycle 1**					**Cycle 2[a]**				**Cycle 3-6[a]**		**Cycle 7+**	**FU[r]**	**EOT**	**Safety FU**
Visit Number	**0**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**1**	**2**	**1**		**—**	**—**
Day/Week/Month	**≤21 days before Cycle 1 Visit 1**	**0d Phase 1 only**	**1d**	**1w**	**2w**	**3w**	**1d**	**1w**	**2w**	**3w**	**1d**	**2w**	**1d**	**Q8w**	**—**	**—**
Visit Window	**—**	**—**	**—**	**±1d**	**±1d**	**±1d**	**±4d**	**±1d**	**±1d**	**±1d**	**±4d**	**±1d**	**±4d**	**±7d**	**±2d**	**±7d**
Response Assessments			X	X	X	X	X									
Bone marrow aspirate/bone marrow biopsy[f]	X[g]										X[g]				X[g]	
IgA, IgM, IgG (M-component serum)	X[o]		X[o]		X[o]		X[o]				X[o]		X	X[o]	X[o]	
M-component (24-hour urine sample)[m]	X		X				X				X		X	X	X	
Free light chain kappa, lambda, and ratio (serum)	X		X		X		X				X		X	X	X	
New cancer assessment[n]																X
New antimyeloma treatment[n]																X
Survival[n]																X

Key: ADCC = antibody-dependent cell-mediated cytotoxicity; CDC = complement-dependent cytotoxicity; CT = computed tomography; d = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = End of Trial; FU = Follow-up; Ig = immunoglobulin; w = week

[a] All cycles are 28-day cycles: the first visit of a cycle should be 4 weeks after the start of the previous cycle.

[b] Informed consent may be obtained outside of the Screening Visit window, ie, before the Screening Visit date.

[c] Signs and symptoms (nonserious adverse events) occurring between the Screening Visit (before the first infusion) and the first study drug treatment at Cycle 1 Visit 1 should be recorded as medical history.

[d] Vital signs are to be measured on days when daratumumab infusions are administered: before the start of the daratumumab infusion and at the end of the infusion.

[e] Electrocardiograms (ECGs) will be performed at the Screening Visit (before the first infusion), before and after daratumumab infusion on Day 1 of each cycle, and at the EOT Visit. Three baseline ECGs should be performed before the first infusion of study drug. Before the ECGs are recorded, the subjects must be resting in a horizontal position for at least 20 minutes.

[f] The computed tomography scan and bone marrow biopsy/aspirate may have been performed within 6 weeks before Cycle 1 Visit 1.

[g] To be completed at Screening for clinical staging, at Cycle 3 Day 1, and to confirm sCR, CR, or relapse from CR. May also be performed to investigate new symptoms or at the physician discretion. A portion of the bone marrow aspirate or biopsy will be utilized for biomarker analyses.

[h] Unless otherwise stated, all blood and urine samples must be taken before administration of daratumumab. Samples must be sent to the central laboratory.

[i] Blood samples drawn for biochemistry assessments will be analyzed for the following: sodium, potassium, blood urea nitrogen, creatinine, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, bone-specific alkaline phosphatase, albumin, calcium, glucose, total creatine kinase, total bilirubin, lactic dehydrogenase, uric acid, β_2-microglobulin, and C-reactive protein.

Table 2: Phase 2 Time and Events Schedule

Note: As of Amendment 8, all subjects are to follow the Time and Events Schedule in Table 4 (see Attachment 9 for additional details)

[j] Blood samples drawn for hematology assessments will be analyzed for the following: red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, white blood cell count with differential, platelet count, and reticulocyte count.

[k] Blood samples for serum pregnancy tests will be collected at the Screening Visit (before the first infusion), every 4 weeks during the treatment and follow-up period, and at the EOT Visit.

[l] If on a daratumumab dosing day, one sample to be collected before (up to 2 hours before but not after the start of infusion) and one sample immediately after (up to 2 hours after but not before the end of infusion) daratumumab administration. For additional information refer to Section 9.2.4.

[m] In addition to quantitation of M-component, urinalysis for total protein (including albumin) and creatinine clearance will be performed.

[n] Subjects will be contacted and asked about the occurrence of new cancers every 3 months for 3 years after their last dose of lenalidomide. Survival data will also be collected.

[o] Serum sample will be split into 2 aliquots, with 1 reserved for potential follow-on testing if daratumumab interference with IFE is suspected.

[p] In addition, any time an infusion-related reaction is observed during the study, an unscheduled blood sample should be drawn as soon as possible after the reaction for potential immune response analysis.

[q] The daratumumab dose does not need to be recalculated for weight changes that are <10% from baseline.

[r] For subjects without disease progression.

Table 3: Time and Events Schedule as of Amendment 7 (see also Attachment 8)

	Treatment Phase		End-of-Treatment	Follow-up
	Start of First Cycle with Amendment 7[a]	**Every Cycle Until Treatment Discontinuation (±4 days)**	**EOT Visit (3 to 5 weeks after the last dose of study drug)**	**Every 6 months for 3 years after last dose of study drug [g] (±7 days)**
Study Procedures				
Informed consent	X			
Administration of Daratumumab	X (Day 1)	X (Day 1)		
Administration of Lenalidomide	X (Days 1-21)	X (Days 1-21)		
Administration of Dexamethasone[b]	X (4 weekly)	X (4 weekly)		
Disease assessments[c]	X	X	X	
SAEs[d]	X	X	X	
Pregnancy testing[e]		X (every 4 cycles)	X	
Best response and new antimyeloma therapy[f]			X	X
New cancer assessment[f]			X	X
Surviva[f]			X	X
Immunogenicity and associated serum daratumumab level[g]			Weeks 4 and 8 (±1 week) after last dose of study drug[h]	

EOT=End-of-Trial; SAE=serious adverse event

[a] This will be the first cycle after the subject completes a cycle and all scheduled assessments under protocol Amendment INT-6 (there should not be a restarting of the cycle number). All cycles are 28-day cycles: the first visit of a cycle should be 4 weeks after the start of the previous cycle.

[b] The administration of dexamethasone may be adjusted at the discretion of the investigator, however, dexamethasone should always be administered at a dose of 20 mg IV on daratumumab infusion days.

[c] Disease assessments/response evaluations are to be performed per local institutional practice.

[d] Includes secondary malignancies. Concomitant medication information associated with SAEs will also be collected (See Attachment 8 for more details).

[e] Samples will be analyzed by a local laboratory.

[f] Subjects will be contacted and asked about the occurrence of new cancers, best response, new antimyeloma treatment, and information on survival every 6 months for 3 years after the last dose of study drug or until termination of the study by the sponsor, whichever occurs first.

[g] Subjects will have blood samples taken only for immunogenicity, the associated daratumumab concentration will be determined from the same sample. In addition, any time an infusion-related reaction is observed during the study, an unscheduled blood sample should be drawn as soon as possible after the reaction for potential immune response analysis.

[h] The Week 4 sample will be collected at the EOT visit.

Table 4: Time and Events Schedule as of Amendment 8 (see also Attachment 9)

Study Procedure	Start of First Dosing with Amendment 8[a]
Informed Consent Amendment 8	X
Administration of Daratumumab	X (Day 1)
Administration of Lenalidomide	X (Day 1-21)
Administration of Dexamethasone[b]	X (4 weekly)
Disease assessments[c]	X
SAEs	X
Secondary Primary Malignancy[d]	X
Immunogenicity Sample[e]	1x before start of the last dose under study Amendment 7

a. This will be the first dosing once Amendment 8 is fully approved at the site, and after the subject completes a final cycle and all scheduled assessments under protocol Amendment 7.
b. The administration of dexamethasone may be adjusted at the discretion of the investigator; however, dexamethasone should always be administered at a dose of 20 mg intravenously on daratumumab infusion days. See Section 6.3 for further detail.
c. Disease assessments/response evaluations are to be performed per local institutional practice.
d. Subjects will be contacted regarding the occurrence of new SPMs every 3 months by phone (month 3, month 9, etc..) or in a site visit (month 6, month 12, etc…). In cases where subjects become aware of the occurrence of a new SPM, they will instructed to report it as soon as possible to their study investigator.
e. As of Amendment 8, blood sample collection will stop and will not be performed after the last dose of daratumumab. One final sample should be collected before the last infusion of daratumumab per Amendment 7 and sent to the central laboratory. Sample will also be assessed for serum daratumumab concentration to ensure proper interpretation of immunogenicity data.

ABBREVIATIONS

Abbreviation	Definition
ADCC	antibody-dependent cell-mediated cytotoxicity
AE	adverse event
ALT	alanine aminotransferase
anti-HBc	antibodies to hepatitis B core antigen
anti-HBs	antibodies to hepatitis B surface antigen
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
auto-SCT	autologous stem cell transplantation
CDC	complement-dependent cytotoxicity
CL	total systemic clearance of drug after IV administration
C_{max}	maximum concentration in serum
C_{min}	minimum or trough concentration in serum
CR	complete response
CrCl	creatinine clearance
CRO	contract research organization
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events, version 4.0
DCF	Data Clarification Form
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DVT	deep vein thrombosis
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOT	End of Trial
EU	European Union
FDA	Food and Drug Administration
FEV1	forced expiratory volume in 1 second
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor
HBsAg	hepatitis B surface antigen
HIV	human immunodeficiency virus
IAT	indirect antiglobulin test
ICF	Informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
Ig	immunoglobulin
IL	interleukin
IMiD	immunomodulatory drugs
IRB	Institutional Review Board
ITT	Intent-to-Treat
IV	intravenous
Len/Dex	lenalidomide and dexamethasone
mAb	monoclonal antibody
MR	minimal response
MTD	maximum tolerated dose
NaCl	sodium chloride
NK	natural killer
ORR	overall response rate
PD	progressive disease
PE	pulmonary embolism
PFS	progression-free survival

PK	pharmacokinetic(s)
PO	orally
PP	Per-Protocol
PQC	product quality complaint
PR	partial response
RBC	red blood cell
RhD	Rh blood group, D antigen
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SPM	second primary malignancy
$t_{1/2}$	elimination half-life
T_{max}	time to maximum concentration in serum
ULN	upper limit of normal
US	United States
V	volume of distribution
V_{cen}	central volume of distribution
VGPR	very good partial response

1. INTRODUCTION

The investigational medicinal product, daratumumab, is an IgG1κ human monoclonal antibody (mAb) that specifically recognizes the CD38 epitope. It is produced in a recombinant Chinese Hamster Ovary cell line. Standard mammalian cell culture and purification techniques are employed in the manufacture of daratumumab.

For the most comprehensive nonclinical and clinical information regarding daratumumab, refer to the latest version of the Investigator's Brochure for daratumumab.

The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

1.1. Background

1.1.1. Multiple Myeloma

Multiple myeloma is a plasma cell disorder, characterized by uncontrolled, malignant proliferation and accumulation of plasma cells. In the majority of patients, the malignant plasma cells produce a monoclonal protein (M protein or paraprotein). The majority of M proteins are immunoglobulin (Ig) G (~ 50%) and IgA (~ 20%). The proliferation of myeloma cells causes displacement of the normal bone marrow. Myeloma cells are highly dependent upon external factors, ie, the microenvironment in bone marrow, including stromal cells and cytokines (eg, interleukin [IL]-6) (Klein 1989, Vidriales 1996).[9,30] In multiple myeloma, the major clinical findings include anemia, monoclonal Ig (M protein) in serum and/or urine, abnormal bone radiographs (bone resorption seen as diffuse osteoporosis or characteristic lytic lesions), hypercalcemia, renal insufficiency or failure, and neurologic complications.

Multiple myeloma accounts for approximately 1% of all malignancies and 10% of all hematologic malignancies, with a higher frequency in African Americans where it accounts for 20% of all hematologic malignancies (Howe 2001).[8] In the United States (US), approximately 11,000 deaths each year are related to multiple myeloma, and the estimated number of new cases has risen from 15,270 in 2004 to 20,180 in 2010.[1] At present, there is no cure available.

1.1.2. Current Treatment of Multiple Myeloma

Treatments include combination chemotherapy, proteasome inhibition, immunomodulatory drugs (IMiDs), high-dose chemotherapy, and autologous stem cell transplantation (auto-SCT). Allogenic transplantation is performed only in a minority of younger patients, and its role as a treatment modality is not determined.

Current first-line treatment regimens have often included the use of an alkylating agent. Melphalan, combined with prednisone, has been the standard of care for many years and results in response rates of 50% to 60%. However, few patients achieve a complete response (CR) by using this approach. More recently, combinational strategies involving new agents have been added to the standard of care. The use of these agents, including IMiDs (eg, thalidomide and lenalidomide) and proteasome inhibitors (eg, bortezomib), has increased response rates and rates

of CR in particular (Palumbo 2006, Rajkumar 2008, Lacy 2007, San Miguel 2008).[20,23,13,25] In younger, healthier patients, auto-SCT has been performed after induction therapy and has resulted in CR rates of 20% to 40% (Attal 2007).[2]

For relapsed multiple myeloma, treatment with bortezomib as a single agent results in a response rate of approximately 38% and a CR rate of 6% (Richardson 2005).[24] However, a combination of bortezomib and dexamethasone gives higher response rates, up to approximately 70% (Kropff 2005).[11] This combination has become standard of care when using bortezomib in patients with relapsed multiple myeloma (NCCN 2011).[19] Because of the side-effect profile of bortezomib, which includes peripheral neuropathy, reduced dose regimens (once weekly) have been investigated and have demonstrated similar efficacy but improved safety (Bringhen 2010).[3] Treatment with dexamethasone has been associated with side effects of gastrointestinal problems, headache, dizziness, insomnia, restlessness, anxiety, acne, bruising, swelling of face and legs, and vision problems.

Combinations of thalidomide or lenalidomide and dexamethasone are approved by the US Food and Drug Administration (FDA) and the European Medicines Agency and are also considered as standard of care for relapsed multiple myeloma. Clinical trials included high-dose dexamethasone and demonstrated response rates of approximately 60% with CR rates of 15.9% (Dimopoulos 2007).[6] High-dose dexamethasone, however, is associated with significant toxicity. More recently, lenalidomide combined with a lower dose of dexamethasone (40 mg weekly) has demonstrated significantly reduced toxicity and increased overall survival when compared with lenalidomide and high-dose dexamethasone (Rajkumar 2010).[22] Low-dose dexamethasone is now widely used when combined with lenalidomide in the treatment of relapsed multiple myeloma.

Lenalidomide (Revlimid®) is approved in the US and the European Union (EU) for the second-line treatment in combination with dexamethasone (Revlimid SmPC).

As previously described, targeting multiple myeloma cells with combination therapy has demonstrated superior clinical responses as compared with single-agent therapy. Using an IMiD with a monoclonal antibody (mAb) combines both indirect and direct antitumor mechanisms, and such a combination has previously indicated efficacy in the treatment of multiple myeloma (Moreau 2011).[18]

1.1.3. Preclinical Pharmacology and Pharmacokinetics

Potential mechanisms of action have been investigated in both in vitro and in vivo pharmacodynamic studies. Results from these studies suggest that complement-dependent cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC) may be the major mechanisms of action for daratumumab, and that these mechanisms are of crucial importance in the treatment of malignancies expressing CD38. Half-maximal killing of myeloma cells in vitro by CDC and ADCC occurred at antibody levels of approximately 0.1 μg/mL and 0.03 μg/mL, respectively. Studies in the xenograft lymphoma model in severe combined immunodeficiency mice have shown that daratumumab potently inhibits the in vivo growth of

CD38-expressing tumor cells at concentrations from 0.5 mg/kg. Thus far, it is uncertain if the inhibition of the enzyme activity of CD38 by daratumumab contributes to its therapeutic effect.

Daratumumab does not induce the production of IL-6 or interferon γ by human mononuclear cells cultured in vitro. Thus, no stimulatory effects of daratumumab have been demonstrated in vitro.

For further information, refer to the Investigator's Brochure.

1.1.4. Preclinical Safety

The safety and toxicity of daratumumab was studied in chimpanzees because daratumumab does not bind to CD38 in other nonhuman primate species.

Overall, the safety study with daratumumab in chimpanzees revealed 2 potential safety issues: cytokine release syndrome and platelet depletion. Administration of a predose infusion of daratumumab before the first full-dose infusion prevented or minimized the clinical signs of cytokine release syndrome in chimpanzees. Therefore, a predose infusion has been incorporated into the Phase 1 dosing regimen of this clinical study. During the first-in-human clinical study (Protocol No. GEN501; ClinicalTrial.gov NCT00574288), no major changes in platelet counts over time have been observed in doses up to and including 4 mg/kg.

Based upon emerging safety data and further understanding of the occurrence of infusion related reaction, the pre-dose infusion is no longer required and will not be utilized in Phase 2. Pre and post medications and dose interruptions of daratumumab in ongoing single agent and combination studies have provided adequate intervention.

Daratumumab binding was investigated by immunohistochemistry in a human tissue cross-reactivity study. As shown by staining, daratumumab binds to lymphoid cells in the spleen, tonsil, lymph nodes, and thymus; capillaries of the pituitary gland; vascular endothelial cells; epithelial cells of the fallopian tubes and prostate; lymphocytes in the ileum serosa; and parathyroid, kidney, testis, and thyroid interstitial cells. Chimpanzee and human CD38 proteins are highly similar, and the interaction of daratumumab with these proteins is comparable regarding in vitro binding.

For further information, refer to the Investigator's Brochure.

1.1.5. Clinical Experience

Daratumumab is currently under investigation in multiple ongoing singe agent and combination studies. Safety information and limited efficacy data from daratumumab clinical studies may be referenced in the Investigator's Brochure.

1.2. Combination Therapy of Daratumumab, Lenalidomide, and Dexamethasone

To date, targeting multiple myeloma cells by a combination therapy approach has demonstrated superior clinical response as compared with that of single agents. In theory, targeting both the

tumor cells and the surrounding stromal compartment, upon which the tumor is dependent, should lead to higher efficacy. The combination of an IMiD and an mAb utilizes indirect and direct antitumor mechanisms and has previously been shown to be effective (Lonial 2010).[16] Based on preclinical data, combining daratumumab and lenalidomide is not expected to induce unacceptable aggravation of the toxicology profile, and the mechanisms of action elucidated by preclinical studies indicate a potential for additive clinical efficacy.

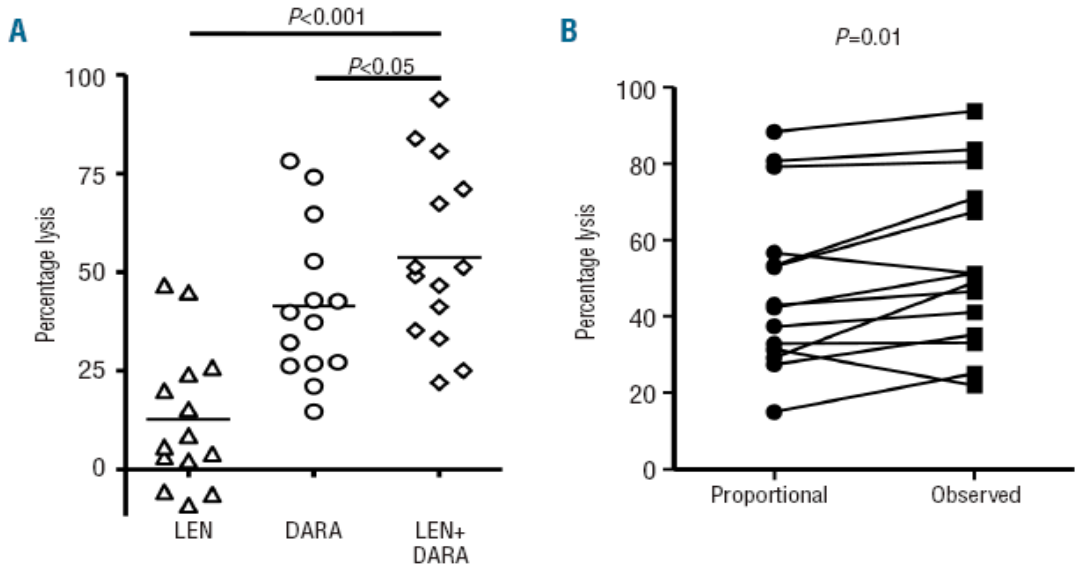
Daratumumab directly targets the tumor cells by selectively binding to CD38 receptors, which are present at high levels on malignant plasma cells in multiple myeloma. Daratumumab has multiple mechanisms of action, including ADCC and CDC (de Weers 2011).[5] Importantly, daratumumab-induced ADCC and CDC does not appear to be affected by the presence of bone marrow stromal cells, indicating that daratumumab can effectively kill multiple myeloma tumor cells in a tumor-preserving bone marrow microenvironment. In vivo studies have shown that daratumumab is highly active and interrupts xenograft tumor growth at low doses (de Weers 2011).[5]

Lenalidomide is an immunomodulatory agent that is thought to mediate antimyeloma activity by 3 main mechanisms: 1) direct antitumor effect; 2) inhibition of the microenvironment support for tumor cells; and 3) an immunomodulatory role (Vallet 2008).[28] The direct tumor effect is described both as growth inhibition of myeloma cell lines and induction of apoptosis. The microenvironment support is affected by down regulation of cell adhesion molecules (eg, intercellular adhesion molecule 1), thus inhibiting stromal cell interaction with tumor cells, and inhibition of growth factors (eg, insulin growth factor 1 and vascular endothelial growth factor) induced by myeloma cell adhesion. Furthermore, lenalidomide has been demonstrated to possess antiangiogenic and antiosteoclastogenic effects. Finally, lenalidomide exhibits immunomodulatory activity including inhibition of proinflammatory signaling molecules (cytokines) such as tumor necrosis factor α, IL-1β, and IL-6, the latter of which is a known growth factor for myeloma cells (Vallet 2008).[28]

Importantly, it has also been shown that lenalidomide causes upregulation of natural killer (NK) cells in myeloma (Kotla 2009)[10] and enhances ADCC of multiple myeloma cells, (Tai 2008, Tai 2005) [26,27] which is a mechanism shown in preclinical studies to be involved in the efficacy of daratumumab.

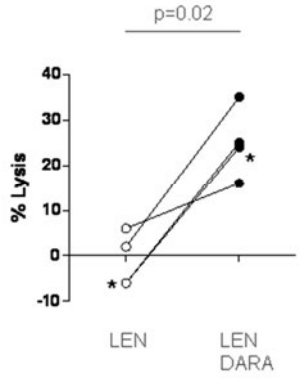
In a preclinical study that used bone marrow mononuclear cells from patients with multiple myeloma, increased killing of tumor cells was demonstrated when daratumumab was combined with lenalidomide as compared with that of either agent alone as shown in Figure 1A (van der Veer 2011).[29] Notably, daratumumab and lenalidomide acted in a synergistic fashion to generate an extra effect of 20% as compared with the expected additive effects of the agents (Figure 1B). This increased activity was retained even in patients whose multiple myeloma was clinically refractory to lenalidomide (Figure 2).

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



Key: DARA = daratumumab; LEN = lenalidomide; MM = multiple myeloma.
Note: (A) Bone marrow mononuclear cells of 14 patients with MM were incubated for 47 hours with the control antibody, with lenalidomide (3 μM), and/or daratumumab (0.1 μg/mL). Surviving MM cells were enumerated by Fluorescence-activated Cell Sorting analysis of CD138+ cells. The percentages of lysis of MM cells treated with lenalidomide, daratumumab, and lenalidomide + daratumumab were calculated by the Tukey's post hoc analysis of repeated measures analysis of variance.
(B) The observed effect (% lysis) of the combination treatment was compared with the expected additive effect (proportional) of the combined treatments. Mixed model analysis supported the conclusion that the combination treatment was synergistic.

Figure 2: Addition of Daratumumab to Lenalidomide Significantly Increases the Lysis of Multiple Myeloma Cells in Bone Marrow Mononuclear Cells of Patients with Lenalidomide-refractory Multiple Myeloma



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

Note: Bone marrow mononuclear cells from 4 patients with lenalidomide-refractory MM were incubated lenalidomide (3 μM), daratumumab (10 μg/mL), or in combination for 48 hours. Surviving MM cells were enumerated by Fluorescence-activated Cell Sorting analysis of CD138+ cells. The percentages of lysis of MM cells treated with lenalidomide, daratumumab, or lenalidomide + daratumumab were calculated as compared with the survival of MM cells treated with the control keyhole limpet hemocyanin antibody alone.

Finally, it was demonstrated that peripheral blood mononuclear cells isolated from patients during or just after lenalidomide treatment showed a significantly increased capacity to mediate daratumumab-dependent ADCC against multiple myeloma cells alone (van der Veer 2011).[29]

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

Based on the current safety data from the ongoing GEN501 study (Section 1.1.5) and the safety information in the label for lenalidomide, the expected safety profile of daratumumab in this combination therapy study is considered manageable.

No major changes in thrombocyte counts over time have been observed during treatment with daratumumab in doses up to 4 mg/kg. Thrombocytopenia was an expected finding based on the data from preclinical studies. Because lenalidomide may cause thrombocytopenia, an additive effect cannot be excluded. Therefore, thrombocytopenia must be closely monitored, and dose adjustments in accordance with the label for lenalidomide must be followed during this study of the combination of daratumumab and lenalidomide. Lenalidomide also increases the risk of DVT and pulmonary embolism (PE). No thromboembolic events have been observed with daratumumab; however, a thrombocyte-sensitizing effect of daratumumab cannot be excluded. Therefore, aspirin should be administered to all subjects, and low-molecular weight heparin should be given to subjects who are at increased risk of thromboembolic events. Intense safety

monitoring by the sponsor and an Independent Data Monitoring Committee (IDMC) will be performed.

No additive adverse effects are expected when combining dexamethasone with daratumumab based on results of the analysis of daratumumab safety data in the GEN501 study.

1.3. Overall Rationale for the Study

The sponsor is evaluating daratumumab as a treatment for subjects with relapsed or relapsed and refractory multiple myeloma.

2. OBJECTIVES AND HYPOTHESIS

2.1. Objectives

Primary Objective

The primary objective is to establish the safety profile of daratumumab when given in combination with Len/Dex in subjects with relapsed or relapsed and refractory multiple myeloma.

Secondary Objectives

The secondary objectives are:

- To evaluate the efficacy of daratumumab when given in combination with Len/Dex in subjects with relapsed or relapsed and refractory multiple myeloma.
- To evaluate the pharmacokinetic (PK) profile of daratumumab when given in combination with Len/Dex in subjects with relapsed or relapsed and refractory multiple myeloma.
- To assess the immunogenicity of daratumumab.

2.2. Hypothesis

No formal statistical hypotheses are planned to be tested.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is an open-label, multicenter Phase 1/2 safety study of daratumumab in combination with Len/Dex in the treatment of subjects with relapsed or relapsed and refractory multiple myeloma. The dose escalation portion of the study (Phase 1) will be a standard 3 + 3 design and will evaluate daratumumab, at doses from 2 mg/kg up to a maximum of 16 mg/kg, in combination with Len/Dex in 28-day treatment cycles. The standard “3 + 3” rules for dose escalation will be applied, However, if the study sites have identified 4 eligible subjects to start a new dose level, all 4 subjects may be enrolled. The MTD will be defined as the highest dose of the combination regimen at which less than 33% of subject’s experience DLT. A recommended Phase 2 dose (RP2D) will be determined during Phase 1. The MTD or any dose evaluated in the range of 2 to 16 mg/kg of daratumumab may be considered as the RP2D based on available safety,

PK/pharmacodynamic, and efficacy data from Phase 1. The RP2D could be selected before escalation to or completion of the 16 mg/kg cohort. Once the RP2D is determined, the expansion (Phase 2) will open to further explore the safety and efficacy of the RP2D in approximately 30 subjects.

For Phase 1 and Phase 2 of the study there will be a Screening Period followed by the first 2 treatment cycles and will consist of weekly daratumumab infusions, totaling 4 infusions during each 28-day cycle. Cycles 3 through 6 will consist of daratumumab infusions administered every other week; Cycle 7 and all subsequent cycles will consist of monthly daratumumab infusions. The combination treatment may continue until the subject experiences disease progression or unacceptable toxicity, whichever comes first. For Phase 1 only, to minimize the risk of cytokine release syndrome, the first infusion of the first cycle will be preceded by a predose infusion the day before the scheduled full-dose infusion. The predose infusion will be 10% of the full dose, but will never be more than 10 mg in total dose. Further measures to prevent cytokine release syndrome will include premedication with antihistamines, acetaminophen, and dexamethasone before each daratumumab infusion (both predose and full dose).

For Phase 1 and Phase 2, lenalidomide will be administered at a dose of 25 mg orally (PO) on Days 1 through 21 of each 28-day cycle, and dexamethasone will be administered at a total dose of 40 mg weekly. As of Amendment 5, subjects older than 75 years or underweight (body mass index [BMI] <18.5), the dexamethasone dose may be administered at a dose of 20 mg weekly. On weeks when daratumumab is administered the 20 mg dose should be administered as the premedication per protocol. Details on the dosing regimens for Len/Dex are provided in Section 6.2 and Section 6.3, respectively.

During Phase 1, decisions to escalate the dose of daratumumab for the next cohort will be based on the safety data obtained from the 3 (+ 3) subjects in the previous cohort during their first treatment cycle (28 days). The IDMC will evaluate all safety data (including SAEs, AEs, and laboratory data) after each cohort completes Cycle 1. The third subject in the cohort must have received all 4 full doses of daratumumab, and data from an observation period of 6 days after the last infusion must be available for the IDMC to review. Based on the results presented in these safety profiles, the IDMC will recommend to the sponsor if it appears safe to escalate the dose. The recommendation will be discussed and confirmed by the sponsor, who will ultimately decide if dose escalation will occur. Subjects who discontinue the study during the first cycle for reasons other than a DLT will be replaced.

The IDMC and sponsor may decide to implement intermediate doses to ensure subject safety and better define the RP2D. The RP2D, as defined by the IDMC and sponsor, or the maximum dose tested will be the dose level at which subjects will be treated in Phase 2 of the study.

In both phases of the study, investigational product will be administered per schedule up to disease progression, intolerability, withdrawal, death, or unless otherwise indicated by IDMC. Daratumumab may be continued until investigator's or sponsor's recommendation of discontinuation, the subject's decision to discontinue for any reason, or disease progression.

The study will have 3 data cutoff time points:

- The first data cutoff will be for the interim safety analysis, which is estimated to be performed approximately 6 months after the last subject in the study receives the first dose of daratumumab. All available data at the time of this data cutoff will be included in the abbreviated Clinical Study Report (CSR).
- The second data cutoff will be for the primary safety analysis, which is estimated to be performed approximately 12 months after the last subject in the study received the first dose of daratumumab. All available data at the time of this data cutoff will be included in the abbreviated CSR.

  As of Amendment 8, the following data cutoff is yet to be completed.

- The third and final data cutoff will be for the updated safety analysis, which is estimated to be performed approximately 24 months after the last subject in the study receives the first dose of daratumumab. All available data at the time of this data cutoff will be included in a final CSR addendum.

3.2. Rationale for Study

3.2.1. Rationale for Subject Population

Despite great strides in treatment, multiple myeloma remains an incurable condition that claims some 11,000 lives a year in the US and an equal number in the EU. There is currently no cure available, and clearly, there is a need for novel therapies, particularly for those patients who are not candidates for auto-SCT.

In Phase 1 (dose escalation), the subject population will include patients with relapsed multiple myeloma after receiving a minimum of 2 and a maximum of 4 prior lines of therapy.

In Phase 2 (cohort expansion), the subject population will include patients with relapsed or refractory multiple myeloma that have received at least 1 prior line of therapy, and are not refractory to lenalidomide.

3.2.2. Rationale for Study Design

In this Phase 1/2 safety study of daratumumab in combination with lenalidomide and low-dose dexamethasone (Len/Dex), a standard Phase 1 "3 + 3" design is appropriate to adequately observe DLTs associated with the regimen while not exposing an undue number of subjects to doses that may be subtherapeutic. The dose escalation phase of the study (Phase 1) will be followed by Phase 2, upon identification of recommended Phase 2 dose (RP2D). Approximately 30 subjects will be enrolled in Phase 2, which will allow for a greater degree of experience with the combination therapy at what is expected to be a therapeutic dose of daratumumab and Len/Dex.

3.2.3. Dose Rationale

3.2.3.1. Phase 1 Dose Escalation

Safety and PK data on daratumumab as a single-agent therapy are currently being obtained and evaluated in the ongoing Phase 1, dose-escalation, clinical study (GEN501). Doses of 0.005 mg/kg up to and including 4 mg/kg have been judged safe, and dose escalation is ongoing.

Preliminary PK analysis of subject data from the GEN501 dose-escalation study has shown low serum recovery of daratumumab in the 0.1 mg/kg cohort. In the 1, 2, and 4 mg/kg cohorts, the maximum concentration in serum (C_{max}) corresponds to a V_{cen} of 54, 54, and 25 mL/kg, respectively, which is consistent with initial distribution into the serum compartment as expected for an antibody. The considerably larger V_{cen} observed in the 0.1 and 0.5 mg/kg cohorts is likely due to target binding.

Plots comparing the observed daratumumab concentrations with concentrations expected in serum from a general IgG PK model show that the observed daratumumab clearance is faster than expected for IgG, which indicates that the PK of daratumumab in humans is affected by a "sink." It is speculated that, in patients with multiple myeloma, tumor load has a large contribution to the "sink", which may explain the observed intersubject variability.

In vitro studies showed that daratumumab may exert antitumor effects at low concentrations, but that maximum efficacy of all potential mechanisms of action requires saturation of the target, which occurs at concentrations greater than approximately 2 μg/mL. Because concentrations of daratumumab in serum of subjects in the 1.0 mg/kg cohort of the GEN501 study were only above this level for a limited time, it was concluded that doses of 1 mg/kg and below would add suboptimal therapeutic support to patients with relapsed multiple myeloma. In addition, it should be noted that concentrations of daratumumab around tumor cells are likely to be below those in serum. Consistent with the existence of a "sink", the increase in the area under the concentration-time curve (AUC) was more than dose-proportional when the dose level was increased from 0.5 to 4 mg/kg. In the 4 mg/kg cohort, the importance of the "sink" seems to become smaller compared with that of the preceding cohorts. One subject in this cohort had trough levels of daratumumab above 10 μg/mL throughout an observation period of more than 5 weeks.

By using a PK model based on the available data, in which the "sink" is represented by a nonlinear route of clearance and assuming that the "sink" remains unchanged during therapy, predictions were made for alternative dosing schedules. For weekly infusions at a dose level of 8 mg/kg, it is expected that the effect of the "sink" will become relatively small, the C_{max} of daratumumab will be in the range of 200 to 300 μg/mL, trough concentrations will be around 100 μg/mL, and no major accumulation will occur. Furthermore, at the proposed dose schedule (where the dose interval after Week 8 is extended to 2 weeks), no accumulation of daratumumab is expected, even if the "sink" diminishes during therapy.

The starting dose of the daratumumab component in this combinational study will be 2 mg/kg. This dose corresponds to ¼ of the dose currently being investigated (8 mg/kg) and ½ of the

highest dose that has been approved by the external IDMC (4 mg/kg) in the ongoing GEN501 monotherapy study.

To prevent cytokine release syndrome, a predose infusion will be administered the day before the first full-dose infusion of daratumumab. The predose infusion will be 10% of the full dose, but never more than 10 mg in total. In Phase 2, the predose will not be administered. Further measures to prevent cytokine release syndrome will include premedication with antihistamines, acetaminophen, and dexamethasone before each infusion (both predose and full dose).

3.2.3.2. Daratumumab RP2D Rationale

The RP2D has been selected based on marked M-protein reduction with an acceptable safety profile in doses up to16 mg/kg, the highest dose of Phase 1. MTD was not reached in Phase 1. The IDMC reviewed the safety data of 2, 4, 8 and 16 mg/kg cohorts and concluded that an acceptable benefit/risk profile was observed in doses up to 16 mg/kg. The majority of the Grade 3 adverse events were neutropenia, which was attributed to lenalidomide. The daratumumab/Len/Dex combination PK-profile was similar to daratumumab alone suggesting Len/Dex does not affect the pharmacokinetic profile of daratumumab.

The rationale of PR2D is also supported by the ongoing single agent daratumumab studies. Clinical pharmacokinetic data have shown the 16 mg/kg dose to be the lowest dose that results in complete target suppression at all time points. This dose and schedule continuously suppressed NK cells throughout dosing. Additionally, the overall response rate (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) as of a cutoff date of 24 January 2014. In Study GEN501, the ORRs (ie, partial response [PR] or greater) were 11% and 40% for the 8-mg/kg (n=28) and 16-mg/kg (n=15) dose regimens, respectively. For the 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 those 2 studies. VGPR had not been observed at lower dose levels. These preliminary data support that full target saturation at the 16-mg/kg dose is needed to achieve higher and deeper response rates. In addition, the 16-mg/kg dose and schedule was shown to have an acceptable and manageable safety profile for the approximately 30 subjects for whom preliminary data were available in Studies GEN501 and MMY2002, and no additive toxicity has been observed in the Phase 1 dose escalation when comparing the safety from 16 mg/kg dose cohort with lower dose cohorts.

4. STUDY POPULATION

4.1. General Considerations

Between 42 and 58 subjects will be enrolled in this study, depending on the number of dose levels included during dose escalation in Phase 1. It is estimated that the screen failure rate will be 25% and that between 56 and 78 subjects will be screened in order to enroll the expected number.

4.2. Inclusion Criteria

Before entering Phase 1 of the study, subjects must:

1. Have relapsed multiple myeloma after receiving a minimum of 2 and a maximum of 4 prior lines of therapy and be eligible for treatment with Len/Dex.
2. Have measurable levels of M-component, defined as serum M-component ≥ 1.0 g/dL and/or urine M-component ≥ 200 mg/24-hour sample.
3. Be ≥ 18 years of age.
4. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 (Attachment 1).
5. Have a life expectancy of ≥ 3 months.
6. Provide signed informed consent after receipt of oral and written information about the study and before any study-related activity is performed.

Before entering Phase 2 of the study, subjects must:

1. – Have received at least 1 prior line of therapy for multiple myeloma (refer to Attachment 2).
   – Have achieved a response (PR or better) to at least one prior regimen.
   – Have documented evidence of progressive disease (PD) as defined by the IMWG criteria on or after their last regimen.
2. Have measurable levels of M-component, defined as serum M-component ≥ 1.0 g/dL and/or urine M-component ≥ 200 mg/24-hour sample.
3. Be ≥ 18 years of age.
4. Have an ECOG performance status score of 0, 1, or 2 (Attachment 1).
5. Have a life expectancy of ≥ 3 months.
6. Provide signed informed consent after receipt of oral and written information about the study and before any study-related activity is performed.

4.3. Exclusion Criteria

Before entering the study, subjects must not:

1. Have previously received an allogenic stem cell transplant.

2. Have received auto-SCT within 12 weeks before the first infusion.

3. Have received antimyeloma treatment, radiotherapy, or any experimental drug or therapy within 2 weeks before the first infusion.

4. Have discontinued lenalidomide due to any treatment-related adverse event or be refractory to any dose of lenalidomide.

   Refractory to lenalidomide is defined as either:

   - Subjects whose disease progresses within 60 days of lenalidomide, or
   - Subjects whose disease is nonresponsive while on any dose of lenalidomide. Nonresponsive disease is defined as either failure to achieve at least an MR or development of PD while on lenalidomide.

5. Have experienced prior DVT of ≥ Grade 3 according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0 (CTCAE).

6. Have experienced prior PE.

7. Have had past or current malignancy, except for:
   - cervical carcinoma of Stage 1B or less;
   - noninvasive basal cell or squamous cell skin carcinoma;
   - malignant melanoma with a CR of > 10 years duration;
   - prostate cancer with a current prostate-specific antigen level < 0.1 ng/mL;
   - any curable cancer with a CR of > 5 years duration.

8. Have any current serious infectious disease requiring systemic treatment.

9. Have clinically significant cardiac disease, including:

   - unstable angina;
   - acute myocardial infarction within 6 months of the Screening Visit (before the first infusion);
   - congestive heart failure (Class III or IV as classified by the New York Heart Association; Attachment 3);
   - a known decreased cardiac ejection fraction of < 50%;

- a screening 12-lead electrocardiogram (ECG) reading showing a baseline QT interval as corrected by Fridericia's formula (QTcF) > 470 msec for females or > 450 msec for males or a complete left bundle branch block (defined as a QRS interval ≥ 120 msec in left bundle branch block form).

10. Have a significant, concurrent, uncontrolled medical condition including, but not limited to, renal (except as related to multiple myeloma), hepatic, hematologic (except as related to multiple myeloma), gastrointestinal, endocrine, pulmonary, neurologic, cerebral, or psychiatric disease.

11. Be exhibiting clinical signs of meningeal involvement of multiple myeloma.

12. Have known severe chronic obstructive pulmonary disease or asthma (defined as a forced expiratory volume in 1 second [FEV1] <60% of predicted normal) or persistent asthma.

13. Have a history of significant cerebrovascular disease.

14. Have known to be seropositive for human immunodeficiency virus (HIV) or have active hepatitis B or hepatitis C.

15. Have screening laboratory test results as the following:

- absolute neutrophil count $\leq 1.5 \times 10^9$/L;
- hemoglobin level ≤ 80 g/L (≤ 5 mmol/L);
- platelet count $< 75 \times 10^9$/L
- alanine aminotransferase (ALT) ≥ 2.5 times the upper limit of normal (ULN);
- alkaline phosphatase level ≥ 2.5 × ULN;
- direct bilirubin level ≥ 2 × ULN;
- creatinine clearance (CrCl) ≤ 60 mL/min within 7 days before the Screening Visit (before the first infusion);
- potassium level < 3.0 mEq/L.

16. Have received granulocyte-colony stimulating factor (G-CSF) or granulocyte/macrophage-colony stimulating factor support for < 1 week or pegylated G-CSF for < 2 weeks before the Screening Visit or before the first infusion.

17. Have received a cumulative dose of corticosteroid ≥ 200 mg (dexamethasone, or equivalent doses of prednisone) within 2 weeks before the first infusion.

18. Have a known hypersensitivity to components of the study drug or combination therapy, or have known allergies, hypersensitivity, or intolerance to monoclonal antibodies or human proteins, or their excipients (refer to Investigator Brochure 2013), or have known sensitivity to mammalian-derived products.

19. Have plasma cell leukemia or Waldenström's macroglobulinemia.

20. Have previously received daratumumab, or other anti-CD38 therapies.

21. Be known to have any contraindications to receiving lenalidomide (as specified in the lenalidomide label).

22. Have received treatment with any nonmarketed drug substance within 4 weeks before the first infusion.

23. Be currently participating in any other interventional clinical study.

24. Be known or suspected of not being able to comply with the study protocol (eg, because of alcoholism, drug dependency, or psychological disorder).

25. Be breastfeeding female.

26. Have a positive pregnancy test at the Screening Visit or before the first infusion.

27. Be unwilling to use adequate contraception for 4 weeks before the first infusion of daratumumab, during the study, and for 6 months after the last infusion of daratumumab if a female of childbearing potential. Adequate contraception is defined as hormonal birth control or an intrauterine device. For subjects in the US, the use of a double-barrier method during interruption periods and for at least 4 weeks after the end of treatment is also considered adequate. Subjects in the EU must follow the Pregnancy Prevention Programme.

28. Be males unwilling to use a latex condom during any sexual contact with females of childbearing potential during and for 6 months after the last infusion of daratumumab, even after having undergone a successful vasectomy.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's status changes (including laboratory results or receipt of additional medical records) after screening but before the first dose of study drug is given such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study. Section 17.4, Source Documentation, describes the required documentation to support meeting the enrollment criteria.

5. TREATMENT ALLOCATION AND BLINDING

5.1. Subject Allocation Procedures

In Phase 1, subjects will be allocated to the dose escalation cohorts in a standard 3 + 3 study design. In Phase 2, subjects will be enrolled to an expansion cohort. Allocation of subjects in both Phases 1 and 2 will be controlled by the contract research organization (CRO).

When a potential subject is identified at a site, the site personnel must contact the CRO regarding the subject. If there is an opening in the currently enrolling cohort, the site will be given approval to start the screening process.

If there is no opening in the currently enrolling cohort, the CRO will place the subject on a list of potential subjects. If another subject fails the screening process, the CRO will alert the site that has the next subject on the waiting list. If the subject is still eligible, the site will be given approval to start the screening process.

5.2. Blinding

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

6. DOSAGE AND ADMINISTRATION

The start of a cycle is defined as the start of any of the study treatments (ie, daratumumab or Len/Dex). If all treatments are held, then it should be reported as a cycle delay.

6.1. Daratumumab

Daratumumab will be administered as an IV infusion. Each subject's dose will be calculated based on the subject's weight rounded to the nearest kilogram, ie, assigned cohort dose in mg/kg × body weight in kg. The dose does not need to be recalculated for weight changes that are <10% from baseline. The weight will be used to determine the number of vials required for dosing. The pharmacist will then calculate the required volume of daratumumab from the number of vials needed for each subject. For subjects whose body mass index is greater than 30 kg/m^2, the investigator should use a weight that, based on the subject's height, corresponds to a maximum body mass index of 30.

For Phase 1, daratumumab will be given as follows:

- Cycle 1: Day 0 (predose infusion), Day 1 (first full-dose infusion), and Days 8, 15, and 22 of a 28-day cycle
- Cycle 2: Days 1, 8, 15, and 22 of a 28-day cycle
- Cycles 3-6: Days 1 and 15 of a 28-day cycle for 4 cycles or until the subject experiences unacceptable toxicity or disease progression, whichever comes first
- Cycles 7+: Day 1 of a 28-day cycle until the subject experiences unacceptable toxicity or disease progression, whichever comes first

For Phase 2, daratumumab will be given as follows:

- Cycle 1: Day 1 (first full-dose infusion), and Days 8, 15, and 22 of a 28-day cycle
- Cycle 2: Days 1, 8, 15, and 22 of a 28-day cycle
- Cycles 3-6: Days 1 and 15 of a 28-day cycle for 4 cycles or until the subject experiences unacceptable toxicity or disease progression, whichever comes first
- Cycles 7+: Day 1 of a 28-day cycle until the subject experiences unacceptable toxicity or disease progression, whichever comes first Table 5 and Table 6 provide recommendations for the rate of infusion.

Table 5: Phase 1 Infusion Rate Recommendations

Predose Infusions		First Full-dose Infusion[a]		Subsequent Full-dose Infusions[a]	
Time (minutes)	**Rate (mL/hour)**	**Time (minutes)**	**Rate (mL/hour)**	**Time (minutes)**	**Rate (mL/hour)**
0 - 240	12.5	0 – 60	50	0 - 60	50[c]
		61 – 180	100	61 - 120	100
		181 -	150[b]	121 - 180	150
				181 -	200
Total volume	50 mL	Total volume	1000 mL	Total volume	1000 mL

[a] Additional details for administration times and rates for the full-dose infusions will be provided in the administration guidelines.
[b] If the infusion is uneventful after 2 hours at a rate of 150 mL/hour, the investigator may increase the infusion rate to 200 mL/hour.
[c] If no infusion reactions occurred during the last full-dose infusion, the infusion rate may start at 100 mL/hour at the investigator's discretion.

Table 6: Phase 2 Infusion Rate Recommendations

First Full-dose Infusion for Approximately 20 Subjects[a]		First Full-dose Infusion for Approximately 10 Subjects[a]		Subsequent Full-dose Infusion for all subjects[a]	
Time (minutes)	**Rate (mL/hour)**	**Time (minutes)**	**Rate (mL/hour)**	**Time (minutes)**	**Rate (mL/hour)**
0 - 60	50	0 – 60	50[c]	0 - 60	50[c]
61 - 180	100	61 – 120	100	61 - 120	100
181 -	150[b]	121 – 180	150	121 - 180	150
		181 -	200	181 -	200
Total volume	1000 mL	Total volume	500 mL	Total volume	500 mL

[a] Additional details for administration times and rates for the full-dose infusions will be provided in the administration guidelines.
[b] If the infusion is uneventful after 2 hours at a rate of 150 mL/hour, the investigator may increase the infusion rate to 200 mL/hour.
[c] If no infusion reactions occurred during the last full-dose infusion, the infusion rate may start at 100 mL/hour at the investigator's discretion.

The sponsor or IDMC may modify the predose infusion, infusion rates, or premedications, prospectively based upon the information collected to date from this and other studies. Additional details for administration times and rates, as well as premedications, will be provided in the administration guidelines.

6.1.1. Premedication

Subjects will receive the following premedications before all infusions with daratumumab:

- Dexamethasone (or equivalent in accordance with local standards) will be administered as described in Section 6.3.
- Paracetamol (acetaminophen) will be administered at a dose of 1 g PO 30 minutes to 2 hours before infusion.
- An antihistamine (clemastine 1 mg IV, cetirizine 10 mg PO, or equivalent) will be administered 30 minutes to 2 hours before infusion.

6.2. Lenalidomide

For Phase 1 and Phase 2, lenalidomide will be administered at a dose of 25 mg PO each day on Days 1 through 21 of each 28-day cycle. Cycle 1, Day 1 will be the day of the first full dose of daratumumab (Cycle 1 Visit 2). Lenalidomide will be administered until the subject experiences disease progression or unacceptable toxicity, whichever comes first.

On daratumumab infusion days, lenalidomide may be administered prior to or at the same time (preferred) as the premedications. A common side effect of lenalidomide is tiredness. On days when daratumumab is not administered, subjects may take their dose of lenalidomide in the evening.

6.2.1. Dose Adjustments of Lenalidomide

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

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

Dose adjustments should be based on the highest grade of toxicity that is ascribed to lenalidomide.

6.2.1.1. Deep Vein Thrombosis and Pulmonary Embolism

Lenalidomide has been associated with DVT and PE. Therefore, all subjects should be prophylactically treated with aspirin at a dose of 100 to 150 mg PO daily. Subjects at increased risk of thromboembolic events (based on their medical history) should be treated with enoxaparin at a dose of 40 mg subcutaneously daily. The injection should be handled according to local practice.

6.2.1.2. Thrombocytopenia

If the subject's platelet count decreases, dose adjustments should be made according to the recommendations in Table 7.

Table 7: Lenalidomide Dose Adjustment for Thrombocytopenia

Platelet Count	Recommended Course of Action
• When count first falls to $< 30 \times 10^9$/L • When count returns to $\geq 30 \times 10^9$/L	• Interrupt lenalidomide treatment, follow complete blood count weekly • Resume lenalidomide at 15 mg
• For each subsequent drop in count to $< 30 \times 10^9$/L • When count returns to $\geq 30 \times 10^9$/L	• Interrupt lenalidomide treatment • Resume lenalidomide at the next lower dose level (10 mg or 5 mg) once daily. Do not decrease dose below 5 mg once daily

6.2.1.3. Neutropenia

If the subject experiences neutropenia, the investigator should consider the use of growth factors in the subject's management. If the neutrophil count decreases below 1.5×10^9/L after the second cycle, the subject should be treated with G-CSF at a dose of 300 μg/day if his or her weight is less than 75 kg or 480 μg/day if his or her weight is 75 kg or more. G-CSF may be given daily or 2 to 3 times a week as appropriate to maintain the subject's neutrophil count above 1.0×10^9/L.

If the subject's neutrophil count decreases further, dose adjustments should be made according to the recommendations in Table 8.

Table 8: Lenalidomide Dose Adjustment for Neutropenia

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

6.2.1.4. Renal Impairment

Because lenalidomide is primarily excreted unchanged by the kidney, adjustments to the dose of lenalidomide are recommended to provide appropriate drug exposure in subjects with moderate or severe renal impairment. Lenalidomide dose adjustment should be instituted for subjects with a CrCl of 60 mL/minute or less. The recommended doses for subjects with multiple myeloma and renal impairment are shown in Table 9.

Table 9: Lenalidomide Dose Adjustment for Renal Impairment

Category	Renal Function[a]	Dose
Moderate renal impairment	CrCl 30-60 mL/min	10 mg every 24 hours
Severe renal impairment	CrCl < 30 mL/min (not requiring dialysis)	15 mg every 48 hours
End-stage renal disease	CrCl < 30 mL/min (requiring dialysis)	5 mg once daily. On dialysis days, administer the dose after dialysis

Key: CrCl = creatinine clearance.

[a] Estimated by CrCl as calculated by the Cockcroft-Gault, Diet in Renal Disease (MDRD), or Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formulas formula (Attachment 7).

6.2.1.5. Other Grade 3 or 4 Adverse Events

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

6.3. Dexamethasone

For Phase 1 and Phase 2, dexamethasone (or equivalent in accordance with local standards; see Attachment 4 for conversion table) will be administered at a total dose of 40 mg weekly. As of Amendment 5, subjects older than 75 years or underweight (body mass index [BMI] <18.5), the dexamethasone dose may be administered at a dose of 20 mg weekly. On weeks when daratumumab is administered the 20 mg dose should be administered as the pre-medication per protocol. During weeks when the subject receives an infusion of daratumumab, dexamethasone will be administered on infusion days at a dose of 20 mg IV before the infusion and 20 mg PO the day after the infusion. During weeks when no daratumumab infusion is administered, dexamethasone will be administered at a dose of 40 mg/week PO. Dexamethasone will be administered until the subject experiences disease progression or unacceptable toxicity, whichever comes first.

After Cycle 6, the dose of dexamethasone may be reduced at the investigator's discretion. The 20-mg IV dose of dexamethasone given before the infusion on the day of daratumumab infusions must not be decreased. When dexamethasone is reduced to 20 mg/week and is given as preinfusion medication, subjects may receive low-dose methylprednisolone (≤20 mg) PO (or equivalent in accordance with local standards), for the prevention of delayed infusion-reaction reactions as clinically indicated.

6.3.1. Dose adjustments of Dexamethasone

Investigators should refer to the manufacturer's full prescribing information for side effects associated with dexamethasone. Dexamethasone administration may be held for up to 2 weeks until the toxicity resolves to Grade 1 or baseline levels.

6.4. Delaying or Skipping Treatment

After completion of each cycle, initiation of a new cycle should be delayed for at least 1 week if the subject experiences toxicity. A subject whose cycle is delayed should be evaluated weekly for resolution or recovery of the toxicity, and a decision regarding further delay or initiation of

the next cycle should be made. However, the start of a new cycle after more than a 3-week delay (with all study therapy withheld) may occur only if there is clear clinical benefit and only after approval by the sponsor.

Refer to Section 6.6.1 for details on management of infusion-related reactions. **ONLY if any of the following criteria below are met, and the event cannot be ascribed to lenalidomide, the daratumumab infusion must be held to allow for recovery from toxicity**. The following parameters must be met on the first day of a new cycle (after Cycle 1):

- Platelet count $\geq 50 \times 10^9$/L
- Febrile neutropenia of any grade
- Neutropenia with infection, of any grade
- Hemoglobin ≥ 8.0 g/dL (≥ 4.96 mmol/L) (prior red blood cell transfusion or recombinant human erythropoietin use is allowed)
- ANC $\geq 0.75 \times 10^9$/L
- Nonhematologic toxicity of Grade 3 or higher must have recovered to baseline or Grade 1 or less unless otherwise specified

A subject whose cycle is delayed should be evaluated at least weekly for resolution of the toxicity. For severe hematologic toxicity (Grade 3 or higher), a complete blood count may be repeated more frequently as necessary until the requirements for reinitiating treatment are met.

6.5. Dose-limiting Toxicities

Overall toxicity occurring during the first treatment cycle of each cohort will be used to assess DLTs for the purposes of dose escalation and subsequent dose assignment. Dose-limiting toxicities must be reported to the sponsor within 24 hours.

Dose-limiting toxicities are defined as any of the following events that occur during the first treatment cycle (28 days):

- Nonhematologic toxicity considered to be a serious adverse event (SAE) of grade 3 or higher and related to daratumumab with the exception of:
  - Any nonhematologic reaction of grade 3 or higher that has an onset after the start of infusion on an infusion day, responds to symptomatic therapy, and resolves within 6 hours from onset
- Adverse reactions that prevent the infusion from being resumed regardless of the length of the reaction
- Hematologic toxicity, considered related to daratumumab, defined as
  - Thrombocytopenia (platelet count < 20,000 cells/μL)
  - Asymptomatic grade 4 neutropenia for more than 3 days
  - Neutropenic fever (defined as grade 3 or 4 neutropenia and temperature > 38.5°C) for more than 3 days

- Inability to receive the Day 1 infusion of Cycle 2 because of any toxicity related to daratumumab

If noncompliance with protocol-defined requirements results in toxicities of Grade 3 or higher, these toxicities should not qualify as DLTs.

Data from the Study GEN501 have shown the presence of free hemoglobin during daratumumab infusions without any clinical impact. Because this study includes escalating doses of daratumumab and combination therapy, the sponsor has specified that hemolysis greater than Grade 3 will be considered a DLT.

Neutropenic fever (defined as Grade 3 or 4 neutropenia and temperature >38.5°C) for more than 3 days has been specified by the sponsor as a DLT because, if the subject has been treated with G-CSF and the neutropenia has not normalized within 3 days, the bone marrow suppression is severe and clinically important.

Transfusion of platelets should be initiated at a platelet count of <20,000 cells/μL to prevent life-threatening thrombocytopenia (<10,000 cells/μL).

Subjects who experience a DLT but have demonstrated a response to study drug therapy may remain in the study at the discretion of the investigator at 1 dose level below that at which the DLT occurred.

6.6. Management of Infusion-related Reactions

Subjects who experienced AEs during the infusion must be treated according to the investigator's judgment and best clinical practice. The infusion may be paused or the infusion rate may be decreased, which may cause a longer-than-anticipated infusion time. Overnight stays at the hospital because of slow infusions times should not be reported as an SAE.

The study staff at the site should be prepared to intervene in case of the occurrence of any infusion reaction, and resuscitation equipment must be available at bedside. Special attention should be paid during each subject's first full-dose infusion.

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

- Antihistamine (clemastine 1 mg IV, cetirizine 10 mg PO, or equivalent) on the first and second days after all full-dose infusions
- Salbutamol aerosol
- Controller medications (eg, inhaled corticosteroids ± long-acting beta agonists for patients with asthma; long-acting bronchodilators such as tiotropium or salmeterol ± inhaled corticosteroids for patients with chronic obstructive pulmonary disease)

In addition, these at-risk patients may be hospitalized for monitoring for up to 2 nights after an infusion. If patients are hospitalized, their FEV1 should be measured before discharge. If these

patients are not hospitalized, follow-up telephone calls should be made to monitor their condition twice daily on the first and second days after all full-dose infusions.

6.6.1. Infusion-related Reactions of Grade 1 or 2

If the investigator judges the AE to be related to the infusion, the infusion should be paused. When the subject is stable, the infusion may be restarted at the investigator's discretion. Upon restart, the infusion rate should be half of that employed before the interruption.

Subsequently, the infusion rate may be increased at the investigator's discretion as described in Table 5 and Table 6.

If the subject experiences a Grade 2 or higher event of bronchospasm or laryngeal edema, the subject must be withdrawn from treatment.

6.6.2. Infusion-related Reactions of Grade 3 or Higher

For infusion-related AEs that are Grade 3 or higher, the infusion must be stopped and the subject must be observed carefully until resolution of the AE.

If the intensity of any other AE remains at Grade 3 or 4 after 2 hours, the subject must be withdrawn from treatment.

If the intensity of any other AE decreases to Grade 1 or 2 within 2 hours, the infusion may be restarted at the investigator's discretion. Upon restart, the infusion rate should be half of that employed before the interruption. Subsequently, the infusion rate may be increased at the investigator's discretion as described in Table 5 and Table 6.

If the intensity of the AE returns to Grade 3 or 4 after restart of the infusion, the procedure described in this section may be repeated at the investigator's discretion. Should the intensity of the AE increase to Grade 3 or 4 for a third time, the subject must be withdrawn from treatment.

7. TREATMENT COMPLIANCE

Compliance for the administration of daratumumab will be ensured by the recording of the following information in the subject's medical records:

- Start and stop dates and times
- Amount of daratumumab infused
- Reason for any interruption of the infusion or decrease in infusion rate

For dexamethasone given on daratumumab infusion days, compliance will be assessed by recording the date, time, and dose of the IV administration before infusion and the PO administration after infusion.

Subject compliance with oral lenalidomide, dexamethasone, and methylprednisolone administration will be assessed by pill counts. Subjects will be required to return all unused study drug at each visit.

8. CONCOMITANT THERAPY

Any medication other than daratumumab, lenalidomide, and dexamethasone (or equivalent) is considered concomitant therapy and must be recorded in the electronic case report form (eCRF) with the following information:

- Start and stop dates (or ongoing at study termination)
- Route of administration
- Dose regimen for glucocorticoid and other multiple myeloma treatment only (units and frequency). (Note: initiation of other multiple myeloma treatment is reason to discontinue the subject from the study [Section 10.2]; however, if the investigator deems it necessary to initiate such treatment, the dose regimen should be recorded)
- Indication/reason for use (if administered to treat an AE, the AE number must be recorded)

Premedications given before infusion of daratumumab must be recorded separately in the eCRF with the following information:

- Start and stop dates and times
- Route of administration
- Dose

Concomitant medications should be recorded beginning at the Screening Visit or before the first infusion and at all subsequent visits.

8.1. Recommended Concomitant Medications

- Prophylactic antibiotic treatment (eg, amoxicillin, ciprofloxacin) is recommended during periods of neutropenia.
- Pneumocystic pneumonia prophylaxis (sulfamethoxazole with trimethoprim) should be given to subjects who have a CD4 lymphocyte count less than 0.2×10^9/L.
- To reduce the need for blood transfusions, recombinant erythropoietin is recommended at dose levels according to international guidelines for the management of anemia in patients with multiple myeloma (Ludwig 2011).[17]
- Subjects with osteopenia or osteolytic lesions should be treated with bisphosphonates in accordance with international guidelines (Kyle 2007).[12]
- Subjects should be monitored for symptoms of tumor lysis syndrome, including dehydration and abnormal laboratory test results such as hyperkalemia, hyperuricemia, and hypocalcemia. It is recommended that high-risk subjects be treated prophylactically in accordance with local standards (eg, rehydration; diuretics; allopurinol 300 mg daily and medication to increase urate excretion).

8.2. Prohibited Medications

During the study, the following therapies are prohibited:

- Concomitant administration of any other anti-neoplastic therapy for the intention of treating multiple myeloma is prohibited, including medications that target CD38, as well as medications used for other indications that have antimyeloma properties (eg, interferon and clarithromycin).
- Any other investigational or nonmarketed drug substance therapy

Local radiotherapy for bone pain is allowed.

9. STUDY EVALUATIONS

9.1. Study Procedures by Visit

9.1.1. Overview

The following sections give a brief overview of the Screening Period, Treatment Period, Follow-up Period, and EOT Visit. The Time and Events Schedule summarizes the frequency and timing of safety, efficacy, pharmacokinetic, pharmacodynamic, and other measurements applicable to this study. As of Amendment 8, follow the schedule of events outlined in Table 4 and additional details are provided in Attachment 9.

9.1.2. Screening Period

Subjects, or their legally acceptable representative, will provide written informed consent before any study-specific procedures are performed. Medical history, vital sign and ECG measurements, and samples for laboratory analysis (hematology, biochemistry, and urinalysis) will be collected, and physical examination, computed tomography (CT) imaging or X-ray, and bone marrow biopsy and aspirate will be performed to determine the subject's baseline disease status and eligibility for the study. Collection of medical history, vital sign and ECG measurements, laboratory analysis, and physical examination must be performed within 21 days before the start of treatment (Cycle 1 Visit 1). The CT imaging or X-ray must be performed within 6 weeks before study entry (Cycle 1 Visit 1). If a bone marrow biopsy report documenting a diagnosis of multiple myeloma within a maximum of 6 weeks before study entry (Cycle 1 Visit 1) is available, a repeat bone marrow aspirate and biopsy is not required. The subject's blood type will be analyzed, and a blood type card will be issued. It is recommended that the subject carry this card at all times while enrolled in the study, including the Follow-up Period. For Phase 2, a sample for pharmacogenomics will also be collected during the Screening Period.

9.1.3. Treatment Period (Cycle X Visit X)

The investigator must evaluate the subject's eligibility and inform the sponsor. The sponsor must approve the enrollment of every subject before the subject receives the first administration of study drug.

For Phase 1 and Phase 2 of the study, the first 2 treatment cycles will consist of weekly daratumumab infusions, totaling 4 infusions during each 28-day cycle. Cycles 3 through 6 will consist of daratumumab infusions administered every other week; Cycle 7 and all subsequent cycles will consist of monthly daratumumab infusions. The combination treatment may continue until the subject experiences disease progression or unacceptable toxicity, whichever comes first.

Daratumumab may be continued until investigator's or sponsor's recommendation of discontinuation, the subject's decision to discontinue for any reason, or disease progression.

To minimize the risk of cytokine release syndrome, the first infusion of the first cycle in Phase 1 will be preceded by a predose infusion the day before the scheduled full dose infusion. The predose infusion will be 10% of the full dose, but will never be more than 10 mg in total dose. Further measures to prevent cytokine release syndrome will include premedication with antihistamines, acetaminophen, and dexamethasone before each daratumumab infusion (both predose and full dose).

For Phase 1 and Phase 2, lenalidomide will be administered on Days 1 through 21 of each 28-day cycle at a dose of 25 mg/day PO. For the first cycle, Day 1 will be the day of the first full-dose infusion of daratumumab (ie, Cycle 1 Visit 2). Lenalidomide will be administered until the subject experiences disease progression or unacceptable toxicity, whichever comes first. All investigators must follow the guidelines of the lenalidomide RevAssist® program in the US and Pregnancy Prevention Programme in the EU.

For Phase 1 and Phase 2, dexamethasone will be administered at a total dose of 40 mg/week (except for the first week of daratumumab dosing; see below). On the day of the predose infusion of daratumumab (Cycle 1 Visit 1), dexamethasone will be administered at a dose of 20 mg IV before the infusion; no dose will be administered after the infusion. During daratumumab infusion weeks, dexamethasone will be administered on the day of daratumumab infusion as 20 mg IV before the infusion and 20 mg PO the day after the infusion. An equivalent dose may be given in accordance with local standards (Attachment 4). During weeks when no daratumumab infusion is planned, dexamethasone will be administered at a dose of 40 mg/week PO. For both Phase 1 and Phase 2, after the completion of Cycle 6, the administration of dexamethasone may be adjusted at the discretion of the investigator; however, dexamethasone should always be administered at a dose of 20 mg IV on daratumumab infusion days. Dexamethasone will be administered until the subject experiences disease progression or unacceptable toxicity, whichever comes first.

At Cycle 1 Visit 2 (the first full-dose infusion of daratumumab), the subject may either remain hospitalized overnight and be released on the following day or may receive outpatient IV administration at the investigator's discretion. This hospitalization should not be reported as an SAE. Hospitalization is not required for the predose infusion (Cycle 1 Visit 1) because no infusion-related SAEs have been observed during or after the predose infusion of 23 subjects during the GEN501 study.

All subsequent infusions will be performed as outpatient visits. If the subject has not experienced a significant medical event but is hospitalized overnight only for observation, the hospitalization should not be reported as an SAE.

Adverse events will be monitored closely during treatment. Escalation to a new dose level can only be done after evaluation of the safety profile of the previous dose level by the IDMC. After this evaluation, the IDMC will make a recommendation regarding dose escalation.

If the subject must stop either daratumumab, lenalidomide, or dexamethasone, the subject may continue the other components until progression or commencing a new regimen for the treatment of multiple myeloma. However, subjects will still receive dexamethasone as premedication to daratumumab.

9.1.3.1. Treatment Follow-up as per Amendment 8

As per Amendment 8, subjects will continue to be dosed as per the Amendment 7 schedule (1 cycle is 28 days) and Table 4.

Data collection will be limited to SAEs and SPMs, see details in Section 12 and Attachment 9.

Daratumumab will be provided by the sponsor until it is approved for use in combination with lenalidomide and dexamethasone for patients with relapsed refractory multiple myeloma and is commercially available or can be accessed from another source. Subjects receiving treatment will be transitioned from study drug to commercial product once commercial product is available in their region (or when daratumumab can be accessed from another source). In these circumstances, the sponsor and investigator will support transition of the subject to ensure that treatment continues and remains uninterrupted. Subjects who are unable to switch to commercial supplies will continue to remain in the study. All subjects will be followed for 3 years after the last dose of lenalidomide, to enable collection of SPMs.

9.1.4. Safety Follow-up Period

After their last dose of lenalidomide, subjects will be followed for 3 years to assess occurrence of new cancers. Investigators will be asked to contact the subjects every 3-6 months to collect this information. In case of the occurrence of a new cancer, the investigator must report this occurrence on an SAE form as described in Section 12.6.

9.2. Assessments Following the Final Analysis

As of Amendment 8, the final analysis will be achieved. All subjects in the study have either received at least 24 months of study drug or have discontinued. Ongoing subjects may continue treatment with study drug. Disease assessments/response evaluations will be performed per local institutional practice. Safety information will be limited to SAEs and SPMs

Data collection will only include SAEs and SPMs; see details in Section 12 and Attachment 9.

9.2.1. Clinical Assessments

9.2.1.1. Demographics

Date of birth, race, ethnicity, and gender will be recorded in the eCRF.

9.2.1.2. Medical History

Any relevant past or current medical conditions will be recorded in the eCRF. In addition, all prior treatment regimens for multiple myeloma will be recorded. Nonserious AEs that occur between the Screening Visit or before the first infusion and the first study drug treatment at

Cycle 1 Visit 1 should be recorded as medical history. Serious AEs occurring during this time should be reported as described in Section 12.6.2.

9.2.1.3. Physical Examination

A general physical examination will be performed at time points as indicated in Table 1 and Table 2. The examination should include general appearance and the following body systems: lymph nodes, mouth and throat, lungs, cardiovascular, abdomen, extremities, musculoskeletal, neurologic, and skin. Clinically significant physical examination findings should be recorded in the appropriate section of the eCRF.

Height (with the subject wearing no shoes) will be measured at the Screening Visit or before the first infusion and the EOT Visit, rounded to the nearest centimeter, and recorded in the eCRF. Body weight (with the subject wearing no overcoat or shoes) will be measured, rounded to the nearest kilogram, and recorded in the eCRF.

9.2.1.4. Electrocardiogram

Electrocardiograms will be performed at the Screening Visit or before the first infusion and before and after each infusion for Phase 1 (Table 1) and before and after the daratumumab infusion on Day 1 of each Cycle for Phase 2 (Table 2) to investigate possible Table 1 cardiac effects of daratumumab and/or combination therapy with special attention to possible QT and corrected QT interval disturbance. A follow-up ECG will be performed at the EOT Visit. Any abnormal ECG finding that meets the criteria for an AE or SAE must be recorded and reported as such.

The ECGs will be recorded digitally at the sites by using the standard 12-leads. Three baseline ECGs should be performed before the first infusion of the study drug as described in the ECG Specification Manual. An overall interpretation of the ECGs will be performed by the investigator or by a local site cardiologist if the task is delegated by the investigator.

Before the ECGs are recorded, the subjects should be resting in a horizontal position for at least 20 minutes. If any irregularity is observed or occurs during the ECG (eg, vomiting, cough), the occurrence should be recorded in the eCRF with a description and time of the event. In these cases, the ECG may be recorded again.

The date, time, and overall interpretation of the ECG will be recorded in the eCRF, along with blood pressure and heart rate.

9.2.1.5. Vital Sign Measurements

Vital signs, defined as blood pressure, pulse, and temperature, will be measured at time points as indicated in Table 1 and Table 2 and recorded in the eCRF. On the days when daratumumab infusions are given, vital signs will be measured at the following time points:

Phase 1:

- Before infusion - just before the planned infusion start time
- During infusion - at 15-minute intervals during the first 2 hours
- During infusion - at 60-minute intervals after the first 2 hours
- End of infusion
- After infusion - at 10 minutes, 30 minutes, 1 hour, and 2 hours

Phase 2:

- Before infusion - just before the planned infusion start time
- End of infusion

Body temperature should be measured by using the same method (eg, ear thermometer) at all times for each individual subject. Likewise, blood pressure should be measured by using the same method (eg, manual or automated sphygmomanometer) and the same arm at all times for each individual subject.

9.2.1.6. Eastern Cooperative Oncology Group Performance Status

The ECOG performance status score should be assessed at time points as indicated in Table 1 and Table 2 and recorded in the eCRF.

9.2.1.7. Concomitant Therapy

Concomitant therapies should be recorded as detailed in Section 8.

9.2.1.8. Adverse Events

Adverse events will be reported and followed by the investigator as determined by the sponsor. Further details on AE reporting are provided in Section 12.

Dose-limiting toxicities will be assessed during the first treatment cycle (28 days). Details on the reporting and handling of DLTs are provided in Section 6.5.

9.2.1.9. Skeletal Survey

A whole-body X-ray or CT scan, including the cranium, is required. Additional surveys (X-ray, CT scan, or magnetic resonance imaging scan) may be performed at the investigator's discretion (eg, to confirm response, to evaluate new symptoms or bone pain). If additional surveys are warranted, the investigator should choose the imaging modality based on the clinical indication. Reading of the skeletal surveys will be done by a radiologist. The overall interpretation of the evaluation will be recorded in the eCRF, and a copy of the evaluation report should be kept in the subject's file.

9.2.2. Clinical Laboratory Assessments

Unless otherwise stated, all blood and urine samples must be taken before administration of daratumumab. Blood tests, such as a blood type assessment, performed after the infusion of daratumumab may be confounded by the drug. The scheduling for all assessments listed in this

section is detailed in Table 1 and Table 2. As of Amendment 7, clinical laboratory assessments (safety and efficacy) will be performed locally and based on local institutional practice. Pregnancy testing will continue, every 4 weeks during treatment and at the EOT visit, but will be performed by a local laboratory (See Table 3 and Attachment 8).

9.2.2.1. Biochemistry

A blood sample will be drawn at each visit for analysis of the following: sodium, potassium, creatinine, blood urea nitrogen, AST, ALT, alkaline phosphatase, bone-specific alkaline phosphatase, albumin, calcium, glucose, total creatine kinase, total bilirubin, lactic dehydrogenase, uric acid, β_2-microglobulin, and C-reactive protein.

9.2.2.2. Hematology

A blood sample will be drawn at each visit for analysis of the following: red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, white blood cell count with differential, platelet count, and reticulocyte count.

In Phase 1, at the Screening Visit or before the first infusion, direct and indirect Coombs tests and a blood type assessment will be performed. In Phase 2, the direct and indirect Coombs tests will only be performed at screening.

Daratumumab Interference with Indirect Antiglobulin Test (IAT) results

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

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/Rh blood group, D antigen (RhD) typing. CD38 is expressed at very low levels on erythrocytes. Daratumumab binds to the CD38 on erythrocytes, which results in a positive IAT (Indirect Coombs Test). This positive result masks the detection of antibodies to minor antigens and may prevent or delay blood banks from issuing donor blood for transfusion. This effect occurs during daratumumab treatment and for up to 6 months after treatment ends. Subjects will receive a patient identification wallet card for the study that includes the blood profile (ABO, Rh, and IAT) determined before the first infusion of daratumumab along with information on the IAT interference for healthcare providers/blood banks. Subjects are to carry this card throughout the treatment period and for at least 6 months after treatment ends. Blood banks can eliminate the daratumumab IAT interference by treating reagent RBCs with dithiothreitol (DTT) (Chapuy 2015).[4]

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.

9.2.2.3. Serology for HIV, Hepatitis B, Hepatitis C, and Cytomegalovirus

In the Phase 1 portion of this study, a blood sample will be drawn at the Screening Visit or before the first infusion for assessment of hepatitis B, as well as antibodies to cytomegalovirus antigen. Blood samples will be drawn for assessment of antibodies to cytomegalovirus antigen after study drug administration.

In the Phase 2 portion of this study, a blood sample will be drawn only at the Screening Visit for the assessment of hepatitis B, hepatitis C, HIV, and antibodies to cytomegalovirus antigen.

9.2.2.4. Pregnancy Test

As of Amendment 8, serum pregnancy tests will continue to be performed by the local laboratory on samples collected every 4 weeks during the Treatment Period (see Table 3).

A blood sample will be drawn at the Screening Visit or before the first infusion from all women of childbearing potential. The sample will be shipped to the central laboratory (BARC) for immediate analysis of human chorionic gonadotropin. Pregnant women will not be allowed to take part in this study and will be considered as screening failures.

Women are considered of childbearing potential unless they have undergone hysterectomy or tubal ligation within 1 year or have been postmenopausal for at least 1 year before the Screening Visit or before the first infusion.

9.2.3. Myeloma-related Laboratory Efficacy Assessments

As of Amendment 8, efficacy laboratory assessments will be performed by the local laboratory and disease/response evaluations will be based on local institutional practice (see Table 4 and Attachment 9). Response to therapy will be evaluated by using the International Myeloma Working Group Uniform Response Criteria. Skeletal surveys will only be done if a subject has developed new symptoms.

9.2.3.1. Bone Marrow Assessments

Bone marrow biopsy and/ or aspirate will be performed at visits as indicated in Table 1 and Table 2. The samples will be evaluated histologically for assessment of the percentage and monoclonality of plasma cells, and determination of other cells in the marrow. An aspirate will be evaluated by flow cytometry with CD45, CD38, CD56, CD138, CD19, CD28, CD117, cytoplasmic light chain kappa/lambda, cytoplasmic IgA+ and IgG+, CD20, and CD27 to characterize CD38, CD46, CD55, and CD59 expression in myeloma cells, as well as to characterize T, B, and NK cells. If the subject's platelet count is low, a platelet transfusion may be given before the bone marrow sampling at the investigator's discretion.

9.2.3.2. Serum Immunoglobulin A, M, and G (M-component)

A blood sample will be drawn for quantitation of M-component by serum protein electrophoresis at visits as indicated in Table 1 and Table 2. Subsequent Ig identification will be done by immunofixation. If the M-component is IgD or IgE, these Ig types should be included in the analysis. A second aliquot of serum shall be stored and analyzed as needed, if daratumumab interference is suspected in the post-treatment serum immunofixation assay.

9.2.3.3. Urinalysis for M-component

A 24-hour urine sample will be collected at the Screening Visit or before the first infusion, on the first day of each cycle, at the EOT, and at all follow-up visits for quantitation of total protein (including albumin) and CrCl, for quantitation of M-component by electrophoresis, and for immunofixation.

Additional sampling may be performed at the investigator's discretion.

9.2.3.4. Serum Free Light Chain Ratio

A blood sample will be drawn for quantitation of the free light chain ratio by immunonephelometry at visits as indicated in Table 1 and Table 2.

9.2.3.5. Prognostic Factors- Phase 1 only

A blood sample will be drawn at the Screening Visit or before the first infusion for later analysis of prognostic factors. The blood sample will be stored at the central laboratory (BARC) for up to 1 year after the last subject's last visit. Analysis of prognostic factors may be done in batches of several samples. Subjects will be asked to sign a separate informed consent form for this analysis.

Prognostic factors indicative of altered responsiveness to treatment and/or survival that may be analyzed include the following:

- Serum β_2-microglobulin and serum albumin in accordance with the International Staging System for multiple myeloma (Greipp 2005) [7]
- Genetic anomalies such as 17p deletion; translocations including t(4,14), t(6,14), t(11,14), t(14,16), t(14,20), t(20,20); and hyperdiploidy

9.2.4. Pharmacokinetics and Immunogenicity Assessments

As of Amendment 8, blood sample collection will stop and not be performed after the last dose of daratumumab. One final sample should be taken before the start of the last infusion per Amendment 7.

Phase 2: 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 the Time and Events Schedule (Table 2). At specified time points, venous blood samples (5 mL per sample) will be collected and the serum will be divided into 3 aliquots (1 aliquot for pharmacokinetic analysis, 1 aliquot for immunogenicity assessment [when appropriate], and 1 aliquot as a back- up). Blood samples should not be drawn from the arm in which the infusion was administered.

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.

Table 10: Phase 1 Sample Collection Times for Determination of Daratumumab Concentration in Serum

	Study Visits														
Sample Collection	**Screening**	**Cycle 1**					**Cycle 2[a]**				**Cycle 3-6**		**Cycle 7-24**	**FU**	**EOT**
Visit Number	**0**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**1**	**2**	**1**	**1-6**	**—**
Day/Week/Month	**≤21 days before Visit C1-1**	**0d**	**1d**	**1w**	**2w**	**3w**	**1d**	**1w**	**2w**	**3w**	**1d**	**2w**	**1d**	**Monthly**	**—**
Visit Window	**—**	**—**	**—**	**±1d**	**±1d**	**±1d**	**±4d**	**±1d**	**±1d**	**±1d**	**±4d**	**±1d**	**±4d**	**±7d**	**±2d**
Before infusion		X	X	X	X	X	X	X	X	X	X	X	X[b]	X[b]	X[b]
End of infusion		X	X	X	X	X	X	X	X	X	X	X	X		
+ 2 hours after infusion			X							X					
+ 5 hours after infusion			X												
+ 12 hours after infusion			X												

Key: d = day; EOT = End of Trial; FU = Follow-up; w = week;

[a] All cycles are 28-day cycles: the first visit of a cycle should be 4 weeks after the start of the previous cycle.

[b] Because there is no infusion on these days, there is no requirement for the timing of the sample collection.

9.2.5. 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.

For Phase 2, all samples collected and received up to the time of the primary study endpoint analysis (first bioanalysis) will be analyzed for serum daratumumab concentration as indicated by the Time and Events Schedule. All data from this first analysis will be considered final and these samples will not be reanalyzed at the end of the study. The final bioanalysis will include all immunogenicity (from Phases 1 and 2) and any remaining pharmacokinetic samples that become available after the primary endpoint analysis. Adjustments to bioanalysis timing may be made if it is later determined that the timing for data needed to facilitate crucial decision-making differs from these 2 planned efforts. However, data from each round of bioanalysis will be considered final and samples will not be reanalyzed in any subsequent efforts.

9.2.6. Pharmacokinetic Parameters

The pharmacokinetic parameters are defined as:

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

Pharmacokinetic samples to determine serum concentration of daratumumab will be obtained from all subjects. The pharmacokinetic parameters include but may not be limited to the following:

- Minimum observed concentration (Cmin)
- Maximum observed concentration (Cmax)

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

9.2.6.1. Immunogenicity Assessments

Serum from venous blood samples will be assessed for the generation of antibodies to daratumumab (immunogenicity) according to the Time and Events Schedule. Daratumumab concentration is also evaluated at all immunogenicity time points (Phases 1 and 2) 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.

9.2.6.2. Biomarker Assessments

9.2.6.2.1. Phase 1 Biomarker Analyses

9.2.6.2.1.1. Levels of Soluble CD38

A blood sample will be drawn for analysis of soluble CD38. The samples will be stored at the central laboratory until a validated assay is available.

9.2.6.2.1.2. Complement

A blood sample will be drawn for analysis of complement (CH50) at visits as indicated in Table 1. This blood sample must be drawn 2 hours after the end of infusions. Analysis of complement will be done in batches of several samples.

9.2.6.2.1.3. Levels of Circulating NK Cells, B, and T Cells (Flow Cytometry)

A blood sample will be drawn for analysis of the following immune cell populations:

CD45+CD38+	CD45+CD19+	CD45+CD3+	CD45+CD3+CD4+
CD45-CD138+	CD45+CD3+CD8+	CD45+CD138+	CD3-CD56+
CD3-CD16+CD56+	CD45+CD138+CD38+		

Additional flow cytometry subgroups may be added for exploratory purposes.

9.2.6.2.2. Phase 2 Biomarker Analyses

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 for all subjects as specified in Table 2.

Biomarker analyses will be focused on further understanding the MOA (ADCC/CDC/ADCP) of daratumumab in combination with lenalidomide and dexamethasone, evaluating predictive markers of response to daratumumab, and determining whether daratumumab can reduce minimal residual disease in patients who achieve a complete response. Whole blood samples will be utilized for immunophenotyping, which includes analysis of NK, T, and B cells. NK cells are known to express CD38 and early clinical data indicates they are rapidly depleted upon daratumumab dosing. Additional immune cell populations that may be studied include macrophages, dendritic cells, myeloid derived suppressor cells, or other flow cytometry subgroups that may be added for exploratory purposes. ADCC and CDC may be evaluated to determine whether lenalidomide and dexamethasone help preserve effective ADCC despite NK cell depletion. T-cell receptor sequences may be evaluated from whole blood PBMC DNA to determine if specific clonal CD8+ T-cell expansion occurs with daratumumab treatment and if this is associated with clinical response.

In addition to whole blood collections, bone marrow aspirates will be collected for biomarker evaluations including multiple myeloma cell phenotyping, evaluation of CD38 and complement inhibitory protein (CIP) expression (CD46/CD55/CD59). Soluble CD38 expression levels may be evaluated in plasma to determine if sCD38 levels influence daratumumab serum levels and are associated with daratumumab response. Serum samples may also be analyzed for complement proteins or for complement dependent cytotoxicity (CDC), which is one mechanism of action for daratumumab. Exploratory proteomics may be utilized to evaluate cytokines, complement proteins, complement associated proteins, soluble CD38, soluble CD46/CD55/CD59, or other proteins associated with daratumumab response and/or resistance.

9.2.6.2.3. Phase 2 Pharmacogenomics

A pharmacogenomic blood sample will be collected to allow for pharmacogenomic research, as necessary (where local regulations permit). Subject participation in the pharmacogenomic research is optional.

Several pharmacogenomics assessments may be performed for those subjects who consent to genomic analyses. A blood sample will be collected and processed to extract DNA, which may be evaluated for single nucleotide variation in genes associated with immune-mediated tumor cell lysis and potentially daratumumab response/resistance. The following single nucleotide polymorphisms (SNP) may be measured: FcgR2A-R131H, FcgR2A-Q62R, FcgR2A-Q62X, FcgR3A-V158F, FcgR3A-V212F, FcgR2B-I232T, and C1QA-A276G. In addition, assessment of copy number variation in FcgR2C, FcgR3A, and FcgR3B may be performed on this sample. Additional polymorphisms, single nucleotide polymorphisms, or copy number variations may be added for exploratory purposes. These genotypes may be evaluated for potential predictive biomarkers as well as for association with daratumumab response and with levels of functional ADCC and CDC before daratumumab treatment. Pharmacogenomic assessments may also

include evaluation of T-cell response through T-cell receptor sequencing from PBMCs isolated from whole blood.

9.3. Endpoints

The primary endpoint for this study will be the incidence of AEs.

The secondary endpoints are:

- The rate of response according to the International Uniform Response Criteria (Rajkumar 2011) [21]
- PK variables (AUC, C_{max}, minimum or trough concentration in serum [C_{min}], time to C_{max} [T_{max}], apparent clearance [CL], volume of distribution [V], and elimination half-life [$t_{1/2}$])
- Time to progression
- Duration of response
- Progression-free survival (PFS)

10. SUBJECT COMPLETION/WITHDRAWAL

Completion

Subjects will be considered as having completed the study if he/she has consented to Amendment 8.

10.1. Discontinuation of Study Treatment

A subject's study treatment should be discontinued if:

- The investigator believes that for safety reasons (eg, adverse event) it is in the best interest of the subject to discontinue study treatment
- The subject becomes pregnant
- The subject has documented PD
- The subject withdraws consent for further treatment
- Treatment is delayed for more than 3 weeks and no approval to continue is given by the sponsor.

If a subject discontinues study treatment or is transferred to commercial supplies, as per Amendment 8, follow-up for the occurrence of SPM will continue for up to 3 years after the last dose of lenalidomide.

10.2. Withdrawal

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

- DLT
- DVT and/or PE

- Tumor lysis syndrome
- Grade 3 skin rash
- Pregnancy
- Subject choice
- Investigator decision
- Disease progression
- Initiation of new treatment against multiple myeloma
- Lost to follow-up
- Intercurrent illness that precludes further participation or requires a prohibited concomitant treatment
- Treatment is delayed for more than 3 weeks and no approval to continue is given by the sponsor
- Other

If a subject discontinues study treatment or is transferred to commercial supplies, as per Amendment 8, follow-up for the occurrence of SPMs will continue for up to 3 years after the last dose of lenalidomide.

The investigator, in consultation with the subject, will decide the future course of treatment for multiple myeloma.

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

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

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

Withdrawal From the Optional Research Samples While Remaining in the Main Study

The subject may withdraw consent for optional research samples while remaining in the study. In such a case, the optional research sample[s] will be destroyed. The sample destruction process will proceed as described above.

Withdrawal From the Use of Samples in Future Research

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

11. STATISTICAL METHODS

The statistical analysis methods for this study are outlined in this section. Further details will be specified in the Statistical Analysis Plan.

11.1. Subject Information

The 2 phases of this study will be analyzed separately. When appropriate, all subjects who are treated with daratumumab may be combined together for comprehensive safety assessment.

Variables will be estimated by using descriptive statistics. Continuous variables will be summarized by using the number of observations (n), mean, standard deviation, median, minimum, and maximum, where n denotes the number of subjects with available data. Categorical variables will be summarized by using n and percentages, where the calculation of the percentages will be based on the number of subjects in the population (N) and the number of subjects with available data (n). Results will be presented by cohort as well as by all subjects combined.

The latest available measurements before study drug administration will serve as baseline values.

11.2. Sample Size Determination

Between 42 and 58 subjects will be enrolled in this study, depending on the number of dose levels included during dose escalation in Phase 1. It is estimated that the screen failure rate will be 25% and that between 56 and 78 subjects will be screened in order to enroll the expected number. The screen failure rate is estimated based on data from the ongoing GEN501 study.

No formal sample size determination was performed for Phase 1 of this study because a standard dose escalation study design of 3 + 3 subjects in each cohort was chosen for Phase 1. For Phase 2, It is assumed that lenalidomide + dexamethasone would achieve an ORR of 50% in the targeted population. With a two-sided alpha of 0.10 and assuming that the addition of daratumumab improves the ORR to 75%, a sample size of approximately 30 subjects would achieve 89% power to detect such a difference. If the addition of daratumumab can improve the ORR to 80%, this sample size would achieve 97% power to detect such a difference.

11.3. Analysis Sets

For Phase 1, one analysis population, the safety population, is defined, which includes all subjects who are exposed to the study drugs (daratumumab, lenalidomide, and dexamethasone). For Phase 1, the safety population will be used for all efficacy and safety analysis.

For Phase 2, three analysis populations are defined:

- Intent-to-Treat (ITT), defined as all subjects enrolled in the study in Phase 2
- Safety, defined as all subjects exposed to the study drugs (ie, daratumumab, lenalidomide, and dexamethasone) in Phase 2
- Per-Protocol (PP), defined as all subjects included in the ITT population excluding those who had deviations from the protocol that might affect the assessment of response to treatment

For Phase 2, the ITT population will be the primary analysis population for all efficacy analyses. The Safety population will be used for all safety analyses. If the ITT and Safety populations are identical, only the ITT population will be used.

The PK evaluable population will be analyzed, which includes all treated subjects who have an evaluable PK profile. The PP population will be used for efficacy as sensitivity analyses. If the difference between the PP and ITT populations is less than 4 subjects, the PP analysis will not be performed.

11.4. Efficacy Analyses

Response to treatment will be determined by the sponsor in accordance with the guidelines provided in Attachment 5. The proportion of subjects with response to treatment (stringent CR [sCR], CR, very good PR [VGPR], and PR) will be estimated. The quality of response (also including subjects who achieve MR) will be summarized. Subjects for whom response cannot be evaluated will be categorized as not evaluable. A determination of not evaluable will count as nonresponse to treatment. The proportions will be presented with corresponding exact 2-sided 95% confidence intervals.

Duration of response, time to progression, and PFS will be estimated using Kaplan-Meier techniques. Data for these variables will be censored in accordance with the FDA guidance on clinical study endpoints for the approval of cancer drugs and biologics (FDA 2011).

11.5. Pharmacokinetic Analyses

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

Phase 1: The PK variables, AUC, C_{max}, C_{min}, T_{max}, CL, V, and t1/2, will be estimated by using noncompartmental methods. The AUC will be calculated separately for Cycles 1 and 2, and extrapolated to infinity. Geometric means will be plotted together for comparison of dose cohorts, and individual subject PK profiles will be plotted with both absolute and log-transformed values.

Phase 2: Descriptive statistics will be used to summarize daratumumab serum concentrations at each sampling time point and pharmacokinetic parameters of daratumumab such as C_{min} and C_{max}. If sufficient data are available, then other pharmacokinetic parameters may be calculated, including but not limited to CL and V.

If sufficient data are available, 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.

11.6. Pharmacokinetic/Pharmacodynamic Analyses

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

11.7. Subgroup and by Center Analyses

Analyses will be performed for the following subgroups:

- Subjects with relapsed multiple myeloma versus subjects with relapsed and refractory multiple myeloma
- Subjects by number of prior therapies

The number of subjects per site is expected to be very low; therefore, no by-center analyses are planned.

11.8. Exploratory Modeling

Exploratory univariate modeling will be used to investigate preliminarily relationships between select efficacy and safety variables and possibly explanatory variables.

A model of the worst toxicity will be attempted to potentially provide a rationale for dose selection in subsequent studies. This model is included in Attachment 6.

11.9. 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.

11.10. Biomarker and Pharmacogenomic 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 or time-to-event

endpoints will identify responsive (or resistant) subgroups in addition to genes and pathways attenuated following treatment with daratumumab.

Any biomarker, pharmacodynamic, and pharmacogenomic measures will be listed, tabulated, and where appropriate, plotted. Subjects will be grouped by prescribed dose. As this is an open-label study with an active control treatment, statistical analyses will be done to aid in the understanding of the results. Correlation of response and pharmacogenomic measures will be explored.

Results of biomarker, pharmacodynamics, and pharmacogenomic 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.

11.11. Safety Analyses

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported adverse events with onset during the treatment phase (ie, treatment-emergent adverse events, and adverse events that have worsened since baseline) will be included in the analysis.

The number and percentage of subjects with treatment-emergent AEs will be summarized according to intensity by using the CTCAE v4.0, drug relationship, and outcome. Laboratory data will be summarized and descriptive statistics will be calculated. Changes in vital sign measurements, physical examination findings, and ECOG performance status will be summarized. Safety laboratory variables will be presented in figures (values versus time) and summarized by value and change from baseline (both absolute and relative).

11.12. Interim Analysis

Results from Phase 1 and Phase 2 will be presented separately. Data from Phase 1 will be analyzed when the MTD has been reached or dose escalation has been stopped. No formal interim analyses that require adjustments of type 1 or 2 errors are planned. However, as part of the preparations for subsequent studies, exploratory analyses of subsets of data may be performed.

11.13. Data Monitoring Committee

An IDMC will be established and have their first meeting before study start (first subject screened). At this meeting, the IDMC will decide the future format and the degree of the information they need in order to monitor safety.

The functions and responsibilities of the IDMC will be described in the IDMC Charter, which will be approved by the IDMC.

The IDMC will receive a package of safety data, including all reported AEs and laboratory data, after each cohort has completed the first cycle of treatment. The IDMC will receive a report of any SAE immediately after review of the event by the sponsor.

Subjects will be enrolled in cohorts of 3 subjects per dose level. The "3 + 3" rules for dose escalation will be applied. However, if the study sites have identified 4 eligible subjects to start a new dose level, all 4 subjects may be enrolled. For each cohort, the IDMC will evaluate aggregate safety data for the 3 subjects in order to recommend whether it is safe to escalate to the next dose level. Before the IDMC review of safety data, at least 3 subjects in a cohort must receive at least 4 full infusions of daratumumab in combination with Len/Dex. The third subject in the cohort must have received all 4 full doses of daratumumab, and data from an observation period of 6 days after the last infusion must be available for the IDMC to review. Dose escalation or de-escalation will follow these rules:

- An initial cohort of 3 subjects will be enrolled at any new dose level, when escalation from the previous dose level has been accepted by the IDMC.
- If a subject at any dose level experiences a DLT, the cohort will be expanded by up to 3 additional subjects, or until a second subject experiences a DLT.
- If, however, no additional DLTs are reported at this dose level, dose escalation may take place to the next planned dose level, or to an intermediate dose level as recommended by the IDMC and approved by the sponsor.
- If no DLTs are experienced by the first 3 subjects at any dose level, the IDMC or sponsor may decide to add 3 more subjects at this dose level based on the need for additional safety data before an escalation can take place.
- If 2 or more subjects out of 6 or less subjects experience DLTs, additional subjects must be included at the previous dose level or at an intermediate dose level as recommended by the IDMC and approved by the sponsor.
- The MTD will be defined as the highest dose level where no subjects or 1 subject out of 6 subjects experiences a DLT.

Noncompliance with the protocol-defined requirements for infusion of the study drug may influence the evaluation of DLTs by the IDMC.

In the dose escalation/de-escalation part, the MTD and/or RP2D will be decided by the sponsor, based upon recommendations by the IDMC and after review of the aggregated safety data.

At least every 6 months, the IDMC will evaluate safety data from this study, including the occurrence of new cancers as noted during the Safety Follow-up Period, and provide a recommendation as to whether the study should continue based on evaluation of these safety data and the reported benefits of daratumumab treatment. The IDMC will no longer be evaluating safety data after the primary analysis.

Minutes from the IDMC meetings will be shared with the regulatory agencies.

There are no current plans to establish an Independent Response Committee for this early-phase study. Response to treatment will be evaluated by the coordinating investigator in collaboration with the sponsor.

12. ADVERSE EVENT REPORTING

12.1. Study Disease

Deterioration of the subject's condition due to multiple myeloma and signs and symptoms that, according to the investigator, are expected and well known consequences of multiple myeloma, both in intensity and frequency should not be reported as AEs or SAEs.

12.2. Pre-existing Conditions

In this study, a pre-existing condition (ie, a disorder that was present before the AE reporting period started and noted in the medical history or physical examination eCRF) should not be reported as an AE. If a pre-existing condition worsens during the Treatment Period, the event should then be reported as an AE.

12.3. Diagnostic and Therapeutic Noninvasive and Invasive Procedures

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as AEs. A medical condition for which an unscheduled procedure was performed should, however, be reported if it meets the definition of an AE. For example, acute appendicitis should be reported as an AE, but not the appendectomy.

12.4. Definitions

12.4.1. Adverse Event Definitions and Classifications

Adverse Event

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

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

Note: The sponsor collects adverse events starting with the signing of the ICF (refer to Section 12.6.1, 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.

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 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 12.4.2.

12.4.2. 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).

12.4.3. Severity Criteria

The severity assessment for an adverse event or serious adverse event should be completed using the NCI CTCAE Version 4.0. Any adverse event or serious adverse event not listed in the NCI CTCAE Version 4.0 will be graded according to investigator clinical judgment by using the standard grades as follows:

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

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

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

Grade 4: Life-threatening or disabling adverse event

Grade 5: Death related to the adverse event

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

12.5. 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
- 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/patient exposure to the sponsor study drug, eg, name confusion)
- Occurrence of SPM

Special reporting situations should be reported to the sponsor. Any special reporting situation that meets the criteria of a serious adverse event should be reported as an SAE to the sponsor.

12.6. Procedures

As per Amendment 8, only SAEs and SPMs will be collected (see Table 4 and Attachment 9). The SAE and SPM data should be entered in the subject file/notes.

Any SPM that occurs during a subject's participation in the study or for 3 years after the last dose of lenalidomide is considered an immediately reportable event. It must be reported to the sponsor within 24 hours after the investigator has gained knowledge of it by using the SPM form attached to the regular SAE form.

12.6.1. All Adverse Events

The investigator must report all directly observed AEs and all AEs reported by the subject, whether spontaneously or in response to general, nondirected questioning (eg, "How has your health been since the last visit?"). For each AE reported by the subject, the investigator should obtain all the information required to complete the AE page of the eCRF, in accordance with the guidelines that accompany it.

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 any component of the treatment regimen. As of Amendment 7, only SAEs will be collected (see Table 3 and Attachment 8). Nonserious medical events (signs, symptoms, diagnosis) that occur between the Screening Visit or before the first infusion and the first study drug treatment at Cycle 1 Visit 1 should be documented in the medical history. All AEs that occur in subjects during the AE reporting period must be reported, whether or not the event is treatment related.

Serious adverse events, including those spontaneously reported to the investigator within 30 days of the last dose of any component of the treatment regimen, must be reported using the Serious 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.

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

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all 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.

The investigator must also record in the eCRF the outcome of the AE by using the following terms:

- Recovered
- Recovered with sequelae
- Not recovered
- Fatal
- Unknown

Instructions for reporting changes in an ongoing AE during the subject's participation in the study are provided in the eCRF completion guidelines.

For all studies with an outpatient phase, including open-label studies, the subject must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the treatment 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
- Any other information that is required to do an emergency breaking of the blind

12.6.2. 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 treatment must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available

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

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

- If the subject has not experienced a significant medical event but is hospitalized overnight only for observation following infusion of 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.

Disease progression should not be submitted as 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 12.4.1, Adverse Event Definitions and Classifications).

12.6.3. Pregnancy

Lenalidomide is an analog of thalidomide, which is a known human teratogen that causes life-threatening birth defects. Results of an embryo-fetal development study in nonhuman primates indicated that lenalidomide produced malformations in the offspring of female monkeys that received the drug during pregnancy. These malformations were similar to birth defects observed in humans after women were exposed to thalidomide during pregnancy. If lenalidomide is used during pregnancy, it may cause birth defects or death to a developing fetus. Women of childbearing potential must be advised to avoid pregnancy while receiving lenalidomide. Effective contraceptive methods should be used for 4 weeks before the first infusion of daratumumab, during therapy, during therapy interruptions, and for at least 6 months after completing therapy. The lenalidomide label warnings and advice must be followed throughout this study. See Exclusion Criterion #27 (Section 4.3) for definitions of effective, adequate methods of contraception.

12.6.3.1. Pregnancy Reporting

Any pregnancy that occurs during a subject’s participation in this study is considered an immediately reportable event. It must be reported to the sponsor within 24 hours after the investigator has gained knowledge of it, by using the Pregnancy Form. The pregnancy must be

followed to determine outcome (including premature termination) and status of mother and infant. Pregnancy complications and elective terminations for medical reasons must be reported as an SAE. 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. After birth, the infant must be followed to at least 1 month of age.

Any SAE occurring in association with a pregnancy that is brought to the investigator's attention after the subject has completed the study and considered by the investigator as related to the study drug must be promptly reported to the sponsor.

In addition, the investigator must attempt to collect pregnancy information on any female partners of male study subjects who become pregnant while the subject is enrolled in the study. Pregnancy information must be reported to the sponsor.

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.

12.7. 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 an SAE, the study-site personnel must report the PQC to the sponsor according to the SAE reporting timelines (refer to Section 12.6.2, 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(s)

The daratumumab supplied for this study is a clear to opalescent, colorless to slightly yellow concentrated solution for IV infusion. It is intended for administration after dilution in sterile, pyrogen-free 0.9% sodium chloride (NaCl) solution. It will be manufactured and provided under the responsibility of the sponsor.

Lenalidomide and dexamethasone will be supplied by each site and should be stored, prepared, and administered in accordance with the label specifications.

14.2. Packaging

Daratumumab is supplied in glass vials containing 5 mL of daratumumab at a concentration of 20 mg/mL (ie, a total of 100 mg of daratumumab per vial). Daratumumab will be supplied to the site/pharmacy as bulk supply cartons containing 5 vials each.

14.3. Labeling

Study drug labels will contain information to meet the applicable regulatory requirements.

14.4. Preparation, Handling, and Storage

A detailed description with instructions for the preparation of the study drug will be supplied to each pharmacy.

Preparation of infusion bags should be done on the day of the planned infusion, and the time of the dilution should be written on the infusion bag. Daratumumab must be administered as an IV infusion. The infusion should be given through a well-functioning IV catheter by using an infusion pump. The study drug must be filtered by using an inline filter (0.2 μm) during the infusion.

For the predose and full-dose infusions, the initial infusion rates should be set as recommended in Table 5 and Table 6. Infusion rates may be adjusted at the investigator's discretion in response to infusion-related reactions (Section 6.6).

Daratumumab must be stored in an appropriate restricted area, which may be accessed only by the investigator, pharmacist, or other duly designated person.

The drug should be stored in a refrigerator at 2°C to 8°C and must not be frozen. A log of daily thermometer readings must be kept to document the temperature.

14.5. Drug Accountability

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The dispensing of study drug to the subject, and the return of study drug from the subject (if applicable), must be documented on the drug accountability form. Subjects, or their legally acceptable representatives where applicable, must be instructed to return all original containers, whether empty or containing study drug. 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, and study drug returned by the subject, 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. Returned study drug must not be dispensed again, even to the same subject. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

15. STUDY-SPECIFIC MATERIALS

As per Amendment 8, the investigator will be provided with the following supplies:

- Drug Accountability Forms
- Pharmacy manual/study site investigational product manual
- Sample ICF
- Investigator Drug Brochure

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

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 total blood volume to be collected is considered to be considered to be within the normal range allowed for this study population.

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

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

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

16.2.2. Independent Ethics Committee or Institutional Review Board

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

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

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

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

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

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s). Furthermore, where required, progress reports/written summaries of the study status will be submitted to the IRB/IEC annually, or more frequently if requested.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion.

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, 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.

Subjects will be asked for consent to provide optional samples for research (where local regulations permit). After informed consent for the study is appropriately obtained, the subject or his or her legally acceptable representative will be asked to sign and personally date a separate ICF indicating agreement to participate in the optional research component. Refusal to participate in the optional research will not result in ineligibility for the study. A copy of this signed ICF will be given to the subject.

16.2.4. Privacy of Personal Data

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

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

The informed consent obtained from the subject (or his or her legally acceptable representative) includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for

study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

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

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

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

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

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

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 CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

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

17.2.2. Required Prestudy Documentation

Documents that must be provided to the sponsor before study drug shipment are as follows:

- Up-to-date curriculum vitae for each investigator and subinvestigator.
- Signed and dated Investigator Agreement.
- Applicable local regulatory documentation (eg, FDA 1572 Form).
- A copy of the formal written notification to the investigator regarding approval of the protocol by an IEC/IRB that is in compliance with regulatory guidelines. The written notification is to be signed by the chairman or authorized designee and must identify the specific protocol. In cases where an IEC/IRB member has a known conflict of interest, abstention of that individual from voting should be documented; an investigator (or subinvestigator) may be a member of the IEC/IRB, but may not vote on any research in which he or she is involved.
- Name and address of the IEC/IRB with a statement that it is organized and operates according to GCP and the applicable laws and regulations, and a current list of the IEC/IRB members. If accompanied by a letter of explanation from the IEC/IRB, a general statement may be substituted for this list.
- A copy of the IEC/IRB approved informed consent form and other adjunctive materials (eg, advertising) to be used in the study, including written documentation of IEC/IRB approval of these items.
- Name and address of any local laboratory conducting tests for the study, a dated copy of the laboratory reference values for tests to be performed during the study, and a copy of the certification or other documentation establishing adequacy of the facility.
- Required financial agreement.

In addition to the documents required before the study, other documentation may be required during the course of the study.

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 CRF: subject identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; concomitant medication; drug receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

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 following data will be recorded directly into the CRF and will be considered source data:

- Race
- History of smoking all nicotine use, eg, cigarettes, cigars, chewing tobacco, patch, gum
- Blood pressure and pulse/heart rate (except if primary efficacy or significant safety issue)
- Height and weight (except if primary efficacy or significant safety issue)
- Details of physical examination

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 electronic CRF, 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 CRF.

Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the subject's source documentation. All data relating to the study must be recorded in CRFs prepared by the sponsor. Data must be entered into CRFs in English. Study site personnel must complete the CRF 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 CRFs are accurate and correct.

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

If corrections to a CRF are needed after the initial entry into the CRF, 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 or designated representative., and direct transmission of clinical laboratory data from a central laboratory (BARC) into the clinical database. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided and reviewed with study-site personnel before the start of the study. eCRFs will be reviewed for accuracy and completeness by the sponsor or designated representative 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 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 Study, 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 or designated representative will perform on-site monitoring visits as frequently as necessary. As per Amendment 8, on site visits are usually made at intervals of at least 24 weeks. A phone call will be done in between (at 12 weeks). The dates of the visits will be recorded by the monitor in a study site visit log to be kept at the site. At these visits, the monitor will monitor the adequate reporting and follow-up of SAEs, SPMs, drug receipt/dispensing/return records and ensure subjects who showed progressive disease stopped the study treatment.

17.9. Close-out of Extended Safety Follow-up

The extended safety follow-up will be completed 3 years after the last subject took the last lenalidomide dose and completed follow-up for the occurrence of SPMs. The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject assessment at that study site, in the time frame specified in the Clinical Trial Agreement Per the study design, The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject assessment at that study site, in the time frame specified in the Clinical Trial Agreement.

Study Termination

The sponsor reserves the right to close the study site or terminate the safety follow-up 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:

- Successful completion of the study at the site
- The required number of subjects for the study has been recruited
- 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
- Safety concerns
- Sufficient data suggesting lack of efficacy
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study drug development

17.10. On-Site Audits

Representatives of the sponsor's or designated representative's Clinical Quality Assurance department may visit the site to carry out an audit of the study in compliance with regulatory guidelines and company policy. Such audits will require access to all study records, including source documents, for inspection and comparison with the eCRFs. Subject privacy must, however, be respected. Sufficient prior notice will be provided to allow the investigator to prepare properly for the audit.

Similar auditing procedures may also be conducted by agents of any regulatory body reviewing the results of this study in support of a Licensing Application. The investigator should immediately notify the sponsor if they have 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 pharmacogenomic or 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 CRF data from all study sites that participated in the study. 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 pharmacogenomic or 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: Eastern Cooperative Oncology Group Performance Status

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

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

Attachment 2: Prior Cancer Therapy for Multiple Myeloma

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

Source: Rajkumar 2011[21]

Attachment 3: New York Heart Association Criteria for Functional Classification

Functional Capacity	Objective Assessment
Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	A. No objective evidence of cardiovascular disease
Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	B. Objective evidence of minimal cardiovascular disease
Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	C. Objective evidence of moderately severe cardiovascular disease
Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	D. Objective evidence of severe cardiovascular disease

The Criteria Committee of the New York Heart Association. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. Boston, Mass: Little, Brown, & Co; 1994:253-6.

Attachment 4: Conversion Table for Glucocorticoid Dose

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

Attachment 5: International Myeloma Working Group Uniform Response Criteria

The following criteria for response to multiple myeloma treatment were presented by Rajkumar, et al.[21]

Response	Response Criteria
Stringent complete response (sCR)	• CR as defined below, *plus* • Normal FLC ratio, *and* • Absence of clonal PCs by immunohistochemistry or 2- to 4-color flow cytometry
Complete response (CR)[a]	• Negative immunofixation of serum and urine, *and* • Disappearance of any soft tissue plasmacytomas, *and* • < 5% PCs in bone marrow
Very good partial response (VGPR)[a]	• Serum and urine M-component detectable by immunofixation but not on electrophoresis, *or* • ≥ 90% reduction in serum M-component plus urine M-component < 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 serum and urine M-protein are not measurable, a decrease ≥ 50% in the difference between involved and uninvolved FLC levels is require in place of the M-protein criteria • If serum and urine M-protein are not measurable, and serum free light chain assay is also not measurable, ≥ 50% reduction in bone marrow PCs is required in place of M-protein, provided baseline percentage was ≥ 30% • In addition to the above criteria, if present at baseline, ≥ 50% reduction in the size of soft tissue plasmacytomas is also required.
Minimal response (MR)	• In patients with relapsed refractory myeloma adopted from the EBMT criteria: • ≥ 25% but ≤ 49% reduction of serum M-protein *and* reduction in 24-hour urine M-protein by 50% to 89% • In addition to the above criteria, if present at baseline, 25% to 49% reduction in the size of soft tissue plasmacytomas is also required • No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response)
Stable disease	• Not meeting criteria for CR, VGPR, PR, or progressive disease
Progressive disease[b]	• Increase of 25% from lowest response value in any of the following: • Serum M-component (absolute increase must be ≥ 0.5 g/dL), *and/or* • Urine M-component (absolute increase must be ≥ 200 mg/24 hours), *and/or* • Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL) • Only in patients without measurable serum and urine M-protein levels and without measurable disease by FLC levels, bone marrow PC percentage (absolute percentage must be ≥ 10%) • Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas • Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL) that can be attributed solely to the PC proliferative disorder

Key: CR = complete response; EBMT = European Group for Blood and Marrow Transplantation; FLC = free light chain; MR = minimal response; PC = plasma cell; PR = partial response; sCR = stringent complete response; VGPR = very good partial response.

[a] Clarifications to the criteria for coding CR and VGPR in patients in whom the only measurable disease is by serum FLC levels: CR in such patients indicates a normal FLC ratio of 0.26 to 1.65 in addition to CR criteria listed above. VGPR in such patients requires a > 90% decrease in the difference between involved and uninvolved FLC levels.

[b] Clarifications to the criteria for coding progressive disease: bone marrow criteria for progressive disease are to be used only in patients without measurable disease by M-protein and by FLC levels; "25% increase" refers to M-protein, FLC, and bone marrow results, and does not refer to bone lesions, soft tissue plasmacytomas, or hypercalcemia and the "lowest response value" does not need to be a confirmed value.

Notes: All response categories (CR, sCR, VGPR, PR, and progressive disease) require 2 consecutive assessments made at any time before the institution of any new therapy; CR, sCR, VGPR, PR, and stable disease categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable on serum, urine, both, or neither. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. For progressive disease, serum M-component increases of ≥ 1 g/dL are sufficient to define relapse if starting M-component is ≥ 5 g/dL.

Rajkumar SV, Harousseau JL, Durie B, Anderson KC, Dimopoulos M, Kyle R, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. Blood. 2011 May 5;117(18):4691-5.

Attachment 6: Model of Worst Toxicity

As part of the rationale for dose selection in subsequent studies, the following modeling of worst toxicity will be attempted. It is based on Model 1 in Simon, et al.[a]

$$y_{ij} = Ln(d_{1ij} + d_{2ij} + a_1 D_{1ij} + a_2 D_{2ij}) + b_i + e_{ij},$$

where

$i = 1, 2, \ldots, n$, the number of patients

j denotes the treatment cycle number

d_{1ij} denotes the total amount of daratumumab (mg) that patient i receives in course j

d_{2ij} denotes the total amount of lenalidomide (mg) that patient i receives in course j

D_{1ij} denotes the total amount of daratumumab (mg) that patient i has received prior to course j

D_{2ij} denotes the total amount of lenalidomide (mg) that patient i has received prior to course j

a_1 represents the influence of prior total dose ($a_1 = 0$ indicates no cumulative toxicity)

a_2 represents the influence of prior total dose ($a_2 = 0$ indicates no cumulative toxicity)

b_i is a random, normally distributed intersubject effect with mean μ_b and standard deviation σ_b

e_{ij} is the normally distributed error term, with mean zero and standard error σ_e, reflecting the within-subject variation

The unobserved variable y_{ij} translates to the observed discrete toxicity levels by means of 3 additional parameters, $k_1 < k_2 < k_3$, which divide the line into the 4 regions representing "minimal" toxicity (usually CTCAE grades 0-1), "moderate" toxicity (usually CTCAE grade 2), DLT, and "unacceptable" toxicity.

Note that the model described above handles the case where subjects receive doses that deviate from the protocol-planned ones.

The following will be estimated from the model:

- Maximum likelihood estimates (MLEs) of the parameters a_1, a_2, σ_b, σ_e, k_1, k_2, and k_3, which yield estimated probabilities of seeing moderate toxicity and DLT at the various dose levels
- Confidence intervals for parameters with nonzero MLE
- Graph of probabilities of CTCAE grades 2+, 3+, and 4+ toxicities, for the first course averaged over the population of patients
- Graphs of probabilities of CTCAE grades 2+, 3+, and 4+ toxicities (for the first course) for patients with b equal to MLE - SD, MLE and MLE + SD.

There are no guarantees that the model will converge and it may need simplifying modifications in order to do so.

[a] Simon R, Freidlin B, Rubinstein L, Arbuck SG, Collins J, Christian MC. Accelerated titration designs for phase I clinical trials in oncology. J Natl Cancer Inst. 1997 Aug 6;89(15):1138-47.

Attachment 7: Calculated Creatinine Clearance

Cockcroft-Gault formula:

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

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

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

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

Modification of Diet in Renal Disease (MDRD)

Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)

Alternatively, creatinine clearance may be calculated or measured according to the MDRD (Levey 2006)[14] or the CKD-EPI (Levey 2009)[15].

For online calculators, please go to https://www.kidney.org/professionals/KDOQI/gfr_calculator.

Attachment 8: Limited Schedule of Events for Subjects Continuing Daratumumab as of Amendment 7

Protocol Amendment 7 will allow those subjects who were receiving daratumumab after the primary analysis to continue receiving study drug. All subjects have received at least 12 months of therapy with daratumumab or have discontinued. Table 3 provides a limited schedule of assessments for subjects who remain on study drug after the primary analysis.

Dosage and Administration

Daratumumab, lenalidomide, and dexamethasone will be administered according to the regimen established prior to Amendment 7.

Treatment Period

As of Amendment 7, subjects will complete their ongoing cycle of treatment and all assessments for that cycle. Subjects must then sign an updated informed consent form to continue receiving study drug. At the start of the next cycle of treatment, follow the schedule outlined in Table 3. For consistency, the cycle number will not restart. Subjects who had discontinued study drug and who were in Follow-up before Amendment 7, will complete an EOT visit and enter the Follow-up Period per Table 3.

EOT Visit

This visit must occur with 3 to 5 weeks after the last dose of study drug. Week 4 immunogenicity sampling should occur at this visit (see Table 3).

Follow-up Period

As of Amendment 7, subjects who are in Follow-up (Table 2) will complete an EOT visit and immunogenicity assessments (if not yet completed) and will enter the modified Follow-up in the Time and Events Schedule (Table 3). Follow-up with Amendment 7 will include collection of best response and new antimyeloma therapy (disease assessments should be per local institutional practice), survival information, and occurrence of new cancers every 6 months for 3 years after the last dose of study drug or termination of the study by the sponsor, whichever occurs first.

Efficacy Evaluations

Investigators should monitor and assess the subjects for response to treatment or disease progression according to local institutional practice.

Safety Evaluations

Study drug administration and SAEs (including secondary malignancies) will be collected. Pregnancy testing will continue every 4 weeks during the Treatment Period and at the EOT visit. Concomitant medications associated with SAEs will also be collected. Serious adverse event reporting should continue as described in Section 12.6.2. The SAEs should be entered in the subject file/source notes.

Source Documentation

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

Attachment 9: Limited Schedule of Events for Subjects Continuing Daratumumab as of Amendment 8

Protocol Amendment 8 will allow those subjects who are receiving daratumumab after the final analysis to continue receiving study drug. All subjects have received at least 24 months of therapy with daratumumab, or have discontinued.

Dosage and Administration

Daratumumab, lenalidomide, and dexamethasone will be administered according to the regimen established prior to Amendment 8.

Visits will occur on a monthly schedule, assessments done need to be captured in the source notes only.

Daratumumab will be provided by the sponsor until daratumumab in combination with lenalidomide and dexamethasone has been approved for use in patients with relapsed/ refractory multiple myeloma and is commercially available in the respective countries.

Treatment Period

As of Amendment 8, subjects will continue until progressive disease, unacceptable toxicity, withdrawal of consent, the investigator decides to stop treatment, the start of subsequent anticancer therapy, or the sponsor ends the study.

Efficacy Evaluations

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

Safety Evaluations

SAEs will be collected. SAE reporting should continue as described in Section 12.6.2. The SAEs should be entered in the subject file/source notes.

SPMs will be collected. SPM reporting should continue as described in Section 12.6.2. The SPMs should be entered in the subject file/source notes.

Source Documentation

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

INVESTIGATOR AGREEMENT

JNJ-54767414 daratumumab Clinical Protocol GEN503 Amendment 8

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

Institution: Janssen Research & Development

Signature PPD Date: PPD

(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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