A Phase 3 Study Comparing Pomalidomide and Dexamethasone With or Without Daratumumab in Subjects With Relapsed or Refractory Multiple Myeloma Who Have Received at Least One Prior Line of Therapy With Both Lenalidomide and a Proteasome Inhibitor: The APOLLO Study

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Amendments below are listed beginning with the most recent amendment.

Amendment 5 (04 March 2024)

The overall reason for the amendment: To extend the time period allowed for subjects who are benefitting from study treatment at the time of the clinical cutoff (CCO) date for the final overall survival (OS) analysis and have no other option for study treatment access than a clinical study, to continue to receive study treatment after the CCO and until 30 September 2024, granting a 6-month extension compared with the Amendment 4 timepoint of 31 March 2024. It is expected that by the third quarter of 2024, these patients will have a study treatment access option outside this study. To update the study Sponsor information and contact information of the Sponsor representative.

Changes provided in the table below are representative of similar changes made throughout the protocol. When changes are provided verbatim, deleted text is shown as strikethrough and added text is shown as bold font.

Applicable Section(s)	Description of Change(s)
Rationale: To revise the date through which treatment may be available from 31 March 2024 to 30 September 2024.	
Protocol Summary (Study Duration); 4.1 Description of the Study Design; 6.1.6 Duration of Therapy; 7.2.5 Sample Collection and Handling (Table 7.3); 7.3.7 End of Study Definition; 14.5 End of Study Report; Appendix 12 Continuation of Treatment After Clinical Cutoff for the Final OS Analysis to End of Study, and treatment period	Text was revised as shown in the example below: Subjects benefiting from the study treatment can continue to receive study treatment after the CCO for the final OS analysis. For these subjects, study treatment will be available through continued access within the current study until it is available through another source such as commercial availability with reimbursement, continued access through a long-term extension study, a patient access program, or after the last subject transitions into the long-term extension phase of the study up to ~~31 March 2024~~ **30 September 2024**, whichever occurs first.
Rationale: Updated the Sponsor address and representative details.	
Cover page (Sponsor); 1 Key Roles	The Sponsor name and address, and contact information for the Sponsor representative were updated.
Rationale: To update the information provided for the daratumumab Investigator's Brochure (IB) in the list of literature references to the latest available edition of the IB.	
17 Literature References	The edition number and date for the IB were deleted from the citation.

Applicable Section(s)	Description of Change(s)
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 4 (21 April 2022)

The overall reason for the amendment: to clarify that sites will be notified of the clinical cutoff (CCO) for the final overall survival (OS) analysis when approximately 166 OS events have occurred, to define the end of the electronic case report form (eCRF) data collection, and to clarify and define the end of study assessments and the transition to the long-term extension phase of the study. The long-term extension phase of this study will begin at the time of the CCO for the final OS analysis and is intended to provide ongoing access to study treatment for subjects who continue to benefit from such treatment. For these subjects, study treatment will be available through continued access within the current study until it is available through another source such as commercial availability with reimbursement, continued access through a long-term extension study, a patient access program, or after the last subject transitions into the long-term extension phase of the study up to 31 March 2024, whichever occurs first.

Applicable Section(s)	Description of Change(s)
Rationale: to provide flexibility in language regarding CCO for the final OS analysis and to clarify language regarding provision of study treatment after the end of data collection.	
Protocol Summary (Study Duration); 4.1 Description of the Study Design	Text in bold has been added, text in strikethrough has been deleted: 'The primary analysis of progression free survival (PFS) will occur after 188 PFS events have been observed. Long-term survival follow-up and data collection will continue until **approximately** 166 deaths have been observed or 5 years after the last subject is randomized**, whichever occurs earlier**. Subjects benefiting from the study treatment can continue **to receive study treatment after the CCO for the final OS analysis. For these subjects, study treatment will be available through continued access within the current study until it is available through another source such as commercial availability with reimbursement, continued access through a long-term extension study, a patient access program, or after the last subject transitions into the long-term extension phase of the study up to 31 March 2024, whichever occurs first.** ~~receiving the study drugs after the end of data collection until the study drugs are commercially available and reimbursable, available from another source (eg, via a dedicated long-term extension study), or until study completion, whichever comes first.~~'
7.2.4 Updated Assessments Following the Positive Primary Analysis of PFS	Text in bold has been added: '… (ie, when **approximately** 166 deaths have occurred or 5 years after the last subject was randomized).'
10.5 Sample Size	Text in bold has been added: 'Long-term survival follow-up will continue until **approximately** 166 deaths have been observed.'
Rationale: to provide via a new appendix, a description of study procedures for subjects who continue to receive study treatment after the CCO for the final OS analysis.	
Schematic of Study Design	Schematic footnote has been updated to reflect availability of schedule of assessments for subjects continuing on study treatment after the CCO for the final OS analysis.
4.1 Description of the Study Design	Text has been added to direct readers to Appendix 12 (and Table 7.3) for the schedule of assessments for subjects continuing on study treatment after the CCO for the final OS analysis.

Applicable Section(s)	Description of Change(s)
Figure 4.1 Study Design	Figure footnote has been updated to reflect availability of schedule of assessments for subjects continuing on study treatment after the CCO for the final OS analysis.
7. Study Procedures and Schedule	Text has been added to direct readers to Appendix 12 for guidance regarding protocol-required procedures/evaluations for subjects continuing on study treatment after the CCO for the final OS analysis.
Table 7.3 Schedule of Events	Text has been added immediately above Table 7.3 to guide readers to Appendix 12 for a description of study procedures for subjects who continue to receive study treatment after the CCO for the final OS analysis. It is also noted that no eCRF data will be collected after the CCO for the final OS analysis.
8. Safety Monitoring and Reporting	Text has been added to direct readers to Appendix 12 for guidance regarding safety monitoring and reporting for subjects continuing on study treatment after the CCO for the final OS analysis.
14. Data Handling and Record Keeping	Text has been added to direct readers to Appendix 12 for guidance regarding data handling and record keeping for subjects continuing on study treatment after the CCO for the final OS analysis.
Appendix 12: Continuation of Treatment After Clinical Cutoff for the Final OS Analysis to End of Study	A new appendix has been incorporated to provide a description of study procedures for subjects who continue to receive study treatment after the CCO for the final OS analysis.
Rationale: to clarify eCRF data collection after CCO for the final OS analysis and to describe continued access to study treatment after the CCO for the final OS analysis for subjects who are benefiting from study treatment.	
6.1.6 Duration of Therapy	The following text has been added to this section: 'The Sponsor will ensure that subjects who are benefiting from study treatment can continue to receive study treatment after the CCO for the final OS analysis. For these subjects, study treatment will be available through continued access within the current study until it is available through another source such as commercial availability with reimbursement, continued access through a long-term extension study, a patient access program, or after the last subject transitions into the long-term extension phase of the study up to 31 March 2024, whichever occurs first. The long-term extension phase of this study will begin at the time of the CCO for the final OS analysis and is intended to provide ongoing access to study treatment for subjects who continue to benefit from such treatment. Certain long-term safety data will continue to be reported for these subjects, as described in Appendix 12. No eCRF data will be collected after the CCO date for the final OS analysis (when approximately 166 deaths have been reported). All eCRF data collected up to this timepoint will be included in the final study analysis and reported in a separate clinical study report.'
Rationale: to clarify efficacy assessments for subjects continuing on the study after the CCO for the final OS analysis.	
7.1.1 Efficacy Assessments	Text in bold has been added under the 'Sponsor Confirmation of Progressive Disease' subheading: 'For subjects continuing on the study after the positive primary analysis **and final OS analysis**, investigator assessment of PD should continue to be performed in accordance with IMWG criteria. Notification of PD and approval by the Sponsor is no longer required.'

Applicable Section(s)	Description of Change(s)
7.1.1.7 Minimal Residual Disease (MRD)	The following text has been added to this section: 'Following the CCO for the final OS analysis, MRD testing will be performed according to the standard of care for subjects without disease progression (see Appendix 12).'
Rationale: to provide further clarity around end of study definition.	
7.3.7 End of Study Definition	The following text has been added: '**End of Study Definition** The end of the study is defined as the timepoint at which all subjects who are still receiving study treatment have access through another source such as commercial availability with reimbursement, continued access through a long-term extension study, a patient access program, or when all subjects have discontinued study treatment after the CCO for the final OS analysis up to 31 March 2024, whichever occurs first.'
14.5 End of Study Report	Text in bold has been added, text in strikethrough has been deleted: 'The Sponsor will notify the accredited IEC and the CA for the end of study within a period of 90 days. The end of the study is defined as ~~the last patient's last visit~~ **the timepoint at which all subjects who are still receiving study treatment have access through another source such as commercial availability with reimbursement, continued access through a long-term extension study, a patient access program, or when all subjects have discontinued study treatment after the CCO for the final OS analysis up to 31 March 2024, whichever occurs first**. In case the study is ended prematurely, the Sponsor will notify the accredited IEC and the CA within 15 days, including the reasons for the premature termination.'
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.
1. Key Roles	Minor updates made within Scientific Committee and Study Manager rows.

Amendment 3 (16 October 2020)

The overall reason for the amendment: Following the positive primary analysis results, subjects continuing on treatment will have a limited schedule of assessments.

Applicable Section(s)	Description of Change(s)
Rationale: To update the protocol following the positive primary analysis results**.**	
Schematic of Study Design; Section 4.1 Description of the Study Design Figure 4.1	Footnote added: The schedule of assessments will be adjusted for subjects remaining on the study after the positive primary analysis and is detailed in section 7.2.4.
Section 4.1 Description of the Study Design	Added the following text: The schedule of assessments will be adjusted for subjects remaining on the study after the positive primary analysis and is detailed in section 7.2.4.
Section 6.1.6 Duration of Therapy	Bold text added to clarify that confirmation of disease progression by sponsor is not required.

Applicable Section(s)	Description of Change(s)
	Added following text: For subjects continuing the study after the positive primary analysis, notification of PD and approval by the Sponsor is no longer required. Please refer to Section 7.1.1 (Sponsor Confirmation of Progressive Disease) for updated study procedures.
Section 7.1.1 Efficacy Assessments- Sponsor Confirmation of Disease Progression	Added following text: For subjects continuing on the study after primary analysis, investigator assessment of PD should continue to be performed in accordance with IMWG criteria. Notification of PD and approval by the Sponsor is no longer required.
Section 7.2 Study schedule Table 7.3 Schedule of Events	Table 7.3: Title text added Following the positive primary analysis some of the below procedures have been adjusted (PD evaluation, PK/Immunogenicity). For more details on the updated procedures, please refer to Section 7.2.4
Section 7.2.4(new) Updated Assessments Following the Positive Primary Analysis of PFS	A new section has been added to describe the conduct and frequency for certain assessments for subjects with and without disease progression following the positive primary analysis.
Rationale: Clarification of collection of laboratory samples	
Section 7.1.1 Efficacy Assessments	Added text to specify disease assessments will be performed locally per sites' standard of care, following the implementation of Amendment 3.
Section 7.1.4.1 Evaluations	Added the following text: After the primary analysis, a limited schedule of PK and immunogenicity assessments would be implemented (refer to Section 7.2.4).
Section 7.2 Study Schedule Table 7.3	Added the following text under Efficacy Assessments: After the primary clinical cut-off date (21 JUL 2020), subject monitoring will be conducted as per Section 7.2.4 Table 7.3: Footnote 16: Added the following text: Following the positive primary analysis of PFS, disease evaluations are to be performed locally per site's standard of care. All subjects must still meet IMWG criteria for progression prior to initiation of subsequent anti-myeloma therapy. Notification of PD and approval by the Sponsor is no longer required.
Section 7.2.4 (new) Updated Assessments Following the Positive Primary Analysis of PFS	Added text to specify that a limited schedule of PK and immunogenicity assessments would be implemented.
Section 7.2.5 Sample Collection and Handling	Heading numbering modified to account for the addition of a new section
Rationale: Clarification of the IDMC's role in data review following the primary PFS analysis	
Section 8.5 Safety Oversight	Added text on IDMC's role following the primary PFS analysis

Applicable Section(s)	Description of Change(s)
Rationale Clarification of study procedures for subjects who may continue to receive study drugs after the data collection has ended**.**	
Protocol Summary Study Duration; Section 4.1 Description of the Study Design; Section 7.2.4 (new) Updated Assessments following the Positive Primary Analysis of PFS	Updated language to include information that subjects benefiting from study treatment can continue receiving the study drugs after the end of data collection until the study drugs are commercially available and reimbursable, available from another source (eg, via a dedicated long-term extension study), or until study completion, whichever comes first.
Rationale: Clarification for end of data collection	
Protocol Summary Study Duration; Section 4.1 Description of Study Design	Added data collection to the following sentence: Long-term survival follow-up and data collection will continue until 166 deaths have been observed or 5 years after the last subject is randomized.
Rationale: Minor changes noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

<u>Amendment 2</u> (03 April 2018)

The overall reason for the amendment: To update the protocol based on German health authority recommendations.

Applicable Section(s)	Description of Change(s)
Rationale: Other text revised to follow the local label for guidance on pregnancy prevention and adhere to local the Pomalidomide Risk Evaluation Mitigation Strategy (REMS) or Global Pregnancy Prevention Plan.	
Section 5.1 Subject Inclusion Criteria	Added language to inclusion criterion #11 that investigators should follow the pomalidomide local label for guidance regarding pregnancy prevention and adhere to the local Pomalidomide REMS or Global Pregnancy Prevention Plan.
Rationale: Modified exclusion criteria with respect to hepatitis and human immunodeficiency virus (HIV) testing, hypersensitivity, and prior vaccinations based on recommendations from health authority discussions.	
Section 5.2 Subject Exclusion Criteria	Defined Exclusion Criterion 9 for hepatitis testing and Exclusion Criterion 10 for HIV testing; added Exclusion Criterion 18 to exclude subjects with allergies, hypersensitivity, or intolerance to any of the study drugs, hyaluronidase, monoclonal antibodies, human proteins, or their excipients (refer to daratumumab IB), or known sensitivity to mammalian-derived products; added Exclusion Criterion 19 to exclude subjects who were vaccinated with live vaccine within 4 weeks prior to randomization.

Applicable Section(s)	Description of Change(s)
Rationale: Clarified text concerning continuation of study treatment when one component of the regimen is discontinued.	
Section 5.3.1 Reasons for Withdrawal or Termination	Added clarification text concerning continuation of study treatment when one component of the regimen is discontinued.
Rationale: Added reference to specific Daratumumab Pharmacy Manuals for clarity.	
Section 6.1.3 Preparation	Added clarification text for specific Daratumumab Pharmacy Manuals
Rationale: Corrected Table 6.1 to accurately represent dosing of study drugs.	
Table 6.1 Dosing and Administration	Modified Table 6.1 to reflect dosing schedules of study drugs.
Rationale: Added section for "Daratumumab (SC)" to provide an overview of Dara-SC administration guidelines to give basic information in the protocol and to align with the Dara IV section.	
Section 6.1.5 Dose Adjustments/Modifications/Delays/Infusion-Related Reaction Management	Added paragraph on Daratumumab SC.
Rationale: Added language regarding pomalidomide for completeness of pomalidomide discontinuation criteria, per Section 5.3.1.	
Section 6.1.5 Dose Adjustments/Modifications/Delays/Infusion-Related Reaction Management	Added language under pomalidomide for discontinuation criteria.
Rationale: Added language regarding pomalidomide and dexamethasone to follow local label.	
Section 6.1.5 Dose Adjustments/Modifications/Delays/Infusion-Related Reaction Management	Added language under pomalidomide for interstitial lung disease, febrile episodes, signs of bleeding, the use of growth factors for neutropenia, and to follow the local label for drug interactions; Added language under dexamethasone to follow local label for drug interactions.
Rationale: Added text in the "M-protein by electrophoresis Serum (SPEP), Urine (UPEP)", "M-protein by immunofixation Serum (sIFE), Urine (uIFE), and "Serum free light chain sFLC" rows to clarify that these assessments should only be done at specific timepoints or under specific circumstances.	
Table 7.1 Disease Assessments	Added "required", as in, "Day 1 of each required cycle", to align with previous body text in Section 7.1.1.
Rationale: Removed text under the "M-protein by immunofixation Serum (sIFE), Urine (uIFE), as IFE is not performed for progressive disease evaluation.	
Table 7.1 Disease Assessments	Removed text, "As needed to confirm disease progression".
Rationale: Added clarification text for screening assessment under the "CT/MRI assessment of STP – to be done locally" row.	
Table 7.1 Disease Assessments	Added screening assessment clarification text.
Rationale: To clarify that prior diagnostic samples could be used for MRD detection if a fresh bone marrow aspirate is not performed at screening. In addition, language added based on the MMY3003 protocol.	
Section 7.1.1.4 Bone Marrow by Local Assessment; Table 7.3 Schedule of Events Footnote 13	Added language that prior diagnostic samples could be used for MRD detection if a fresh bone marrow aspirate is not performed at screening. In addition, text added in the event that fresh biopsy/aspirate cannot be collected.

Applicable Section(s)	Description of Change(s)
Rationale: Added summary table for bone marrow testing to present a more concise presentation of bone marrow sampling requirements.	
Table 7.2 Bone Marrow Testing	Added Table 7.2 for bone marrow testing.
Rationale: Added text to clarify that skeletal survey results within 42 days are also accepted.	
Section 7.1.1.6 Skeletal Survey	Added clarification text for skeletal survey.
Rationale: Added text in the case that bone marrow aspirate cannot be collected at screening.	
Section 7.1.1.7 Minimal Residual Disease (MRD)	Added clarification text for screening procedures.
Rationale: Added text to clarify AE/SAE categorization of disease progression, death, and laboratory abnormalities.	
Section 7.1.2.1 Adverse Events; Section 8.1.1 Definition	Added clarification text for disease progression, death, and laboratory abnormalities.
Rationale: Rephrased to clarify, as only subjects treated with Dara IV will be monitored as described in-text.	
Section 7.1.2.3 Vital Signs	Rephrased text for clarification.
Rationale: Added clarification text on bone marrow aspirate procedures.	
Section 7.1.2.7 Biomarker Assessments	Added clarification text.
Rationale: To update Schedule of Events to reflect protocol changes and requests from German Health Authorities.	
Table 7.3 Schedule of Events	Note: This was Table 7.2 in Amendment #1; however, a Table 7.2 (Bone Marrow Testing) was added to this Amendment #2, thereby changing this Schedule of Events Table to Table 7.3. Footnote 5 revised to add clarification text concerning visits at 4 and 8 weeks post-discontinuation and PK sampling to avoid confusion. Modified footnote 9 (was #10 before #8 was deleted) under hematology assessments based on pomalidomide SmPC, and added the following text, based on German Health Authorities request: Complete blood counts should be monitored at baseline, weekly for the first 8 weeks and monthly thereafter. Revised note on screening assessments. Deleted footnote 8 (all footnotes following are now one number less). Added row for Hepatitis B serology and, therefore, added footnote #14. Added row under Lab Assessments for HBV testing. For HBV testing: Added footnote #15 for HBV testing and added additional timepoints of every 12 weeks (+/- 7 days) and at 8 weeks after last dose.

Applicable Section(s)	Description of Change(s)
Rationale: Added language for levofloxacin prophylaxis for 12-weeks duration, based on the ASH abstract.	
Section 7.3.3 Other Concomitant Medications	Added text for levofloxacin prophylaxis.
Rationale: Revised text since both serious and non-serious AEs are captured in the AE section of the eCRF.	
Section 8.3 Time Period and Frequency for Event Assessment and Follow-Up	Revised text concerning seriousness, severity, and relationship.
Rationale: Adapted pregnancy section to reflect that subjects must stop treatment with pomalidomide and that continuation of treatment with daratumumab will be assessed by the investigator. Other text revised to follow the local label for guidance on pregnancy prevention and adhere to the local Pomalidomide Risk Evaluation Mitigation Strategy (REMS) or Global Pregnancy Prevention Plan.	
Section 8.4.4 Pregnancy	Added clarification text on stopping treatment and language that investigators should follow the pomalidomide local label for guidance regarding pregnancy prevention and adhere to local the Pomalidomide REMS or Global Pregnancy Prevention Plan.
Rationale: Revised text in order to provide clarification that PQCs will not be reported as SAEs, rather they will be reported in the same timelines as SAEs.	
Section 8.4.5 Product Quality Complaint	Added clarification text.
Rationale:	Revised text required addition of literature reference (Drayson MT, 2017).
Section 17 Literature References	Added reference: Drayson MT, et al. "Tackling Early Morbidity and Mortality in Myeloma (TEAMM): Assessing the Benefit of Antibiotic Prophylaxis and Its Effect on Healthcare Associated Infections in 977 Patients." Blood. 2017;130(1):903.
Rationale: Updated cut-offs (inclusive) of M-component so as to be in line with the latest IMWG criteria.	
Appendix 2 Modified International Myeloma Working Group (IMWG) Uniform Response Criteria for Multiple Myeloma	Updated M-component cut-offs.
Rationale: Deleted footnote #1 to avoid confusion on PK collection.	
Appendix 10 Schedule of Events: PK / Immunogenicity Sample Collection Times for Subjects receiving Daratumumab via IV Administration, ONLY	Deleted footnote #1.
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 1 (13 Oct 2017)

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

The overall reason for the amendment: To allow for inclusion of subcutaneous (SC) route of administration of daratumumab (Dara) in this study.

Applicable Sections	Description of Changes
Rationale: To expand the study design to include the subcutaneous administration of daratumumab; to establish the definition of Dara IV and Dara SC terms.	
Protocol Summary: Methods; Section 4.1: Description of Study Design	The text was revised to indicate that all new subjects will be dosed subcutaneously with daratumumab and subjects who already began treatment with Dara IV will have the option to switch to Dara SC on Day 1 of any cycle starting with Cycle 3 or later. The terms Dara IV and Dara SC were defined.
Rationale: To establish that subjects who began treatment with Dara IV prior to Amendment 1 and switched to Dara SC for the remainder of their participation in the study will be counted toward the total of 302 subjects.	
Protocol Summary: Methods; Section 4.1: Description of Study Design; Section 10.6.1: Enrollment/Randomization/Masking Procedures	Text was added to indicate that subjects who began treatment with Dara IV prior to Amendment 1 and switched to Dara SC for the remainder of their participation in the study will be counted toward the total of 302 subjects.
Rationale: Clarification text added to provide the dose of Dara SC.	
Protocol Summary: Description of Study Treatments; Section 4.1: Description of Study Design; Table 6.1: Dosing and Administration; Section 6.1.4: Dosing and Administration, Daratumumab	The 1800 mg subcutaneous dose concentration was added. Note: The table numbering in the original version was "Table 6.1.4"; however, this numbering was an error and was corrected to "Table 6.1" for Amendment 1.
Rationale: Dara SC is co-formulated with recombinant human hyaluronidase, therefore, the immunogenicity of rHuPH20 will be evaluated.	
Protocol Summary: Objectives; Protocol Summary: Endpoints; Section 3.2: Secondary Objectives; Section 4.2.2: Secondary Endpoints; Section 7.1.4: Pharmacokinetics and Immunogenicity; Table 7.2.1; Section 10.3: Analysis Datasets; Appendix 9	Text added to describe evaluations of the immunogenicity of rHuPH20.
Rationale: Text added to clarify inclusion criteria #4 and #5 are based on the investigator's assessment of response.	
Protocol Summary: Population; Section 5.1: Subject Inclusion Criteria #4 and #5	Inclusion criterion #4 revised as shown below: 4. The subject must have had a response (ie, partial response or better based on the investigator's determination of response as defined by the modified IMWG criteria) to prior therapy. Inclusion criterion #5 revised as shown below: 5. Subjects must have documented evidence of progressive disease (PD) based on the investigator's determination of response as defined by the modified IMWG criteria on or after the last regimen.

Applicable Sections	Description of Changes
Rationale: Clarification of screening period to avoid site confusion/errors.	
Schematic of Study Design; Figure 4.1: Study Design	Changed “approximately 28 days” to “maximum 28 days”
Rationale: Since the time of preparation of the original protocol, the DaraPomDex combination has been approved by the FDA.	
Section 2.1.2: Daratumumab	Added text to describe the details of the regulatory approval.
Rationale: Since the study will now allow for SC administration, rationale added for the use of rHuPH20 to facilitate SC administration of protein therapeutics.	
Section 2.2: Rationale	Added text describing details of rHuPH20 as it pertains to the subcutaneous infusion of daratumumab.
Rationale: Since Dara SC administration is being added to the study, adverse event information for SC route was added.	
Section 2.3.1: Known Potential Risks	Added subsection titled “Daratumumab for Subcutaneous Injection” along with adverse event information.
Rationale: Since Dara SC administration is being added to the study, benefits of SC route were added.	
Section 2.3.2: Known Potential Benefits	Added benefits text for SC administration.
Rationale: Text revised in inclusion criteria #10 b and #10c to clarify that transfusions are not permissible in order to meet the inclusion criteria.	
Section 5.1: Subject Inclusion Criterion #10	Revisions made to inclusion criterion #10 as shown below: b) Hemoglobin level ≥7.5 g/dL (≥4.65 mmol/L) (transfusions are not permitted to reach this level); c) Platelet count ≥75 × 10^9/L in subjects in whom <50% of bone marrow nucleated cells are plasma cells and platelet count ≥50 x 10^9/L in subjects in whom ≥50% of bone marrow nucleated cells are plasma cells (transfusions are not permitted to reach this level);
Rationale: Exclusion criterion #8a revised to add temporal reference.	
Section 5.2: Exclusion Criteria	Revisions made to exclusion criterion #8a as shown below: 8. Clinically significant cardiac disease, including: a) Myocardial infarction within 6 months before C1D1, or unstable or uncontrolled condition (eg, unstable angina, congestive heart failure, New York Heart Association Class III-IV).
Rationale: Text added to clarify approval of patient eligibility via eCRF.	
Section 5.2: Exclusion Criteria	Sponsor will review and approve (through eCRF) the subject eligibility data submitted by the investigational site before randomization.

Applicable Sections	Description of Changes
Rationale: As there is an embryo-fetal risk with pomalidomide, clarification added regarding compliance with the pomalidomide pregnancy prevention program.	
Section 5.1: Subject Inclusion Criteria	Added the following text: Because of the embryo-fetal risk of pomalidomide, all subjects must adhere to the pomalidomide pregnancy prevention program applicable in their region. Investigators should comply with the local label for pomalidomide for specific details of the program.
Rationale: To clarify drug supplies.	
Section 6.1.1: Formulation, Appearance, Packaging, and Labeling	Text regarding study treatment drug supplies was clarified.
Rationale: Text added to provide information on the preparation of Dara SC; text added to clarify the Dara IV infusion solution.	
Section 6.1.3: Preparation	Text below was added: <u>Dara SC product will be prepared according to the Investigational Product Preparation Instructions.</u> Dara SC will be provided as a fixed dose, combination drug product containing rHuPH20 drug substance (2000 U/mL) and daratumumab drug substance (120 mg/mL) in a single vial. Infusion solution will be prepared as a 1,000-mL (first dose) or 500-mL (second and subsequent doses) dilution of Dara IV in sterile, pyrogen-free 0.9% NaCl.
Rationale: Text added to clarify the dexamethasone administration scheme when it overlaps with the dexamethasone pre-infusion medication requirements.	
Section 6.1.4: Dosing and Administration, Dexamethasone	Paragraph added as shown below: <u>During the weeks when the subject receives daratumumab, half of the dexamethasone dose (20 mg) will be administered on the day of infusion as the pre-infusion medication (IV preferred, see Section 7.3.1) and the remaining dose (20 mg PO) will be self-administered by the subject the following day. This applies only for subjects who are taking the full 40mg dexamethasone dose. The subjects who are taking 20 mg of dexamethasone (≥75 years of age) will receive the entire 20 mg dose as a pre-infusion medication on the day of daratumumab infusion.</u>
Rationale: Text added for clarity on managing infusion-related reactions.	
Section 6.1.5: Dose Adjustments/Modifications/Delays/Infusion-Related Reaction Management	Text was added to describe how IRRs are to be managed and guidelines for reporting IRR adverse events.
Rationale: To provide information regarding daratumumab dose delays and modifications.	
Section 6.1.5: Dose Adjustments/Modifications/Delays/Infusion-Related Reaction Management	Text was added to describe how to manage daratumumab-related toxicities and the actions to be taken regarding treatment discontinuation.

Applicable Sections	Description of Changes
Rationale: To clarify that disease progression must be confirmed for subjects diagnosed with disease progression.	
Section 6.1.6: Duration of Therapy; Section 7.1.1: Efficacy Assessments	Text was added to clarify that disease progression should be confirmed with a consecutive assessment if based on M-protein/serum FLC levels.
Rationale: To provide additional details and to describe the review process regarding reporting disease progression to the Sponsor.	
Section 7.1.1: Efficacy Assessments	Details on the procedures regarding reporting disease progression to the Sponsor's Medical Reviewer and the review process by the Medical Reviewer were added.
Rationale: To clarify when disease assessments should be performed.	
Section 7.1.1: Efficacy Assessments; Table 7.1: Disease Assessments (Footnote 1)	Added text as shown below: All efficacy laboratory assessments will be collected locally and analyzed centrally unless otherwise indicated in Table 7.1. <u>The disease assessments SPEP, UPEP, and serum calcium corrected for albumin should be collected every cycle for the first 14 months of the study and every other month thereafter. After Cycle 1, IFE should only be done when endogenous M-protein is 0 or nonquantifiable. For subjects who are followed by FLC only, these assessments are performed every other cycle after 14 months.</u> If the subject does not have documented disease progression as defined in Appendix 2 at the time of study drug discontinuation, then disease assessments must continue to be performed according to the same schedule shown in Table 7.2 until disease progression even if a subsequent anti-myeloma treatment is started prior to disease progression.
Rationale: Added that local hematology and clinical chemistry tests can be performed earlier (up to 3 days) than the treatment visit AND that they must be evaluated before drug administration. This window offers flexibility to the site so that results can be evaluated in a timely manner before drug administration. Also clarified that for C1D1, these tests do not have to be repeated if performed within 7 days.	
Section 7.1.2.2: Clinical Laboratory Tests	Text added as shown below: <u>Hematology and clinical chemistry tests may be performed up to 3 days before the study treatment administration day. The results from these tests must be evaluated before each study drug administration. At C1D1, these tests do not need to be repeated if they have been performed within 7 days.</u>
Rationale: Since Dara SC administration was added, clarification text for evaluations also needed to be added.	
Section 7.1.4.1: Evaluations; Table 7.2.1; Appendix 9; Appendix 10	Revised the text to refer to the 3 event schedules outlining pharmacokinetic and immunogenicity assessments: (new) Table 7.2.1: Subjects receiving daratumumab via subcutaneous administration, only (new) Appendix 9: Subjects who started daratumumab via IV infusion and switched to daratumumab subcutaneous administration (new) Appendix 10: Subjects receiving daratumumab via intravenous administration, only

Applicable Sections	Description of Changes
Rationale: Since Dara SC administration is now permitted, information regarding immunogenicity assessments for antibodies to rHuPH20 was added.	
Section 7.1.4.2: Analytical Procedures; Section 7.1.4.4: Immunogenicity Assessments	Text added regarding analyzing plasma samples for generation of antibodies to rHuPH20.
Rationale: To describe the collection of 2 blood samples, if possible, any time an infusion-related reaction is reported in a subject receiving Dara SC.	
Section 7.1.4.4: Immunogenicity Assessments	The following text was added: <u>In addition, 2 separate blood samples should be obtained, if possible, for the assessment of antibodies to daratumumab and rHuPH20 any time an infusion-related reaction is reported in a subject receiving Dara SC (according to Table 7.2.1 and the laboratory manual) in association with the second administration or beyond. Daratumumab serum concentration will also be determined from the daratumumab infusion reaction sample for the purpose of interpreting immunogenicity data.</u>
Rationale: Text added to allow flexibility for the disease evaluation assessments.	
Section 7.2: Study Schedule	Paragraphs added as shown below: <u>At each visit, study assessments should be completed before administration of the study treatment, unless otherwise stated. All visit-specific PRO assessments should be completed before any study procedures for that visit to prevent influencing the subject's perceptions.</u> <u>Post-baseline disease evaluations may be conducted ± 3 days from the scheduled (based on C1D1) visit date, if necessary. At the following visit, the subject should return to the original planned schedule.</u>
Rationale: To clarify the requirements for tests scheduled during the Screening period.	
Section 7.2.1: Screening	Removed the text that any screening assessment done outside the screening window must be repeated prior to randomization; this provision is provided in the Schedule of Events. Clarified that a laboratory test repeated to satisfy eligibility criteria should be completed within the 28-day window from C1D1. The following text was added: <u>Serum M-protein, urine M-protein, and serum FLC baseline disease evaluations must be performed within 14 days before C1D1. It is not mandatory to collect these samples again at the C1D1 visit. Results from the skeletal survey or the radiologic assessments for extramedullary plasmacytomas, which have been performed as routine follow-up within 42 days before C1D1, may be used without these tests being repeated</u>. The following text was added: <u>Subjects who are screening failures may be rescreened if their condition changes. Rescreening must be discussed and approved by the Sponsor on a case by case basis. Subjects who are determined eligible for rescreening must sign a new ICF.</u>

Applicable Sections	Description of Changes
Rationale: Clarification to specify the allowed period between randomization and first dose**.**	
Section 7.2.2: Treatment Period	Added the following text: Subjects should start study treatment within 3 days after randomization.
Rationale: To clarify evaluations and assessments in the Schedule of Events.	
Table 7.2: Schedule of Events	Removed Daratumumab pharmacokinetic and immunogenicity timepoints and replaced with references to the appropriate table or appendix for sampling depending on the daratumumab formulation(s) being used. Added the following table notes: ***** For sites where β2-microglobulin is measured locally, the local assessment of serum albumin (instead of the one measured centrally) will be used to determine the ISS stage. ****** Unless otherwise stated, all blood and urine samples must be obtained before administration of study treatment [10] Hematology and clinical chemistry tests may be performed up to 3 days before the study treatment administration day. Laboratory assessments do not need to be repeated if done within 7 days of Cycle 1 Day 1. [11] Disease assessments SPEP, UPEP, and serum calcium corrected for albumin, should be collected every cycle for the first 14 months of the study and every other month thereafter. After Cycle 1, IFE should only be done when endogenous M-protein is 0 or nonquantifiable. For subjects who are followed by FLC only, these assessments are performed every other cycle after 14 months. [12] Every effort should be made to follow the planned dosing schedule; however, doses within 3 days of the scheduled dose will be permitted. Subjects should start study treatment within 3 days after randomization. The dose does not need to be recalculated for weight changes that are <10% from baseline. [13] EOT visit to occur 4 weeks after the last dose of study treatment or as soon as possible before the start of subsequent therapy.
Rationale: Since Dara SC administration was added, a table was created to detail pharmacokinetic / immunogenicity sample collection times for subjects who receive Dara SC.	
Table 7.2.1: Schedule of Events: Pharmacokinetic / Immunogenicity Sample Collection Times for Subcutaneous Daratumumab Subjects	Added pharmacokinetic / immunogenicity sample collection times for Dara SC subjects.

Applicable Sections	Description of Changes
Rationale: Text added to clarify the definition of subjects with higher risk of respiratory complications.	
Section 7.3.2: Post-infusion Medication in High-Risk Subjects	Text added as shown below: For subjects with a higher risk of respiratory complications (ie, subjects with COPD who have an FEV1 <80% of predicted normal, or subjects with mild asthma), the following post-infusion medications should be considered:
Rationale: Additional details regarding the reporting timelines for second primary malignancies and suspected transmission of infectious agents were added.	
Section 8.4.3: Events of Special Interest	Added the following text: In addition, any events of secondary primary malignancies and suspected transmission of infectious agents will follow the same SAE reporting timelines and procedures outlined in Section 8.4.2.
Rationale: Updated the timing of the IDMC safety review based on the Dara SC group.	
Section 8.5: Safety Oversight	Revised the text as shown below: Safety data will be reviewed by the study IDMC approximately every 6 months (after first randomized subject started Dara SC administration).
Rationale: Since Dara SC administration is now added, biostatistical considerations needed to be revised.	
Sections 10.3: Analysis Datasets; Section 10.6.1: Enrollment/Randomization/Masking Procedures	Statistical text updated throughout to account for SC versus IV administration.
Rationale: Information was added regarding source documentation requirements for inclusion/exclusion criteria	
Section 11: Source Documents and Access to Source Data/Documents	Text added as shown below: **Inclusion/Exclusion Criteria Source Documentation Requirements** The minimum source documentation requirements for the Inclusion/Exclusion criteria that specify a need for documented medical history (see Section 5.1 and Section 5.2) are the following: ● Referral letter from treating physician ● Complete history of medical notes at the site ● Discharge summaries
Rationale: Updated language on how to quantify the increase in size of lesions based on 2016 IMWG criteria	
Appendix 2: Modified IMWG Criteria	Added text to "Progressive Disease" row as shown below: ➢ Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas (≥50% increase from nadir in SPD[7] of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in the short axis). Footnote 7 added: [7] SPD = sum of the products of the maximal perpendicular diameters of measured lesions

Applicable Sections	Description of Changes
Rationale: To clarify that the validated computer algorithm used to derive the primary analysis of PFS will be in accordance with modified IMWG criteria.	
Section 10.1: Statistical and Analytical Plans	Text was added to indicate that analysis of PFS will use response or progression status as derived by a validated computer algorithm in accordance with modified IMWG response criteria.
Rationale: Added a new Appendix to include the definition for a New Line of Therapy	
Appendix 11: Prior Multiple Myeloma Therapy Lines	Text added as shown below: **Appendix 11: Prior Multiple Myeloma Therapy Lines** In order to achieve a uniform stratification of all subjects, the number of prior lines of therapy will be derived according to the following definition: An administered regimen is considered as **New Line of Therapy** when EITHER: ● There is a six-month treatment-free interval since the last regimen OR ● Patient has documented evidence of PD since the last regimen
Rationale: To include that a sensitivity analyses for PFS and ORR may be conducted.	
Section 10.4.2: Analysis of the Primary Efficacy Endpoint(s); Section 10.4.3: Analysis of the Secondary Endpoint(s)	Text added as shown below: A sensitivity analysis of PFS/ORR may be conducted by excluding those subjects who already began treatment with Dara IV prior to Amendment 1.
Rationale: Revised for clarity and to include updated information.	
Section 2.1.2: Daratumumab; Section 2.2: Rationale; Section 2.3.1: Known Potential Risks; Section 2.3.2: Known Potential Benefits; Section 6.1.4: Dosing and Administration	Text updated based on current program information and revised for clarity.
Rationale: Values were updated due to incorrect conversions to molar concentrations.	
Appendix 2: Modified IMWG Criteria	Progressive Disease/Development of Hypercalcemia: 2.65 mmol/L to 2.87 mmol/L Clinical Relapse/Hypercalcemia: 2.65 mmol/L to 2.87 mmol/L Clinical Relapse/ Hemoglobin: 1.25 mmol/L to 1.24 mmol/L Clinical Relapse/Creatinine: 177 mmol/L to 177 µmol/L
Rationale: Value was updated to include place value to the hundredths.	
Section 5.1: Subject Inclusion Criteria	Inclusion criterion #10: Hemoglobin Level: 5 mmol/L revised to 4.65 mmol/L
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BM	Bone Marrow
C1D1	Cycle 1 Day 1
CA	Competent Authority
CCO	Clinical Cutoff
CI	Confidence Interval
CMP	Clinical Monitoring Plan
COPD	Chronic Obstructive Pulmonary Disease
CR	Complete Response
CRAB	Calcium elevation, Renal dysfunction, Anemia, Bone destruction
CRO	Contract Research Organization
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
Dara CF	Daratumumab and recombinant human hyaluronidase for subcutaneous injection: co-formulated
Dara IV	Daratumumab for intravenous infusion
DaraPomDex	Daratumumab + Pomalidomide + Dexamethasone
Dara SC	Daratumumab administered subcutaneously
DoR	Duration of Response
DSIFE	Daratumumab-specific Immunofixation Electrophoresis
DVT	Deep Vein Thrombosis
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 item
EQ-5D-5L	European Quality of Life Five Dimensions Questionnaire
EU	European Union
FDA	Federal Drug Administration
FEV1	Forced Expiratory Volume in 1 Second
FFPE	Formalin-fixed Paraffin Embedded
FISH	Fluorescent In Situ Hybridization
GCP	Good Clinical Practice
HBV	hepatitis B virus
HR	Hazard Ratio
HRQoL	Health-related Quality of Life
IAT	Indirect Antiglobulin Test
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFE	Immunofixation electrophoresis
IgA	Immunoglobulin A
IgG	Immunoglobulin G
ILD	Interstitial lung disease
IMiD	Immunomodulatory Drug
IMWG	International Myeloma Working Group

IRB	Institutional Review Board
IRR	Infusion-Related Reaction
ISS	International Staging System
ITT	Intent-to-Treat
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
MM	Multiple Myeloma
M-protein	Monoclonal Paraprotein
MR	Minimal Response
MRD	Minimal Residual Disease
NGS	Next-Generation Sequencing
NK	Natural Killer
OR	Odds Ratio
ORR	Overall Response Rate
OS	Overall Survival
PCR	Polymerase chain reaction
PD	Progressive Disease
PFS	Progression Free Survival
PI	Proteasome Inhibitor
PomDex	Pomalidomide + Dexamethasone
PQC	Product Quality Complaint
PR	Partial Response
PRO	Patient Reported Outcomes
PT	Preferred Term
QLQ-MY20	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Multiple Myeloma Module
REMS	Risk Evaluation Mitigation Strategy
rHuPH20	recombinant human hyaluronidase
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
sCR	Stringent Complete Response
SD	Standard Deviation
sFLC	Serum Free Light Chain
sIFE	Serum Immunofixation
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SPEP	Serum Protein Electrophoresis
STP	Soft Tissue Plasmacytoma
TEAEs	Treatment-Emergent Adverse Events
uIFE	Urine Immunofixation
UPEP	Urine Protein Electrophoresis
US	United States
VGPR	Very Good Partial Response
VTE	Venous Embolic or Thrombotic
WHO	World Health Organization
WOCBP	Women of Childbearing Potential

STATEMENT OF COMPLIANCE

This study will be conducted in accordance with the Declaration of Helsinki, the guidelines for Good Clinical Practice (GCP) of the International Conference on Harmonisation (ICH E6), and all applicable laws and regulations. The Principal Investigators will assure that no deviation from, or changes to, the protocol will take place without prior agreement from the Sponsor and documented approval from the accredited Independent Ethics Committee (IEC) and/or Competent Authority (CA), except where necessary to eliminate an immediate hazard to the study subjects.

PROTOCOL SUMMARY

Study Title:

A Phase 3 Study Comparing Pomalidomide and Dexamethasone With or Without Daratumumab in Subjects With Relapsed or Refractory Multiple Myeloma Who Have Received at Least One Prior Line of Therapy With Both Lenalidomide and a Proteasome Inhibitor: The APOLLO Study

Methods:

This is a multicenter, randomized, open-label study. The original design of this study was to treat subjects with daratumumab for intravenous (IV) infusion (Dara IV); however, as of Amendment 1, all new subjects will be dosed subcutaneously with daratumumab co-formulated with recombinant human hyaluronidase rHuPH20 (hereafter referred to as Dara SC). Subjects who already began treatment with Dara IV (ie, prior to Amendment 1) will have the option to switch to Dara SC on Day 1 of any cycle starting with Cycle 3 or later. It is to be noted that throughout this document, text has been added to highlight any differences between Dara IV and Dara SC dosing; and where there is no clarification, it is implied that the descriptions are the same for both Dara IV and Dara SC.

Approximately 302 subjects will be randomized in a 1:1 ratio to receive either daratumumab + pomalidomide + dexamethasone (DaraPomDex) or pomalidomide + dexamethasone (PomDex). Subjects who already began treatment with Dara IV prior to Amendment 1 will have the option to switch to subcutaneous administration of daratumumab for the remainder of their participation in the study and they will be counted toward the total of 302 subjects. Treatment cycles have a duration of 28 days. Subjects will receive treatment until disease progression or unacceptable toxicity. Drug administration and follow-up visits will occur more frequently for early cycles (eg, weekly or bi-weekly).

Assessment of myeloma response and disease progression will be conducted in accordance with the modified International Myeloma Working Group (IMWG) response criteria. Disease evaluations will occur monthly and consist primarily of measurements of myeloma proteins. Other measures may include bone marrow examinations, skeletal surveys, assessment of extramedullary plasmacytomas, and measurements of serum calcium corrected for albumin. Survival status, subsequent anti-myeloma treatment data, and patient reported outcome (PRO) measures will continue to be collected post-treatment.

Objectives:

The primary objective of this study is to compare progression free survival (PFS) between treatment arms.

The secondary objectives are the following:

- To compare Overall Response Rates (ORR) between treatment arms
- To compare Duration of Response (DoR) between treatment arms
- To compare time to next therapy between treatment arms

- To compare Overall Survival (OS) between treatment arms
- To assess the safety and tolerability of the investigational combination treatment
- To assess the depth of response by analysis of minimal residual disease (MRD) rate for subjects with complete response (CR/sCR) and for subjects with suspected CR/sCR
- To compare health-related quality of life (HRQoL) and health utility between treatment arms
- To evaluate the immunomodulatory effects of daratumumab on T cells
- To evaluate daratumumab pharmacokinetics and immunogenicity and the immunogenicity of rHuPH20

Endpoints:

Primary endpoint: Progression free survival
Secondary Endpoints:

- ORR
- Very good partial response (VGPR) or better rate
- CR or better rate
- MRD negativity rate
- Time to response
- DoR
- Time to next therapy
- OS
- Safety (adverse events)
- Scale and domain scores of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 item (global health status, physical functioning, emotional functioning, fatigue, pain) and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Multiple Myeloma Module (disease symptoms, side effects of treatment)
- European Quality of Life Five Dimensions Questionnaire health utility values
- Immunomodulatory effects of daratumumab on T cells
- Daratumumab pharmacokinetic concentrations (IV and SC)
- Daratumumab and rHuPH20 immunogenicity

Population:

Approximately 302 subjects will be enrolled. Main inclusion criteria are the following:

1. Males and females at least 18 years of age.
2. Voluntary signed informed consent form (ICF) before performance of any study-related procedure.
3. Subject must have measurable disease of multiple myeloma as defined by the criteria below:
   - IgG multiple myeloma: Serum monoclonal paraprotein (M-protein) level ≥1.0 g/dL or urine M-protein level ≥200 mg/24 hours, or
   - IgA, IgD, IgE, IgM multiple myeloma: Serum M-protein level ≥0.5 g/dL or urine M-protein level ≥200 mg/24 hours, or
   - Light chain multiple myeloma, for subjects without measurable disease in the serum or urine: Serum immunoglobulin free light chain (FLC) ≥10 mg/dL and abnormal serum immunoglobulin kappa lambda FLC ratio.

4. Subjects must have received prior anti-myeloma treatment. The prior treatment must have included both a proteasome inhibitor (PI-) and lenalidomide-containing regimens. The subject must have had a response (ie, partial response or better based on the investigator's determination of response as defined by the modified IMWG criteria) to prior therapy.
5. Subjects must have documented evidence of progressive disease (PD) based on the investigator's determination of response as defined by the modified IMWG criteria on or after the last regimen.
6. Subjects who received only 1 line of prior treatment must have demonstrated PD on or within 60 days of completion of the lenalidomide-containing regimen (ie, lenalidomide refractory).
7. Eastern Cooperative Oncology Group (ECOG) performance status score ≤2.
8. Women of childbearing potential (WOCBP) must have 2 negative serum or urine pregnancy tests, one 10-14 days prior to start of the study drugs and one within 24 hours prior to the start of study drugs. Women must not be breastfeeding. WOCBP must agree to follow instructions for methods of contraception for 4 weeks before the start of treatment with study drugs, for the duration of treatment with study drugs, and for a total of 3 months after cessation of daratumumab treatment. Males who are sexually active with WOCBP must always use a latex or synthetic condom during any sexual contact with females of reproductive potential, even if they have undergone a successful vasectomy.

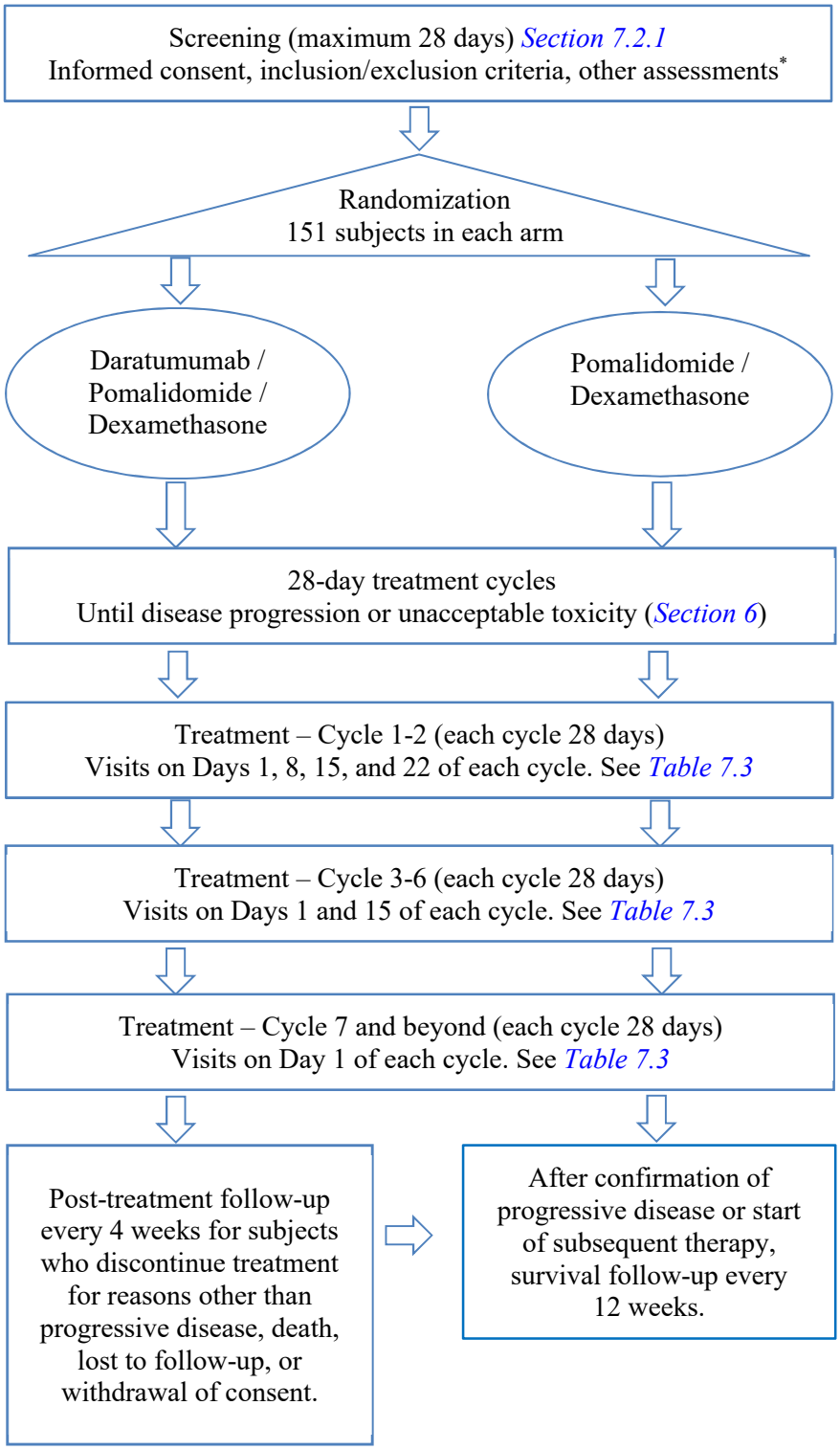
Phase: 3

Description of Study Treatments: Daratumumab will be given at a dose of 16 mg/kg administered as an IV infusion (Dara IV) or 1800 mg subcutaneously (Dara SC) at weekly intervals (QW) for 8 weeks, then every 2 weeks (Q2W) for an additional 16 weeks, then every 4 weeks (Q4W) thereafter. Pomalidomide is taken orally as a 4-mg tablet once daily on Days 1 to 21 of repeated 28-day cycles. Dexamethasone will be administered according to standard clinical practice. The recommended dose of dexamethasone is 40 mg (20 mg for subjects ≥75 years of age) orally once daily on Days 1, 8, 15, and 22 of each 28-day treatment cycle.

Subject Duration: Subjects will receive treatment until disease progression or unacceptable toxicity. Survival status, subsequent anti-myeloma treatment data, and PRO measures will continue to be collected post-treatment.

Study Duration: The primary analysis of PFS will occur after 188 PFS events have been observed. Long-term survival follow-up and data collection will continue until approximately 166 deaths have been observed or 5 years after the last subject is randomized, whichever occurs earlier. Subjects benefiting from the study treatment can continue to receive study treatment after the CCO for the final OS analysis. For these subjects, study treatment will be available through continued access within the current study until it is available through another source such as commercial availability with reimbursement, continued access through a long-term extension study, a patient access program, or after the last subject transitions into the long-term extension phase of the study up to 30 September 2024, whichever occurs first.

SCHEMATIC OF STUDY DESIGN



*The schedule of assessments will be adjusted for subjects remaining on the study after the positive primary analysis and is detailed in *Section 7.2.4*. A schedule of assessments is provided in *Appendix 12* (and detailed in *Table 7.3*) for subjects continuing on study treatment after the CCO for the final OS analysis.

1 KEY ROLES

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2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 BACKGROUND INFORMATION

2.1.1 Multiple Myeloma

Multiple myeloma (MM) is a malignant plasma cell disorder that is characterized by the production of monoclonal immunoglobulin in a majority of patients and that invades adjacent bone tissue. Common manifestations include bone pain, renal insufficiency, hypercalcemia, anemia, and recurrent infections.

Based on data from the United States (US) from 2009-2013, the number of new cases of myeloma was 6.5 per 100,000 men and women per year. The number of deaths was 3.3 per 100,000 men and women per year. In 2013, there were an estimated 95,688 people living with myeloma in the US. Approximately 30,300 people in the US were expected to receive a new diagnosis of MM in 2016 (1.8% of all new cancer cases) and 12,650 were expected to die from MM (*Howlader et al 2016)*.

A hallmark feature of MM is the production of abnormal antibodies or serum monoclonal paraproteins (M-proteins). The M-protein produced by the malignant plasma cells is immunoglobulin G (IgG) in about 50%-54% of myeloma patients and immunoglobulin A (IgA) in about 20% of patients. Of those patients producing either IgG or IgA, 40% also have Bence Jones proteinuria, ie, the presence of free monoclonal kappa (κ) or lambda (λ) light chains in urine. In 15%-20% of patients, plasma cells secrete only light chain protein (light chain myeloma) (*CIBMTR 2013*).

Multiple myeloma is characterized by osteolytic lesions, usually in the pelvis, spine, ribs, and skull. Lesions are caused by expanding plasmacytomas or by cytokines secreted by myeloma cells that activate osteoclasts and suppress osteoblasts. Increased bone loss may also lead to hypercalcemia. Solitary extraosseous plasmacytomas are unusual but may occur in any tissue, especially in the upper respiratory tract. In many patients, renal failure is present at diagnosis or develops during the course of the disorder and is caused by the deposition of light chains in the distal tubules or by hypercalcemia. Patients also often develop anemia due to kidney disease or suppression of erythropoiesis by cancer cells, but sometimes also due to iron deficiency. These signs and symptoms are commonly denoted as CRAB (Calcium elevation, Renal dysfunction, Anemia, Bone destruction).

The terms used to define patient populations studied in clinical trials have been standardized based on the American Society of Hematology–Food and Drug Administration (FDA) panel on endpoints in myeloma (*Rajkumar et al 2011*):

- **Refractory myeloma:** Disease that is nonresponsive while on primary or salvage therapy, or progresses within 60 days of last therapy. Nonresponsive disease is defined as either failure to achieve minimal response (MR) or development of PD while on therapy.
  - Relapsed and refractory myeloma: Disease that is nonresponsive while on salvage therapy or progresses within 60 days of the last therapy in patients who had achieved MR or better at some point previously before progressing in their disease course.
  - Primary refractory myeloma: Disease that is nonresponsive in patients who have never achieved a MR or better with any therapy.

- **Relapsed myeloma:** Previously treated myeloma that progresses and requires the initiation of salvage therapy but does not meet criteria for either "primary refractory myeloma" or "relapsed-and-refractory myeloma" categories.

Currently approved treatments for patients with relapsed/refractory MM include proteasome inhibitors (PIs) (eg, bortezomib, carfilzomib), immunomodulatory drugs (thalidomide, lenalidomide, or pomalidomide), histone deacetylase inhibitors, and monoclonal antibodies (elotuzumab, daratumumab) (*Ludwig et al 2010*). However, there is no cure, and current therapies only slow disease progression, prolong survival, and reduce symptoms. Although recent advances in the development of targeted therapeutics and stem cell transplantation have improved overall and event-free survival, the great majority of patients with myeloma will relapse and experience disease progression.

2.1.2 Daratumumab

Daratumumab is a human IgGκ monoclonal antibody that targets CD38, which is an important immunotherapy target due to its high expression on malignant plasma cells and low expression on other normal lymphoid and myeloid cells and is an important modulator of intracellular signaling.

The main anti-myeloma effect of daratumumab is attributed to its antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity (*Phipps et al 2015*). An additional mode of action appears to be the induction of apoptosis via Fragment Crystallizable-receptor (FcR)-mediated crosslinking (*Jansen et al 2012*). Further experiments using a Burkitt's lymphoma (Daudi) cell line mixed with human macrophages in the presence of daratumumab showed daratumumab-specific antibody-dependent cellular phagocytosis that resulted in a 50% reduction in tumor cells. Dose-dependent daratumumab-specific phagocytosis was also observed with patient-derived MM cell lines transduced with CD38 (*Overdijk et al 2012*). Daratumumab has also been demonstrated to have immunomodulatory activity that removes immune suppressive populations of $CD38^+$ MDSC, $CD38^+$ TReg, and $CD38^+$ BReg cells and T cell clonal expansion (*Krejcik et al 2016*). See the *Daratumumab Investigator's Brochure (IB)* for more details.

In November 2015, DARZALEX® (daratumumab) was approved by the U.S. FDA for the treatment of patients with MM who have received at least 3 prior lines of therapy, including a PI and an immunomodulatory drug (IMiD), or who are double refractory to a PI and an IMiD agent. This indication was approved under accelerated approval based on the results of the pivotal, open-label, Phase 2 MMY2002 (SIRIUS) study in which treatment with single-agent daratumumab resulted in an ORR of 29.2% (95% Confidence Interval [CI]: 20.8, 38.9). Median DoR was 7.4 months (95% CI: 5.5, not estimable [NE]). Ninety-five percent (95%) of subjects in the study were double refractory to a PI and IMiD and subjects had received a median of 5 prior lines of therapy. While 4.7% of subjects discontinued treatment due to adverse events (AEs), none of which were considered drug-related, no subjects discontinued treatment due to infusion-related reactions (IRRs). Stringent complete response (sCR) was reported in 2.8% of subjects, VGPR in 9.4% of subjects, and partial response (PR) in 17% of subjects. The most common AEs, which occurred in more than 20% of subjects, were fatigue, anemia, nausea, thrombocytopenia, back pain, neutropenia, and cough (*Lonial et al 2016*).

These results were supported by those of the Phase 1/2 GEN501 study, which confirmed daratumumab as an effective single-agent treatment option for patients with relapsed and refractory myeloma, especially those with disease that is otherwise resistant to other treatments or those who have unacceptable side effects from other treatments. Daratumumab had an acceptable safety profile, with the majority of IRRs Grade 1 or Grade 2 including mild and transient bronchospasm, headache, dyspnea, and fever across the 2 dose

cohorts; 1 subject had Grade 3 IRRs. Most events occurred during the first infusion, and no subject discontinued treatment because of an IRR. Daratumumab demonstrated a 36% ORR in subjects treated with a 16 mg/kg dose, with responses improving (or "deepening") over time (*Lokhorst et al 2015*).

In May 2016, the European Commission granted approval of daratumumab for the monotherapy of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a PI and an IMiD and who demonstrated disease progression on the last therapy.

In July 2016, the FDA granted a Breakthrough Therapy Designation to daratumumab in combination with lenalidomide (an IMiD agent) and dexamethasone, or bortezomib (a PI) and dexamethasone, for the treatment of patients with MM who have received at least 1 prior therapy. This second Breakthrough Therapy Designation was granted based on data from 2 Phase 3 studies: MMY3003 and MMY3004.

The MMY3003 (POLLUX) study is a Phase 3, multinational, open-label, randomized, multicenter, active-controlled study of 569 subjects with MM who have received a median of 1 prior line of therapy. Subjects were randomized to receive either daratumumab combined with lenalidomide and dexamethasone or lenalidomide and dexamethasone alone. Subjects were treated until disease progression, unacceptable toxicity, or if they had other reasons to discontinue the study. The study was unblinded after meeting its primary endpoint of improved PFS in a pre-planned interim analysis. In fact, the daratumumab + lenalidomide + dexamethasone combination achieved a 63% reduction in the risk of disease progression or death (PFS) compared with lenalidomide + dexamethasone alone (Hazard Ratio [HR]=0.37; 95% CI: 0.27, 0.52; p<0.0001). Additionally, daratumumab significantly increased the ORR (93% vs. 76%; p<0.0001) and doubled the rate of CR or better (43% vs. 19%; p<0.0001), as well as the rate of VGPR or better (76% vs. 44%; p<0.0001). Overall, the safety of the daratumumab combination therapy was consistent with the known safety profile of daratumumab monotherapy and with lenalidomide plus dexamethasone. Daratumumab-associated IRRs (48% of subjects) were mainly Grade 1 or 2 (Grade 3 or 4: 5% and 0%, respectively), and most (92%) occurred during the first infusion *(Dimopoulus et al 2016*). Patient reported outcome (PRO) results indicated that, in general, subjects in both groups maintained their HRQoL while remaining on treatment.

MMY3004 (CASTOR) is a Phase 3, multinational, open-label, randomized, multicenter, active-controlled study that enrolled 490 subjects with MM who received a median of 2 prior lines of therapy. Thirty-three percent of subjects were refractory to an IMiD agent and 32% were refractory to their last line of prior therapy. Subjects were randomized to receive either daratumumab combined with subcutaneous (SC) bortezomib and dexamethasone (n=251) or bortezomib and dexamethasone alone (n=247). Subjects were treated with daratumumab until disease progression or unacceptable toxicity. The daratumumab + bortezomib + dexamethasone combination demonstrated a 61% reduction in the risk of disease progression or death (PFS) compared with bortezomib + dexamethasone alone (HR=0.39; 95% CI: 0.28, 0.53); p<0.0001). As in the POLLUX study, daratumumab significantly increased the ORR (83% vs. 63%; p<0.0001) and doubled CR or better rates (19% vs. 9%; p<0.0012), including doubling VGPR rates (59% vs. 29%; p<0.0001) (*Palumbo et al 2016*). Patient-reported outcome results indicated that there was no significant detriment to overall HRQoL with the addition of daratumumab to bortezomib and dexamethasone.

On 21 November 2016, the U.S. FDA approved daratumumab in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with MM who have received at least 1 prior therapy.

An ongoing, multicenter, Phase 1b study (MMY1001, discussed in further detail below) is currently evaluating the safety and efficacy of daratumumab combined with pomalidomide plus dexamethasone (DaraPomDex). For the 103 subjects treated with DPd regimen, the ORR was 59%. Forty-two percent (42%) of subjects had a response of VGPR or better, 8% of subjects had a stringent CR, and 14% of subjects had CR or better. After a median duration of follow-up of 9.8 months, the median DoR was 13.6 months. At the time of the clinical cutoff (CCO), 48% of subjects had experienced PFS events; the median PFS was 10.4 months. The median time to progression was 10.9 months. The median OS was not reached, but based on the Kaplan-Meier estimate, the 12-month OS rate was 72% (*Chari et al 2015*).

Study MMY1004 is an ongoing, open-label, dose-escalation, Phase 1b study to assess the safety and pharmacokinetics of SC administration of daratumumab. Part 1 is to evaluate the intermediate form of daratumumab SC which is a mix-and-deliver SC presentation (Dara MD); Dara IV mixed with rHuPH20 at the study center before administration. Part 2 is to evaluate the final form of daratumumab SC (daratumumab coformulated with rHuPH20) (Dara CF or Dara SC). Preliminary efficacy data suggest that SC administration of Dara MD may enable comparable response rates with Dara IV. Furthermore, to date, the rate of IRRs with SC administration of Dara MD and Dara SC has been lower than the rate reported with Dara IV (see *Section 2.3.1* for details). The SC administration of daratumumab would offer several tangible benefits for both patients and health care providers:

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

Despite substantial progress, myeloma remains an incurable disease plagued by multiple relapses and increasing resistance to therapy. Emerging therapies, however, appear promising and may change the therapeutic landscape in MM. The aim of this study (APOLLO) is to further investigate the efficacy and safety of a DaraPomDex combination in order to provide physicians with a novel therapeutic strategy for treating patients with relapsed/refractory MM, as well as to confirm the preliminary data from the MMY1001, single-arm study. On 16 June 2017, DARZALEX® in combination with pomalidomide and dexamethasone was approved by the FDA for the treatment of patients with multiple myeloma who have received at least 2 prior therapies including lenalidomide and a PI. However, DaraPomDex is not an approved regimen anywhere in the European Union (EU).

2.2 RATIONALE

Synergistic combinations that target various mechanisms to overcome drug resistance need to be examined in order to realize daratumumab's full potential. To this end, daratumumab is being investigated as part of multidrug chemotherapy regimens. The cytotoxicity induced by the anti-CD38 antibody, together with the immunomodulatory effects of pomalidomide, could represent an important and effective anti-myeloma combination therapy.

Clinical studies have demonstrated the efficacy and safety of combining daratumumab with bortezomib and with lenalidomide. Apart from the daratumumab infusion reactions, which can be minimized with premedication, AEs in these studies were similar to those reported in studies of either bortezomib or lenalidomide alone. Since lenalidomide and pomalidomide are in the same drug class and have a similar

safety and pharmacokinetic profile, the addition of daratumumab to pomalidomide should give rise to a similar safety profile as did the lenalidomide - daratumumab combination.

Pomalidomide is an option for patients who have relapsed/refractory MM and who live in the US, the EU, or elsewhere that pomalidomide has a marketing authorization. The FDA granted accelerated approval for pomalidomide based on a Phase 2 study of subjects with relapsed and refractory disease after at least 2 prior regimens, including lenalidomide and bortezomib. Subjects received either pomalidomide alone (n=108) or in combination with 40 mg/week dexamethasone (n=113) (*Richardson et al 2014*). With a median follow-up of 14.2 months, median PFS was 4.2 and 2.7 months (HR=0.68; p = 0.003); ORR (≥PR) was 33% vs. 18% (p=.013); median response duration was 8.3 vs. 10.7 months; and median OS was 16.5 vs. 13.6 months, respectively for the pomalidomide + dexamethasone arm compared with the pomalidomide alone arm. The most common hematologic Grade 3 or 4 AEs were neutropenia (41% vs. 48%), anemia (22% vs. 24%), and thrombocytopenia (19% vs. 22%), respectively for the pomalidomide + dexamethasone vs. pomalidomide alone arm. The most common non-hematologic AEs were pneumonia (22% vs. 15%) and fatigue (14% vs. 11%) in the pomalidomide + dexamethasone arm compared with the pomalidomide alone arm, respectively.

The European Medicines Agency (EMA) granted approval for pomalidomide based on a Phase 3 study (MM-003/NIMBUS® study) that evaluated the combination of pomalidomide with low-dose dexamethasone vs. high-dose dexamethasone in subjects with refractory or relapsed and refractory MM. Subjects were randomized to receive pomalidomide plus low-dose dexamethasone (n=302) or high-dose dexamethasone (n=153) (*San Miguel et al 2013; Weisel et al 2015*). Pomalidomide was dosed at 4 mg orally on Days 1-21 of each 28-day cycle and dexamethasone was given at a low dose of 40 mg/day on Days 1, 8, 15, and 22 or at a high dose of 40 mg/day on Days 1-4, 9-12, and 17-20. Treatment continued until disease progression or unacceptable toxicity. Median PFS with pomalidomide plus low-dose dexamethasone was 4.0 months (95% CI: 3.6, 4.7) vs. 1.9 months (CI: 1.9, 2.2) with high-dose dexamethasone (HR=0.48; 95% CI: 0.39, 0.60; p <0.0001). Median OS was also significantly longer (12.7 months [95% CI: 10.4, 15.5] vs. 8.1 months [CI: 6.9, 10.8]; (HR=0.74 [CI: 0.56, 0.97]; p=0.0285). Overall response rate after a median follow-up of 10 months was 31% in the pomalidomide plus low-dose dexamethasone group vs. 10% in the high-dose dexamethasone group (Odds Ratio [OR] 4.22 [2.35–7.58]; p <0.0001). In the pomalidomide plus low-dose dexamethasone and high-dose dexamethasone arms, respectively, the most common Grade 3/4 hematological AEs were neutropenia (48% vs. 16%), anemia (33% vs. 37%), and thrombocytopenia (22% vs. 26%). The most common Grade 3/4 non-hematological AEs were pneumonia (13% vs. 8%), bone pain (7% vs. 5%), and fatigue (5% vs 6%). Clinically meaningful improvements in health-related quality-of-life were observed more frequently in subjects receiving pomalidomide plus low-dose dexamethasone than high-dose dexamethasone.

A recent Phase 2 study of pomalidomide in combination with low-dose dexamethasone assessed the efficacy and safety in subjects with MM who relapsed after, or were refractory to, a lenalidomide-based, second-line therapy (*Siegel et al 2017*). A total of 51 subjects were enrolled with a median number of 2 prior lines of therapy. With a median follow-up of 13.6 months, the ORR was 29.4% and median PFS was 13.8 months. Anemia was the most common (25%) Grade 3 or Grade 4 treatment-emergent adverse events (TEAEs). The most common non-hematological Grade 3 or Grade 4 TEAEs were infections (20%), including pneumonia (10%). Compared with previous studies with the PomDex combination in subjects with relapsed/refractory MM, this study showed lower rates of hematologic TEAEs and a longer median PFS than previously reported in subjects with more than 1 prior line of therapy (*San Miguel et al 2013; Richardson et al 2014*).

The planned dose of pomalidomide in this study will be 4 mg orally on Days 1-21 of each 28-day cycle in combination with low-dose dexamethasone (40 mg/day on Days 1, 8, 15, and 22, orally). This is the approved dose and schedule of pomalidomide, as well as the same dose and scheduled used in the MMY1001 study.

Rationale for Daratumumab Subcutaneous Dose Selection

Dara IV infusion requires a large volume (500 mL to 1000 mL) of infusate, resulting in a median infusion time of 7 hours for the first infusion. Subsequent infusions are approximately 3 to 4 hours. To shorten the infusion time and decrease the risk of IRRs, daratumumab is combined with a technology based on an rHuPH20 to facilitate SC administration. rHuPH20 is the active ingredient of the commercial product Hylenex® recombinant (hyaluronidase human injection), which was approved for use in the US in December 2005. Daratumumab has been administered in combination with rHuPH20 in a Phase 1 study (see *Section 2.1.2*).

The maximum trough concentration (C3D1 C_{trough}) was defined as the daratumumab effective concentration based on exposure-ORR analyses from the historical IV monotherapy data. In Study MMY1004, the fixed dose for the SC infusion of 1800 mg was selected from Part 1 of the study based on cumulative review of pharmacokinetics and safety data. Similar or greater maximum trough concentrations (C3D1 C_{trough}) were observed following administration of 1800 mg Dara MD compared to 16 mg/kg IV daratumumab when administered on the same dose schedule (weekly [QW] for 8 weeks, then every 2 weeks [Q2W] for an additional 16 weeks, then every 4 weeks [Q4W] thereafter). Preliminary data following administration of 1800 mg Dara CF in Part 2 of the study also supported selection of this dose level, indicating the dose is sufficient to produce a similar or greater maximum trough concentration compared with 16 mg/kg IV. Daratumumab exhibits a wide therapeutic window and there is no apparent relationship between drug exposure in the therapeutic dose range and AEs of interest, which also supports the feasibility of utilizing a fixed-dose approach in SC administration.

2.3 POTENTIAL RISKS AND BENEFITS

2.3.1 Known Potential Risks

Daratumumab

As of 30 June 2016, 3,147 subjects have been enrolled in studies using daratumumab via intravenous (IV) infusions; 762 subjects received daratumumab alone and 2,385 subjects received daratumumab in combination with other drugs used to treat MM. Given that daratumumab is not approved in Europe for the indication under study, not all the possible side effects and risks related to daratumumab are known and new side effects may occur. A description of the events observed when daratumumab was given via an IV infusion in combination with other drugs is provided below (see also *Daratumumab IB*).

Daratumumab IV Combination Studies

The safety profile of daratumumab in combination with standard background regimens (bortezomib, lenalidomide, pomalidomide, dexamethasone, melphalan, prednisone, thalidomide, carfilzomib) is consistent with those of the background regimens and single-agent daratumumab.

Among the 318 subjects treated with 16 mg/kg of daratumumab in combination with lenalidomide and dexamethasone in Study MMY3003 and Phase 2 of Study GEN503:

- Treatment-emergent adverse events (TEAE) leading to discontinuation of study treatment were reported in 27 subjects (9%).
- Seventeen subjects (5%) died within 30 days of last dose due to an AE.
- The most frequently reported TEAEs (reported in ≥25% of subjects) were neutropenia (63%), diarrhea (48%), fatigue (36%), anemia (33%), cough (32%), upper respiratory tract infection (32%), muscle spasms (30%), constipation (29%), thrombocytopenia (28%), nasopharyngitis (27%), and nausea (26%). No TEAEs of tumor lysis syndrome, hemolysis, or transfusion reaction were reported.
- Serious adverse events (SAEs) were reported in 174 subjects (55%); the most frequently reported SAEs were pneumonia (9%), influenza (4%), febrile neutropenia (4%), pyrexia (3%), bronchitis (3%), pulmonary embolism (3%), lower respiratory tract infection (2%), and diarrhea (2%).
- Grade 3 or 4 TEAEs were reported in 267 subjects (84%); the most frequently reported Grade 3 or 4 TEAEs were neutropenia (56%), anemia (14%), and thrombocytopenia (14%).
- Infections or infestations were reported in 87% of subjects. The most frequently reported were upper respiratory tract infection (32%), nasopharyngitis (27%), bronchitis (17%), pneumonia (15%), and respiratory tract infection (11%).

Among the 243 subjects treated in Study MMY3004 with daratumumab in combination with bortezomib and dexamethasone:

- Treatment-emergent adverse events leading to discontinuation of study treatment were reported in 22 subjects (9%).
- Fourteen deaths (6%) were reported within 30 days after the last dose. Twelve subjects died due to TEAEs and 2 subjects died due to disease progression.
- The most frequently reported TEAEs (reported in ≥25% of subjects) were thrombocytopenia (60%), peripheral sensory neuropathy (49%), diarrhea (34%), upper respiratory tract infection (30%), anemia (28%), and cough (27%).
- Serious adverse events were reported in 118 subjects (49%); the most frequently reported were pneumonia (21 subjects; 9%), anemia, bronchitis, thrombocytopenia, atrial fibrillation, upper respiratory tract infection (3% each), and pyrexia (2%).
- Grade 3 or 4 TEAEs were reported in 193 subjects (79%); the most frequently reported Grade 3 or 4 TEAEs were thrombocytopenia (45%), anemia (15%), and neutropenia (13%).
- Infections or infestations were reported in 73% of subjects. The most frequently reported were upper respiratory tract infection (30%), pneumonia (14%), and bronchitis (13%).

Infusion-Related Reactions (IRR)

Infusion-related reactions were reported in approximately half of all subjects treated with daratumumab and usually occurred with the first infusion and during or within the first few hours of the start of the infusion. Signs and symptoms of IRRs may include respiratory symptoms, such as stuffy nose, cough, throat irritation, as well as chills, vomiting, and nausea. Less common symptoms are difficulty breathing (wheezing), runny nose, fever, chest discomfort, itching, hypotension, or hypertension. Most of the observed IRRs were mild or moderate, and ended by temporarily stopping the infusion and by providing medication. Severe reactions have occurred including bronchospasm, hypoxia, dyspnea, hypertension, and laryngeal and pulmonary edema. See *Section 6.1.5* for information regarding the management of IRRs and

Section 7.3.1 and *Section 7.3.2* for recommendations concerning the use of pre- and post-infusion medication, respectively.

Daratumumab for Subcutaneous Injection (Dara MD and Dara SC)

Study MMY1004 is a Phase 1b study to assess the safety and pharmacokinetics of SC administration of daratumumab. In Part 1 of this study, a mix and-deliver SC presentation (Dara MD) of the currently approved daratumumab IV formulation was used: rHuPH20 and daratumumab were mixed just prior to delivery. Up to 90 mL of Dara MD was administered SC weekly for 8 weeks, every 2 weeks for 16 weeks, and then every 4 weeks thereafter. Subjects in Part 2 of this study receive the final formulation of daratumumab for SC administration in which daratumumab has been co-formulated with recombinant human hyaluronidase (rHuPH20 [referred to as Dara CF or Dara SC in this protocol]). Dara CF is supplied as a single, pre-mixed vial (120 mg/mL daratumumab containing 30,000 U rHuPH20, 15 mL injection volume for an 1800 mg dose level). It is administered at 1800 mg following the same schedule as Dara MD and can be administered in 3 to 5 minutes by manual SC injection in the periumbilical area of the abdominal wall.

Preliminary data from this study show that SC administration is feasible and has a substantially shortened administration time compared with standard IV administration. Fifty-three (53) subjects who received Dara MD (1200 mg [n=8]; 1800 mg [n=45]) between November 2015 and August 2016 were evaluable for safety and efficacy. Treatment-emergent adverse events for Dara MD in this study appeared to be similar to those reported in single-agent studies of Dara IV (*Lokhorst 2015; Lonial 2016*). After a median treatment duration of 2.6 months (range 0.7-12) for the 1200 mg cohort and 3.4 months (range 0.7-8.6) for the 1800 mg cohort, the key safety findings are as follows:

For subjects receiving Dara MD, the incidence of all-grade IRRs was 13% and 24% in the 1200 mg and 1800 mg cohorts, respectively).

- IRRs were mostly Grade 1 or 2 and included chills, pyrexia, non-cardiac chest pain, edema of the tongue, nausea, vomiting, dyspnea, wheezing, flushing, hypertension, hypotension, oropharyngeal pain, rash, paresthesia and pruritus. Only 1 subject (in the 1200 mg cohort) developed Grade 3 dyspnea; no Grade 4 IRR was reported in either cohort.
- All IRRs developed during or within 6 hours of the start of the first Dara MD infusion and were controlled with antihistamine, corticosteroid, or bronchodilator treatment and did not result in treatment discontinuation. No IRRs were reported on subsequent infusions.
- The most frequently reported TEAEs (>20% of all subjects) were upper respiratory tract infection (1200 mg: 38%; 1800 mg: 22%), insomnia (1200 mg: 38%; 1800 mg: 11%), decreased appetite (1200 mg: 38%; 1800 mg: 7%), thrombocytopenia (1200 mg: 38%; 1800 mg: 18%), viral upper respiratory tract infection (1200 mg: 25%; 1800 mg: 13%), vomiting (1200 mg: 25%; 1800 mg: 13%), hyperuricaemia (1200 mg: 25%; 1800 mg: 2%), hypokalaemia (1200 mg: 25%; 1800 mg: 4%), blood creatinine increased (1200 mg: 25%; 1800 mg: 4%), anemia (1200 mg: 25%; 1800 mg: 33%), fatigue (1200 mg: 25%; 1800 mg: 20%) pyrexia (1200 mg: 25%; 1800 mg: 27%), diarrhea (1200 mg: 25%; 1800 mg: 22%), headache (1200 mg: 25%; 1800 mg: 18%), cough (1200 mg: 25%; 1800 mg: 13%), epistaxis (1200 mg: 25%; 1800 mg: 4%), hypertension (1200 mg: 25%; 1800 mg: 7%), rhinitis allergic (1200 mg: 25%; 1800 mg: 2%), nasal congestion (1200 mg: 25%; 1800 mg: 2%), rectal hemorrhage (1200 mg: 25%; 1800 mg: 0%), and asthenia (1200 mg: 13%; 1800 mg: 20%).
- Grade 3 or 4 TEAEs were reported in 63% and 49% of subjects in the 1200 mg and 1800 mg cohorts, respectively. By comparison, Grade 3 or 4 TEAEs were reported in 57% of subjects in single-agent studies of Dara IV 16 mg/kg.

Preliminary safety data for 25 subjects in Part 2 treated with at least 1 dose Dara CF (also referred to as Dara SC), administered subcutaneously as of the clinical data cutoff (03 August 2017) are presented below:

The most frequently reported TEAEs (≥3 [12%] subjects) were lymphopenia (32%); thrombocytopenia, pyrexia, fatigue, asthenia, back pain, nausea, headache, insomnia (16% each); and leukopenia, anemia, chills, and diarrhea (12% each).

Grade 3 or 4 TEAEs were experienced by 9 (36%) of the 25 subjects. The most frequently reported Grade 3 or 4 TEAEs (≥2 [8%] subjects) were lymphopenia (16%) and thrombocytopenia (8%). No subject discontinued study treatment due to a TEAE.

SAEs were experienced by 2 (8%) of the 25 subjects. The SAEs were pyrexia, asthenia, fatigue, hyponatremia, febrile neutropenia, leukopenia, and thrombocytopenia.

No deaths were reported during the Treatment Phase for subjects receiving Dara CF 1800 mg SC.

Two (8%) of the 25 subjects receiving Dara CF 1800 mg had treatment-emergent IRRs as assessed by the investigator. The events were chills, dyspnea, and allergic rhinitis. The IRRs occurred during Cycle 1 Day 1, were Grade 1 or 2, and did not require treatment modifications. None of the IRRs reported were considered SAEs.

Adverse events in relation to SC injection in the periumbilical area were reported in 3 of 25 subjects treated with Dara CF and consisted of Grade 1 injection-site discoloration/injection-site induration (although no measurable induration was reported in this subject), Grade 1 hematoma, and Grade 1 erythema.

The preliminary safety and pharmacokinetics data from Study MMY1004 Part 2 support the 1800 mg Dara SC dose selection for Phase 3 studies. The pharmacokinetic data indicate that an 1800 mg dose of Dara SC would be anticipated to result in a similar or greater Cycle 3 Day 1 trough concentration (C3D1 C_{trough}) compared to 16 mg/kg IV administration. The variability in C3D1 C_{trough} for an1 800 mg Dara SC appeared to be similar to the 16 mg/kg IV dose and the 1800 mg Dara MD dose with a %CV of 46% to 58% across these groups. The C_{max} after the last weekly dose of 1800 mg Dara SC remained within the range observed for the 1800 mg Dara MD and 16 mg/kg IV (C3D1 C_{max}) cohort from Study MMY2002. Study MMY1004 Part 2 also showed that Dara SC can be administered by manual injection with a median of 5 minutes (ranging from 2 to 11 minutes) and it is associated with low incidence of IRRs (overall incidence of 8% without Grade 3 or 4 events). The overall safety profile for the Dara SC cohort is similar to prior experience with daratumumab IV administration and subcutaneous administration with Dara MD. There are no new safety signals with the Dara SC administration.

For further details and the most up to date information about Study MMY1004, refer to the Investigator's Brochure.

Pomalidomide

The most commonly reported adverse reactions in clinical studies have been Blood and Lymphatic System Disorders including anemia (45.7%), neutropenia (45.3%), and thrombocytopenia (27%); in General Disorders and Administration Site Conditions including fatigue (28.3%), pyrexia (21%) and edema peripheral (13%); and in Infections and Infestations including pneumonia (10.7%). Peripheral neuropathy adverse reactions were reported in 12.3% of subjects, and venous embolic or thrombotic (VTE) adverse reactions were reported in 3.3% of subjects. The most commonly reported Grade 3 or 4 adverse reactions

were in the Blood and Lymphatic System Disorders including neutropenia (41.7%), anemia (27%), and thrombocytopenia (20.7%); in Infections and Infestations including pneumonia (9%); and in General Disorders and Administration Site Conditions including fatigue (4.7%), pyrexia (3%), and edema peripheral (1.3%). The most commonly reported serious adverse reaction was pneumonia (9.3%). Other serious adverse reactions reported included febrile neutropenia (4.0%), neutropenia (2.0%), thrombocytopenia (1.7%), and VTE adverse reactions (1.7%).

Adverse reactions tended to occur more frequently within the first 2 cycles of treatment.

Pomalidomide is an analog of thalidomide. Thalidomide is a known human teratogen that causes severe life-threatening human birth defects. If pomalidomide is taken during pregnancy, it may cause birth defects or death to an unborn baby.

Daratumumab in combination with pomalidomide and dexamethasone

The following events occurred among the 103 subjects treated in Study MMY1001 with daratumumab in combination with pomalidomide and dexamethasone:

- Treatment-emergent adverse events leading to discontinuation of study treatment were reported in 15 subjects (15%).
- Nine deaths (9%) were reported during study treatment or within 30 days after the last dose. Six subjects died due to TEAEs; 2 subjects died due to disease progression; and 1 subject died due to unknown reason.
- The most frequently reported TEAEs (reported in ≥25% of subjects) were neutropenia (80%), anemia (54%), fatigue (52%), diarrhea (43%), thrombocytopenia (42%), cough (38%), dyspnea (32%), pyrexia (30%), leukopenia (37%), constipation (34%), nausea (31%), upper respiratory tract infection (28%), back pain (28%), and muscle spasms (27%).
- Serious adverse events were reported in 55 subjects (53%); the most frequently reported were pneumonia (9%), sepsis and febrile neutropenia (5% each), fall (4%), and anemia and dyspnea (3% each).
- Grade 3 or 4 TEAEs were reported in 102 subjects (99%). The most frequently reported Grade 3 or 4 TEAEs were neutropenia (77%), anemia (28%), thrombocytopenia (19%), lymphopenia (14%), and fatigue (12%).
- Infections or Infestations were reported in 72% of subjects. The most frequently reported were upper respiratory tract infection (28%), pneumonia (15%), sinusitis (14%), and bronchitis (12%).

2.3.2 Known Potential Benefits

The prognosis of MM patients who become refractory to lenalidomide and bortezomib is very poor, indicating the need for new therapeutic strategies for these patients. Daratumumab has already shown marked activity as a monotherapy in heavily pre-treated patients. Its approval by the FDA in November 2016 when used in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, highlights the potential clinical benefit of daratumumab as a backbone therapy for the treatment of patients with MM who have received at least 1 prior therapy. The combination of daratumumab with pomalidomide, a third-generation IMiD drug, is also likely to provide clinical benefits to patients with relapsed or refractory MM.

Several other protein therapeutics are approved for SC administration in combination with rHuPH20. Study MMY1004 provided preliminary efficacy data which suggest that, in this patient population, SC administration of Dara MD (an "intermediate formulation" that is a solution that requires mixing of the daratumumab drug product with rHuPH20 prior to delivery) may enable comparable or better response rates compared with Dara IV. Furthermore, to date, the rate of IRRs with SC administration of Dara MD has been substantially lower than the rate reported with Dara IV. The final SC daratumumab, Dara SC, which will be used in Study MMY3013 is a co-formulated drug product intended for a fixed-dose administration, containing rHuPH20 and daratumumab in a single vial and will offer several tangible benefits for both patients and health care providers as described above.

3 OBJECTIVES AND PURPOSE

The purpose of this study is to evaluate the effects of the addition of daratumumab to pomalidomide and dexamethasone in subjects with relapsed or refractory MM.

3.1 PRIMARY OBJECTIVE

The primary objective of this study is to compare PFS between treatment arms.

3.2 SECONDARY OBJECTIVES

The secondary objectives of the study are the following:

- To compare ORRs between treatment arms.
- To compare DoR between treatment arms.
- To compare time to next therapy between treatment arms.
- To compare OS between treatment arms.
- To assess the safety and tolerability of the investigational combination treatment.
- To assess the depth of response by analyzing MRD negativity rate for CR or better and for suspected CR/sCR.
- To compare health-related quality-of-life (HRQoL) and health utility between treatment arms.
- To evaluate the immunomodulatory effects of daratumumab on T cells.
- To evaluate daratumumab pharmacokinetics and immunogenicity and the immunogenicity of rHuPH20.

4 STUDY DESIGN AND ENDPOINTS

4.1 DESCRIPTION OF THE STUDY DESIGN

This is a multicenter, Phase 3, randomized, open-label study comparing daratumumab, pomalidomide and low-dose dexamethasone (DaraPomDex) with pomalidomide and low-dose dexamethasone (PomDex) in subjects with relapsed or refractory MM who have received at least 1 prior treatment regimen with both lenalidomide and a PI and have demonstrated disease progression. The original design of this study was to treat subjects with daratumumab for IV infusion (Dara IV); however, as of Protocol Amendment 1, all new subjects will now be dosed subcutaneously with daratumumab co-formulated with recombinant human hyaluronidase rHuPH20 (Dara SC). Subjects who already began treatment with Dara IV (ie, prior to Amendment 1) will have the option to switch to Dara SC on Day 1 of any cycle starting with Cycle 3 or later. It is to be noted that throughout this document, text was added to highlight any differences between Dara IV and Dara SC dosing; and where there is no clarification, it is implied that the descriptions are the same for both Dara IV and Dara SC.

Approximately 302 subjects will be randomized in a 1:1 ratio to receive either daratumumab + pomalidomide + dexamethasone (DaraPomDex) or pomalidomide + dexamethasone (PomDex). Subjects who already began treatment with Dara IV prior to Amendment 1 will be allowed to switch to subcutaneous administration of daratumumab on Day 1 of any cycle starting with Cycle 3 or later for the remainder of their participation in the study, and they will be counted toward the total of 302 subjects. Treatment cycles have a duration of 28 days.

Pomalidomide will be administered at full dose of 4 mg orally (PO) on Days 1 through 21 of each 28-day cycle.

Daratumumab will be given at a dose of 16 mg/kg administered as an IV infusion (Dara IV) or 1800 mg subcutaneously (Dara SC) at weekly intervals (QW) for 8 weeks, then every 2 weeks (Q2W) for an additional 16 weeks, then every 4 weeks (Q4W) thereafter. Subjects will receive pre-infusion medications before infusions to mitigate potential IRRs.

Dexamethasone will be administered according to standard clinical practice and at a recommended total dose of 40 mg weekly for both treatment groups (20 mg weekly for subjects ≥75 years of age).

Subjects will receive treatment until disease progression or unacceptable toxicity.

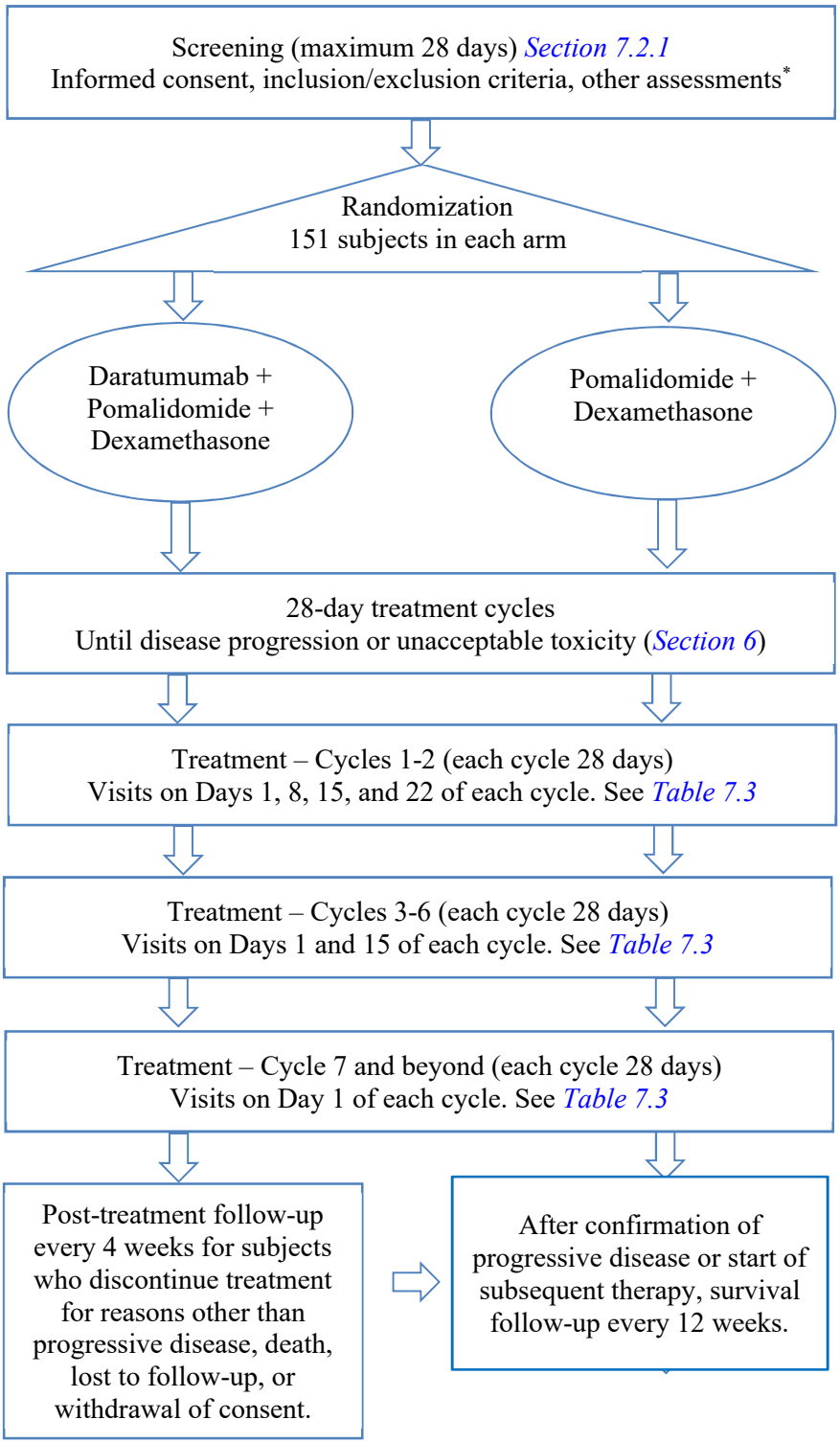
Drug administration and follow-up visits will occur more frequently for early cycles (eg, weekly or bi-weekly) (see *Table 7.3*). Disease evaluations will occur every cycle and consist mainly of measurements of myeloma proteins. Other parameters may include bone marrow examinations, skeletal surveys, assessment of extramedullary plasmacytomas, and measurements of serum calcium corrected for albumin. Patient reported outcome measures will be administered on Day 1 of each treatment cycle, prior to receiving treatment or any other assessment. The schedule of assessments will be adjusted for subjects remaining on study after the positive primary analysis and is detailed in *Section 7.2.4*. A schedule of assessments is provided in *Appendix 12* (and detailed in *Table 7.3*) for subjects continuing on study treatment after the CCO for the final OS analysis.

Assessment of myeloma response and disease progression will be conducted in accordance with the modified IMWG response criteria.

Survival status, subsequent anti-myeloma treatment data, and PRO measures will continue to be collected post-treatment.

The primary analysis of PFS will occur after 188 PFS events have been observed. Long-term survival follow-up and data collection will continue until approximately 166 deaths have been observed or 5 years after the last subject is randomized, whichever occurs earlier. Subjects benefiting from the study treatment can continue to receive study treatment after the CCO for the final OS analysis. For these subjects, study treatment will be available through continued access within the current study until it is available through another source such as commercial availability with reimbursement, continued access through a long-term extension study, a patient access program, or after the last subject transitions into the long-term extension phase of the study up to 30 September 2024, whichever occurs first.

Figure 4.1: Study Design



*The schedule of assessments will be adjusted for subjects remaining on the study after the positive primary analysis and is detailed in *Section 7.2.4*. A schedule of assessments is provided in *Appendix 12* (and detailed in *Table 7.3*) for subjects continuing on study treatment after the CCO for the final OS analysis.

4.2 ENDPOINTS

4.2.1 Primary Endpoint

- Progression free survival

4.2.2 Secondary Endpoints

- Overall response rate
- VGPR or better
- Complete response (CR) or better
- MRD negativity rate
- Time to response
- Duration of response (DoR)
- Time to next therapy
- Overall survival
- Safety (adverse events)
- Scale and domain scores of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 item (EORTC QLQ-C30) (global health status, physical functioning, emotional functioning, fatigue, pain) and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Multiple Myeloma Module (EORTC QLQ-MY20) (disease symptoms, side effects of treatment)
- European Quality of Life Five Dimensions Questionnaire (EQ-5D-5L) health utility values
- Immunomodulatory effects of daratumumab on T cells
- Daratumumab pharmacokinetic concentrations (Dara IV and Dara SC)
- Daratumumab and rHuPH20 immunogenicity in subjects who receive Dara SC

5 STUDY ENROLLMENT AND WITHDRAWAL

All criteria MUST be met to be included in the study.

5.1 SUBJECT INCLUSION CRITERIA

1. Males and females at least 18 years of age.
2. Voluntary written informed consent before performance of any study-related procedure.
3. Subject must have measurable disease of MM as defined by the criteria below:

    - IgG multiple myeloma: Serum M-protein level ≥1.0 g/dL or urine M-protein level ≥200 mg/24 hours, or
    - IgA, IgD, IgE, IgM multiple myeloma: Serum M-protein level ≥0.5 g/dL or urine M-protein level ≥200 mg/24 hours, or
    - Light chain multiple myeloma, for subjects without measurable disease in the serum or urine: Serum immunoglobulin FLC ≥10 mg/dL and abnormal serum immunoglobulin kappa lambda FLC ratio.

4. Subjects must have received prior anti-myeloma treatment. The prior treatment must have included both a PI- and lenalidomide-containing regimens. The subject must have had a response (ie, PR or better based on the investigator's determination of response as defined by the modified IMWG criteria) to prior therapy.
5. Subjects must have documented evidence of PD based on the investigator's determination of response as defined by the modified IMWG criteria on or after the last regimen.
6. Subjects who received only 1 line of prior treatment must have demonstrated PD on or within 60 days of completion of the lenalidomide-containing regimen (ie, lenalidomide refractory).
7. Eastern Cooperative Oncology Group (ECOG) performance status score of ≤2.
8. Willingness and ability to participate in study procedures.
9. For subjects experiencing toxicities resulting from previous therapy, the toxicities must be resolved or stabilized to ≤Grade 1.
10. All of the following laboratory test results during Screening:

a) Absolute neutrophil count ≥1.0 × 10^9/L;
b) Hemoglobin level ≥7.5 g/dL (≥4.65 mmol/L) (transfusions are not permitted to reach this level);
c) Platelet count ≥75 × 10^9/L in subjects in whom <50% of bone marrow nucleated cells are plasma cells and platelet count ≥50 x 10^9/L in subjects in whom ≥50% of bone marrow nucleated cells are plasma cells (transfusions are not permitted to reach this level);
d) Alanine aminotransferase (ALT) level ≤2.5 times the upper limit of normal (ULN);
e) Aspartate aminotransferase (AST) level ≤2.5 x ULN;
f) Total bilirubin level ≤1.5 x ULN, (except for Gilbert Syndrome: direct bilirubin ≤1.5 × ULN);
g) Creatinine clearance ≥30 mL/min (Appendix 6);
h) Serum calcium corrected for albumin ≤14.0 mg/dL (≤3.5 mmol/L), or free ionized calcium ≤6.5 g/dL (≤1.6 mmol/L).

11. Criterion (letter "g") modified per Amendment 2:

11.1 Reproductive Status

a) Women of childbearing potential (WOCBP) must have 2 negative serum or urine pregnancy tests, one 10-14 days prior to start of study treatment and one within 24 hours prior to the start of study treatment. Females are not of reproductive potential if they have been in natural menopause for at least 24 consecutive months, or have had a hysterectomy and/or bilateral oophorectomy.
b) Women must not be breastfeeding.
c) WOCBP must agree to follow instructions for methods of contraception for 4 weeks before the start of study treatment, for the duration of study treatment, and for 3 months after cessation of daratumumab or 4 weeks after cessation of pomalidomide, whichever is longer.
d) Males who are sexually active must always use a latex or synthetic condom during any sexual contact with females of reproductive potential, even if they have undergone a successful vasectomy. They must also agree to follow instructions for methods of contraception for 4 weeks before the start of study treatment, for the duration of study treatment, and for a total of 3 months post-treatment completion.
e) Male subjects must not donate sperm for up to 90 days post-treatment completion.
f) Female subject must not donate eggs for up to 90 days post-treatment completion.
g) Azoospermic males and WOCBP who are not heterosexually active are exempt from contraceptive requirements. However, WOCBP will still undergo pregnancy testing as described in this section.

Highly effective methods of contraception have a failure rate of <1% when used consistently and correctly. Subjects must agree to the use of 2 methods of contraception, with 1 method being highly effective and the other method being additionally effective.

Because of the embryo-fetal risk of pomalidomide, all subjects must adhere to the pomalidomide pregnancy prevention program applicable in their region. Investigators should comply with the local label for pomalidomide for guidance on subject education and ensure that all subjects adhere to the local Pomalidomide Risk Evaluation Mitigation Strategy (REMS) program. When no local pomalidomide REMS program exists, subjects must adhere to the pomalidomide Global Pregnancy Prevention Plan.

5.2 SUBJECT EXCLUSION CRITERIA

1. Previous therapy with any anti-CD38 monoclonal antibody.
2. Previous exposure to pomalidomide.
3. Subject has received anti-myeloma treatment within 2 weeks or 5 pharmacokinetic half-lives of the treatment, whichever is longer, before the date of randomization. The only exception is emergency use of a short course of corticosteroids (equivalent of dexamethasone 40 mg/day for a maximum of 4 days) for palliative treatment before Cycle 1, Day 1 (C1D1).
4. Previous allogenic stem cell transplant; or autologous stem cell transplantation (ASCT) within 12 weeks before C1D1.
5. History of malignancy (other than MM) within 3 years before the date of randomization (exceptions are squamous and basal cell carcinomas of the skin, carcinoma in situ of the cervix or breast, or other non-invasive lesion that in the opinion of the investigator, with concurrence with the Sponsor's medical monitor, is considered cured with minimal risk of recurrence within 3 years).
6. Clinical signs of meningeal involvement of MM.
7. Chronic obstructive pulmonary disease (COPD) with a Forced Expiratory Volume in 1 second (FEV1) <50% of predicted normal. Note that FEV1 testing is required for subjects suspected of having COPD and subjects must be excluded if FEV1 <50% of predicted normal. (Appendix 4).
8. Clinically significant cardiac disease, including:
   a) Myocardial infarction within 6 months before C1D1, or unstable or uncontrolled condition (eg, unstable angina, congestive heart failure, New York Heart Association Class III-IV).
   b) Cardiac arrhythmia (Common Terminology Criteria for Adverse Events [CTCAE] Grade 3 or higher) or clinically significant electrocardiogram (ECG) abnormalities.
   c) Electrocardiogram showing a baseline QT interval as corrected QTc >470 msec.
9. Criterion modified per Amendment 2:
   9.1 Known:
   a) Active hepatitis A
   b) To be seropositive for hepatitis B (defined by a positive test for hepatitis B surface antigen [HBsAg]). Subjects with resolved infection (ie, subjects who are positive for antibodies to hepatitis B core antigen [antiHBc] and/or antibodies to hepatitis B surface antigen [antiHBs]) must be screened using real-time polymerase chain reaction (PCR) measurement of hepatitis B virus (HBV) DNA levels. Those who are PCR positive will be excluded. EXCEPTION: Subjects with serologic findings suggestive of HBV vaccination (antiHBs positivity as the only serologic marker) AND a known history of prior HBV vaccination, do not need to be tested for HBV DNA by PCR.
   c) To be seropositive for hepatitis C (except in the setting of a sustained virologic response, defined as aviremia at least 12 weeks after completion of antiviral therapy).

10. Criterion Revised per Amendment 2
    10.1 Known to be seropositive for human immunodeficiency virus.
11. Gastrointestinal disease that may significantly alter the absorption of pomalidomide.
12. Subject has plasma cell leukemia (>2.0 × 10^9/L circulating plasma cells by standard differential) or Waldenström's macroglobulinemia or POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes) or amyloidosis.
13. Any concurrent medical or psychiatric condition or disease (eg, active systemic infection, uncontrolled diabetes, acute diffuse infiltrative pulmonary disease) that is likely to interfere with the study procedures or results or that, in the opinion of the investigator, would constitute a hazard for participating in this study.
14. Ongoing ≥Grade 2 peripheral neuropathy.
15. Subject had ≥Grade 3 rash during prior therapy.
16. Subject has had major surgery within 2 weeks before randomization, or has not fully recovered from an earlier surgery, or has surgery planned during the time the subject is expected to participate in the study or within 2 weeks after the last dose of study drug administration. Note: subjects with planned surgical procedures to be conducted under local anesthesia may participate. Kyphoplasty or vertebroplasty are not considered major surgery.
17. Pregnant or nursing women.
18. Subject has known allergies, hypersensitivity, or intolerance to any of the study drugs, hyaluronidase, monoclonal antibodies, human proteins, or their excipients (refer to daratumumab IB), or known sensitivity to mammalian-derived products.
19. Subject was vaccinated with live vaccines within 4 weeks prior to randomization.

Sponsor will review and approve (through eCRF) the subject eligibility data submitted by the investigational site before randomization.

5.3 SUBJECT WITHDRAWAL OR TERMINATION

5.3.1 REASONS FOR WITHDRAWAL OR TERMINATION

Every subject has the right to discontinue study participation at any time, for any reason, and every subject may be discontinued from the study for any reason beneficial to his/her well-being.

Subjects MUST discontinue investigational product(s) for any of the following reasons:

- Withdrawal of informed consent.
- Any AE, laboratory abnormality or intercurrent illness that, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject.
- Pregnancy.
- Progressive disease.
- Subjects experiencing angioedema, Grade 4 rash, exfoliative or bullous rash, Stevens-Johnson syndrome, or toxic epidermal necrolysis related to pomalidomide.
- Grade 4 IRRs to daratumumab (see *Section 6.1.5*).
- When the study ends/is terminated.

For subject whose daratumumab treatment is discontinued, they may continue to receive pomalidomide/dexamethasone. For subjects whose pomalidomide/dexamethasone treatment is discontinued, daratumumab treatment may be continued.

5.3.2 HANDLING OF SUBJECT WITHDRAWALS OR TERMINATION

All subjects, except those who withdraw consent, will be followed up according to the study procedures. Subjects should be encouraged to continue participation in the study until determination of disease progression. Those who discontinue study therapy before progression should allow the collection of necessary central laboratory results until disease progression criteria are fulfilled. If the study treatment is discontinued prior to disease progression, the reason for the discontinuation must be documented in the electronic case report form (eCRF).

If lost to follow-up, the investigator should contact the subject or a relative by telephone followed by registered mail or through a personal visit to establish as completely as possible the reason for the withdrawal.

5.4 PREMATURE TERMINATION OR SUSPENSION OF STUDY

The study can be terminated for any reason and at any time by the Sponsor. Should this be necessary, the subject should be seen as soon as possible and treated as a prematurely withdrawn subject. All measures will be adopted to ensure the safeguarding of the subject's interests.

6 STUDY TREATMENT

6.1 STUDY TREATMENTS AND CONTROL DESCRIPTION

6.1.1 Formulation, Appearance, Packaging, and Labeling

This is an open-label study. Daratumumab, pomalidomide, and dexamethasone (study treatments) may be supplied by the Sponsor and are packaged and labeled as applicable and in compliance with health authority requirements.

6.1.2 Product Storage and Stability

Investigational treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designees have access. Upon receipt, all investigational treatment should be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol. Medication labels will be in the local language and comply with the legal requirements of each country.

Daratumumab vials should be stored at 2°-8° C in its original package to protect from light. Pomalidomide and oral dexamethasone do not require any special storage conditions.

6.1.3 Preparation

The Dara IV product is to be prepared according to the instructions in the Summary of Product Characteristics (SmPC) and the Daratumumab IV Pharmacy Manual, and the Dara SC product will be prepared according to the Investigational Product Preparation Instructions provided in the Daratumumab SC Pharmacy Manual.

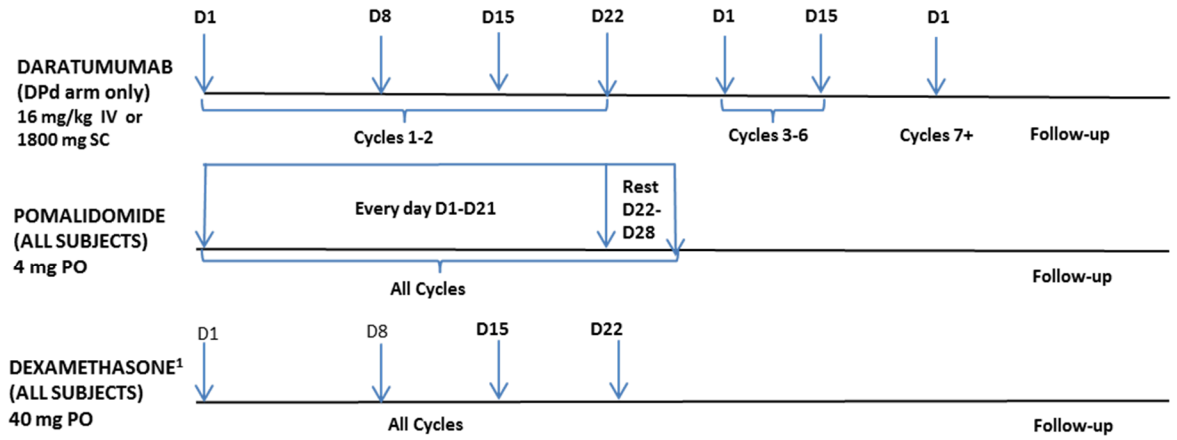
Dara SC will be provided as a fixed dose, combination drug product containing rHuPH20 drug substance (2000 U/mL) and daratumumab drug substance (120 mg/mL) in a single vial.

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

6.1.4 Dosing and Administration

Table 6.1 shows dosing and administration of daratumumab, pomalidomide and dexamethasone. See section below for details.

Table 6.1: Dosing and Administration



1. On days when daratumumab is administered, dexamethasone will be administered to subjects in DPd arm in the clinic and will serve as the treatment dose of steroid as well as the required pre-medication prior to daratumumab infusion. Note 20 mg PO weekly for subjects ≥75 years of age.

- Daratumumab

Daratumumab will be given at a dose of 16 mg/kg administered as an IV infusion (Dara IV) or 1800 mg subcutaneously (Dara SC) at weekly intervals (QW) for 8 weeks, then every 2 weeks (Q2W) for an additional 16 weeks, then every 4 weeks (Q4W) thereafter. See *Section 6.1.5* for guidelines for the IV/SC infusion of daratumumab and *Section 7.3.1* for pre-infusion medications and *Section 7.3.2* for post-infusion medications to be given to mitigate potential IRRs and the management of these reactions.

Subjects should be monitored throughout the infusion and the post-infusion period.

See the SmPC for more details about daratumumab.

- Pomalidomide

The recommended starting dose of pomalidomide is 4 mg once daily taken orally on Days 1 to 21 of repeated 28-day cycles. Dosing is continued or modified based upon clinical and laboratory findings. Pomalidomide should be taken at the same time each day. The capsules should not be opened, broken, or chewed. This medicinal product should be swallowed whole, preferably with water, with or without food. If the subject forgets to take a dose of pomalidomide on one day, then the subject should take the normal prescribed dose as scheduled on the next day. Subjects should not adjust the dose to make up for a missing dose on previous days.

See the SmPC for more details about pomalidomide.

- Dexamethasone

The recommended dose of dexamethasone is 40 mg (20 mg for patients ≥75 years of age) orally, once daily on Days 1, 8, 15, and 22 of each 28-day treatment cycle. During the weeks when the subject receives daratumumab, half of the dexamethasone dose (20 mg) will be administered on the day of infusion as the pre-infusion medication (IV preferred, see *Section 7.3.1*) and the remaining dose (20 mg PO) will be self-administered by the subject the following day. This applies only for subjects who are taking the full 40 mg dexamethasone dose. The subjects who are taking 20 mg of dexamethasone (≥75 years of age) will receive the entire 20 mg dose as a pre-infusion medication on the day of daratumumab infusion.

See the SmPC for more details about dexamethasone.

6.1.5 Dose Adjustments/Modifications/Delays/Infusion-Related Reaction Management

- Daratumumab (IV)

Infusion reactions may lead to the interruption of daratumumab administration. Pre-infusion medications should be administered prior to treatment to reduce the risk of IRRs (see *Section 7.3.1*).

Following dilution, daratumumab infusion should be administered IV at the appropriate initial infusion rate, as presented in the table below. Incremental escalation of the infusion rate should be considered only if the previous infusion of daratumumab was well tolerated.

Table 6.2: Infusion rates for daratumumab intravenous

	Dilution volume	Initial infusion rate (first hour)	Increments of infusion rate	Maximum infusion rate
First infusion	1,000 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Second infusion[a]	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Subsequent infusions[b]	500 mL	100 mL/hour	50 mL/hour every hour	200 mL/hour

[a] If the subject's first infusion of daratumumab is well tolerated (defined as an absence of >Grade 1 infusion-related reactions during the first 3 hours), the second infusion will be administered as indicated in the table above. If the previous infusion rate is not well tolerated, instructions for the first infusion volume and rate will be used for the second infusion.
[b] If the subject's first 2 infusions of daratumumab are well tolerated (defined as an absence of >Grade 1 infusion-related reactions during a final infusion rate of ≥100 mL/hour), subsequent infusions will be administered as indicated in the table above. If the previous infusion rate is not well tolerated, instructions for the second infusion rate will be followed.

- Infusion-Related Reaction Management for Dara IV

Subjects should be observed carefully during daratumumab infusions. Trained study staff at the clinic should be prepared to intervene in case of an infusion reaction, and resources necessary for resuscitation must be available. Attention to staffing should be considered when multiple subjects will be dosed at the same time. For infusion-related reactions of any grade/severity, immediately interrupt the daratumumab infusion and manage symptoms. Management of infusion reactions may further require reduction in the rate of infusion, or treatment discontinuation of daratumumab.

- Grade 1-2 (mild to moderate): Once reaction symptoms resolve, resume the infusion at no more than half the rate at which the reaction occurred. If the subject does not experience any further reaction symptoms, infusion rate escalation may resume at increments and intervals as appropriate as outlined in *Table 6.2*.
- Grade 3 (severe): Once reaction symptoms resolve, consider restarting the infusion at no more than half the rate at which the reaction occurred. If the subject does not experience additional symptoms, resume infusion rate escalation at increments and intervals as outlined in *Table 6.2*. Repeat the procedure above in the event of recurrence of Grade 3 symptoms. Permanently discontinue daratumumab upon the third occurrence of a Grade 3 or greater infusion-related reaction.
- Grade 4 (life threatening): Permanently discontinue daratumumab treatment.

➢ Daratumumab (SC)

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

➢ Local Injection-Site Reactions

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

➢ Infusion-Related Reaction Management for Dara SC

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

If an IRR develops, then daratumumab administration should be temporarily interrupted. Subjects who experience AEs during daratumumab administration must be treated for their symptoms. Subjects should be treated with acetaminophen, antihistamine, or corticosteroids, as needed. Intravenous saline may be indicated. For bronchospasm, urticaria, or dyspnea, subjects may require antihistamines, oxygen, corticosteroids, or bronchodilators. For hypotension, subjects may require vasopressors. In the event of a life-threatening IRR (which may include pulmonary or cardiac events) or anaphylactic reaction, daratumumab should be discontinued and no additional daratumumab should be administered to the subject.

Infusion-related Reactions of Grade 1 or Grade 2 for Dara SC

If the investigator assesses a Grade 1-2 IRR AE to be related to administration of study drug, then the daratumumab administration should be paused. When the subject's condition is stable, daratumumab administration may be restarted at the investigator's discretion.

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

Infusion-related Reactions of Grade 3 or Higher for Dara SC

For IRR AEs (other than laryngeal edema or bronchospasm) that are Grade 3, the daratumumab administration must be stopped and the subject must be observed carefully until resolution of the AE or until the intensity of the event decreases to Grade 1, at which point the daratumumab administration may be restarted at the investigator's discretion. If the intensity of the AE returns to Grade 3 after restart of the daratumumab administration, then the subject must be withdrawn from daratumumab treatment.

For IRR adverse events that are Grade 4, the daratumumab administration must be stopped and the subject withdrawn from daratumumab treatment.

Recurrent Infusion-related Reactions for Dara SC

If a Grade 3 IRR (or Grade 2 or higher event of laryngeal edema, or a Grade 2 or higher event of bronchospasm) recurs during or within 24 hours after a subsequent daratumumab administration, the daratumumab treatment must be discontinued.

- Daratumumab Dose Delays and Modification

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

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

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

Study treatment should be resumed when the toxicity has resolved to ≤Grade 2. If study drug administration does not commence within the prespecified window of the scheduled administration date (*Table 6.3*), then the dose will be considered a missed dose. Administration may resume at the next planned dosing date. A missed dose will not be made up.

Table 6.3: Daratumumab administration schedule

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

Any dose withholding of more than 28 days due to toxicity will result in permanent discontinuation of daratumumab. Dose withholdings of more than 28 days for other reasons should be discussed with the Sponsor. If a dose delay occurs, then pharmacokinetic and pharmacodynamic assessments should be performed on the actual day of study drug administration, not on the original scheduled administration day.

A study drug dose withheld for more than 3 days from the per-protocol administration date for any reason other than toxicities suspected to be related to daratumumab should be brought to the attention of the Sponsor at the earliest possible time. Subjects missing ≥3 consecutive planned doses of study drug for reasons other than toxicity should be withdrawn from treatment, unless, upon consultation with the Sponsor and the review of safety and efficacy, continuation is agreed upon.

- Pomalidomide

Doses of pomalidomide may be modified/interrupted following hematologic adverse reactions (neutropenia or thrombocytopenia) and for other Grade 3 or 4 adverse reactions judged to be related to the drug.

Pomalidomide interruption or discontinuation should be considered for Grade 2-3 skin rash. Pomalidomide must be discontinued for angioedema, Grade 4 rash, exfoliative or bullous rash and for Stevens-Johnson syndrome/toxic epidermal necrolysis related to pomalidomide, and should not be resumed following discontinuation for these reactions.

Interstitial lung disease (ILD) and related events, including cases of pneumonitis, have been observed with pomalidomide. Careful assessment of subjects with an acute onset or unexplained worsening of pulmonary symptoms should be performed to exclude ILD. Pomalidomide should be interrupted pending investigation of these symptoms and if ILD is confirmed, appropriate treatment should be initiated. Pomalidomide should only be resumed after a thorough evaluation of the benefits and the risks.

Based on the pomalidomide SmPC, subjects should be advised to report febrile episodes promptly. Physicians should observe subjects for signs of bleeding including epistaxis, especially with use of concomitant medicinal products known to increase the risk of bleeding. Complete blood counts should be monitored at baseline, weekly for the first 8 weeks and monthly thereafter. A dose modification may be required. Patients may require use of blood product support and/or growth factors.

If strong inhibitors of CYP1A2 (ie,. ciprofloxacin, enoxacin, and fluvoxamine) are co-administered with pomalidomide, reduce the dose of pomalidomide by 50%.

Instructions for dose interruptions and reductions for pomalidomide related to hematological adverse reactions are outlined in the table below:

Toxicity	**Dose Modification**
• Neutropenia o ANC* <0.5 x 10^9/L or febrile neutropenia (fever ≥38.5° C and ANC <1 x 10^9/L)	Interrupt pomalidomide treatment, follow CBC** weekly.
o ANC return to ≥1 X 10^9/L	Resume pomalidomide at 3 mg daily
o For each subsequent drop <0.5 x 10^9/L	Interrupt pomalidomide treatment
o ANC return to ≥1 X 10^9/L	Resume pomalidomide treatment at 1 mg less than the previous dose.
• Thrombocytopenia o Platelet count <25 x 10^9/L	Interrupt pomalidomide treatment, follow CBC** weekly
o Platelet count return to ≥50 x 10^9/L	Resume pomalidomide treatment at 3 mg daily
o For each subsequent drop <25 x 10^9/L	Interrupt pomalidomide treatment
o Platelet count return to ≥50 x 10^9/L	Resume pomalidomide treatment at 1 mg less than the previous dose

* ANC – Absolute Neutrophil Count, ** CBC Complete Blood Count

To initiate a new cycle of pomalidomide, neutrophil count must be ≥1 X 10^9/L and the platelet count ≥50 x 10^9/L.

In case of neutropenia, the physician should consider the use of growth factors.

For other Grade 3 or 4 adverse reactions judged to be related to pomalidomide, stop treatment and restart treatment at 1 mg less than the previous dose when an adverse reaction has resolved to ≤Grade 2 at the physician's discretion. If adverse reactions occur after dose reductions to 1 mg, then the medicinal product should be discontinued.

Investigators should follow the local label of pomalidomide for the management of interactions with other medical products.

- Dexamethasone

Instructions for dose modifications of dexamethasone are shown in the table below. Refer to this table for recommended dose reductions, and to the dexamethasone package insert, which states that dosage requirements are variable and must be individualized. Note that this table represents suggested dose modifications of dexamethasone, but physician discretion and clinical judgment should prevail.

Dyspepsia = Grade 1-2	Maintain dose and treat with histamine (H2) blockers or equivalent. Decrease by one dose level if symptoms persist.
Dyspepsia ≥3	Interrupt dose until symptoms are controlled. Add H2 blocker or equivalent and decrease one dose level when dose restarted.
Edema ≥Grade 3	Use diuretics as needed and decrease dose by one dose level.
Confusion or mood alteration ≥Grade 2	Interrupt dose until symptoms resolve. When dose restarted decrease dose by one dose level.
Muscle weakness ≥Grade 2	Interrupt dose until muscle weakness ≤Grade 1. Restart with dose decreased by one level.
Hyperglycemia ≥Grade 3	Decrease dose by one dose level. Treat with insulin or oral hypoglycemic agents as needed
Acute pancreatitis	Discontinue subject from dexamethasone treatment regimen.
Other ≥Grade 3 dexamethasone-related adverse events	Stop dexamethasone dosing until adverse event resolves to ≤Grade 2. Resume with dose reduced by one level.

Dexamethasone dose reduction levels:
Dose reduction levels (<75 years of age): Starting dose 40 mg; dose level -1 20 mg; dose level-2 10 mg on Days 1, 8, 15 and 22 of each 28-day treatment cycle.
Dose reduction levels (≥75 years of age): Starting dose 20 mg; dose level -1 12 mg; dose level-2 8 mg on Days 1, 8, 15 and 22 of each 28-day treatment cycle.
If recovery from toxicities is prolonged beyond 14 days, then the dose of dexamethasone will be decreased by one dose level.

Investigators should follow the local label of dexamethasone for the management of interactions with other medical products.

6.1.6 Duration of Therapy

Treatment with study drug continues until disease progression, unacceptable toxicity (AE related to study drug), or the subject meets other criteria for discontinuation of study drug outlined in *Section 5.3*.

The Sponsor will ensure that subjects who are benefiting from study treatment can continue to receive study treatment after the CCO for the final OS analysis. For these subjects, study treatment will be available through continued access within the current study until it is available through another source such as commercial availability with reimbursement, continued access through a long-term extension study, a patient access program, or after the last subject transitions into the long-term extension phase of the study up to 30 September 2024, whichever occurs first.

The long-term extension phase of this study will begin at the time of the CCO for the final OS analysis and is intended to provide ongoing access to study treatment for subjects who continue to benefit from such treatment. Certain long-term safety data will continue to be reported for these subjects, as described in *Appendix 12*.

No eCRF data will be collected after the CCO date for the final OS analysis (when approximately 166 deaths have been reported). All eCRF data collected up to this timepoint will be included in the final study analysis and reported in a separate clinical study report.

The investigational sites are requested to notify the Sponsor within 1 working day if a subject has been diagnosed with disease progression (that is also confirmed with a consecutive assessment if based on M-protein/serum FLC levels) and provide documentation of disease progression. The Sponsor's medical monitor will review the data provided to confirm that the IMWG criteria for PD have been met, refer to *Section 7.1.1* (Sponsor Confirmation of Progressive Disease). For subjects continuing the study after the positive primary analysis, notification of PD and approval by the Sponsor is no longer required. Please refer to *Section 7.1.1* (Sponsor Confirmation of Progressive Disease) for updated procedures.

6.2 STUDY TREATMENT ACCOUNTABILITY PROCEDURES

The investigator, or a pharmacist or other appropriate individual who is designated by the investigator, will maintain accurate records of the product's delivery to the study site, the inventory at the site, the use by each subject, and the return to the Sponsor or alternative disposition of unused product(s). Monitoring of drug accountability will be performed by the field monitor during the study conduct and a copy of the final drug accountability and reconciliation log will be provided by the investigator(s) at the completion of the study.

Daratumumab will be administered by qualified staff and the details of each administration will be recorded in the electronic case report form (eCRF).

A diary will be used to assess compliance with the administration of pomalidomide and dexamethasone.

7 STUDY PROCEDURES AND SCHEDULE

Refer to *Appendix 12* for guidance regarding protocol-required procedures/evaluations for subjects continuing on study treatment after CCO for the final OS analysis.

7.1 STUDY PROCEDURES/EVALUATIONS

7.1.1 Efficacy Assessments

The primary endpoint of this study is PFS. Secondary efficacy endpoints are OS, ORR, DoR, and time to next therapy.

Response or disease progression will be assessed by the investigator for treatment decision based on the analysis of serum and urine protein electrophoresis (SPEP and UPEP), serum and urine immunofixation (sIFE and uIFE), serum free light chain protein (sFLC), imaging and bone marrow assessments, per modified IMWG guidelines (Appendix 2). The statistical analysis will use derived response or disease progression based on a validated computer algorithm that has been shown to provide consistent review of the data necessary to determine disease progression and response according to the modified IMWG criteria.

All efficacy laboratory assessments will be collected locally and analyzed centrally unless otherwise indicated in *Table 7.1*. The disease assessments SPEP, UPEP, and serum calcium corrected for albumin should be collected every cycle for the first 14 months of the study and every other month thereafter. After Cycle 1, IFE should only be done when endogenous M-protein is 0 or nonquantifiable. For subjects who are followed by FLC only, these assessments are performed every other cycle after 14 months. If the subject does not have documented disease progression as defined in Appendix 2 at the time of study drug discontinuation, then disease assessments must continue to be performed according to the same schedule

shown in *Table 7.3* until disease progression even if a subsequent anti-myeloma treatment is started prior to disease progression:

- Laboratory analysis for response assessment (SPEP, UPEP, sIFE, uIFE, sFLC)
- Minimal Residual Disease analysis for subjects with suspected CR or better performed by next-generation sequencing according to *Table 7.1* and the Schedule of Events (*Table 7.3*)
- Daratumumab-specific Immunofixation Electrophoresis (DSIFE) for subjects with IgGk sub-type achieving VGPR or better

The following assessments will be carried out at local laboratory, if available, or at the Erasmus laboratory:

- Cytogenetics by means of Fluorescence In Situ Hybridization (FISH) at study entry

Disease assessments will be collected locally and analyzed centrally unless otherwise indicated in *Table 7.1*.

Table 7.1: Disease assessment

M-protein by electrophoresis Serum[1] (SPEP), Urine (UPEP)	Screening and baseline Day 1 of each required cycle End of treatment Post-treatment follow-up every 4 weeks As needed to confirm disease progression
M-protein by immunofixation Serum[1] (sIFE), Urine (uIFE)	Screening and baseline Day 1 of each required cycle End of treatment Post-treatment follow-up every 4 weeks
Serum free light chain sFLC[1]	Screening and baseline Day 1 of each required cycle End of treatment Post-treatment follow-up every 4 weeks As needed to confirm disease progression for subjects with serum FLC only disease
DSIFE (see *Section 7.1.1.3*)	To confirm a VGPR or better in subjects with IgG kappa myeloma when daratumumab interference is suspected based on SPEP- and sIFE results
Clinical assessment of soft tissue plasmacytoma (STP) – to be done locally	Screening and baseline Day 1 of each cycle End of treatment Post-treatment follow-up every 4 weeks As needed to confirm disease progression
CT/MRI assessment of STP – to be done locally	At screening upon positive findings from clinical assessment and as clinically indicated. For subjects with plasmacytomas identified at screening, CT/MRI should be done every 3 cycles
Plasma cell count in bone marrow - to be done locally	At screening and during the study as clinically indicated to substantiate CR.
Skeletal survey by X-ray and/or CT/MRI – to be done locally	At screening and as clinically indicated, CT/MRI in case of newly symptomatic areas with no X-ray finding.

Corrected calcium[1]	Screening and baseline Day 1 of each cycle End of treatment Post-treatment follow-up every 4 weeks As needed to confirm disease progression
MRD by means Next-Generation Sequencing	To be performed at time of suspected CR/sCR and 6, 12, 18, 24, and every 12 months (yearly assessments ±3 months) post CR/sCR in subjects who maintain CR or sCR, until PD is observed.

[1] Disease assessments SPEP, UPEP, and serum calcium corrected for albumin, should be collected every cycle for the first 14 months of the study and every other month thereafter. After Cycle 1, IFE should only be done when endogenous M-protein is 0 or nonquantifiable. For subjects who are followed by FLC only, these assessments are performed every other cycle after 14 months.

Additional local laboratory tests will be collected in accordance with standard clinical practice and medicinal products' SmPCs

Confirmation of Response

Based on modified IMWG criteria, response must be confirmed for all categories other than SD in order to rule out errors. A consecutive assessment can be performed at any time and confirmation should be obtained by M-protein assessments.

- Bone marrow assessments do not need to be repeated, but at least 1 bone marrow assessment is required to substantiate a CR.
- If imaging studies were done, they need to rule out new lytic bone lesions.
- Should confirmation assessments reveal a better category (eg, VGPR after PR), the response category of the previous assessment will be considered as confirmed (PR).
- Should confirmation assessments reveal a worse category, (eg, VGPR after CR), the response category of the subsequent assessment will be considered as confirmed (VGPR).
- Should repeated measurements of a variable result in more values, the worst assessment is to be considered.

Laboratory Confirmation of Progressive Disease

A diagnosis of PD requires confirmation if determined based on M-protein measurement or serum FLC levels. Confirmation of an increase in M-protein or FLC should be obtained as soon as possible.

See *Section 7.1.1.3* for information concerning possible false protein electrophoresis (PEP) and immunofixation (IFE) results.

Sponsor Confirmation of Progressive Disease

A diagnosis of PD (that is also confirmed with a consecutive assessment if based on M-protein/serum FLC levels) must be reported, via email, to the Sponsor's Medical Reviewer within 1 working day using the Progressive Disease Notification Form together with all supporting documentation for the diagnosis. The Medical Reviewer will check that the investigator's assessment of PD is consistent with the IMWG criteria and will provide a confirmation on the same form and return it via email to the site. In the case that the investigator's assessment is not deemed consistent with the IMWG criteria, the Medical Reviewer will

provide comments in the relevant section of the notification form and may also contact the investigator to discuss the subject further.

Study treatment discontinuation and start of subsequent anti-myeloma therapy should occur only after Sponsor confirmation of PD.

For subjects continuing on the study after the positive primary analysis and final OS analysis, investigator assessment of PD should continue to be performed in accordance with IMWG criteria. Notification of PD and approval by the Sponsor is no longer required.

7.1.1.1 Serum and Urine Sample Collection for M-protein Assessment by PEP and IFE

Response to treatment is based on M-protein levels in serum and urine. Two methods are required:

- Protein electrophoresis provides quantitative measurements.
- Immunofixation provides qualitative measurements (present/absent). It is a more sensitive method than PEP and is used to confirm the absence of M-protein by PEP (CR).

- Serum and urine IFE is required at baseline and to confirm CR regardless of whether measurable M-protein was present at baseline.
- Subjects with measurable disease in SPEP will be assessed for response based on SPEP and not by the serum FLC assay.
- Subjects with measurable disease in both SPEP and UPEP will be assessed for response based on these 2 tests and not by the serum FLC assay.

Blood (serum) and 24-h urine for M-protein assessment will be collected as indicated in *Table 7.3*.

Analysis by IFE will be done for all subjects at screening and baseline and thereafter only in subjects at time points in case of disappearance of M-protein by PEP.

7.1.1.2 Free Light Chain (FLC) Protein Assessment

The serum FLC assay measures free kappa light chain (0.33-1.94 mg/dL) and free lambda light chain (0.57-2.63 mg/dL). The FLC ratio is defined as the kappa serum level divided by the lambda serum level. Lambda is the involved light chain if FLC ratio <0.26. Kappa is the involved light chain if FLC ratio is > 1.65.

The FLC ratio is considered normal if FLC ratio is within 0.26-1.65 and Abnormal if FLC ratio is <0.26 or >1.65.

FLC serves to monitor disease status when serum M-protein or urine M-protein or both, assessed by PEP, is/are non-measurable (ie, serum M-protein <0.5 g/dL [5 g/L] or urine M-protein <200 mg [0.2 g] per 24 hours) and to identify sCR if CR criteria are met.

Blood (serum) for FLC assessment will be collected as indicated in *Table 7.3*. FLC will be analyzed only when serum M-protein or urine M-protein or both assessed by PEP is/are non-measurable and to identify sCR.

7.1.1.3 Daratumumab-specific Immunofixation Electrophoresis (DSIFE)

Daratumumab may be detected on SPEP and sIFE assays used for monitoring disease monoclonal immunoglobulins (M-protein). This can lead to false positive SPEP and sIFE assay results for subjects with IgG kappa myeloma protein and affect assessments of responses based on modified IMWG criteria.

Therefore, a DSIFE will be performed when daratumumab interference is suspected based on SPEP and sIFE results. This reflex assay relies on the use of a daratumumab-specific murine anti-idiotype antibody that binds and shifts daratumumab's migration pattern during electrophoresis, thus distinguishing daratumumab from the endogenous myeloma M-protein (*McCudden et al 2015*). The DSIFE will be performed at a central laboratory to confirm a VGPR or better in subjects with IgG kappa myeloma when daratumumab interference is suspected based on SPEP- and sIFE results.

7.1.1.4 Bone Marrow by Local Assessment

A BM aspirate, a biopsy, or both should be performed for every subject at screening. A portion of screening BM aspirate (first or second pull preferred) is also required for MRD, FISH and Biomarker assessments (central assessments: see *Table 7.2* and *Sections 7.1.1.7, 7.1.1.9* and *7.1.2.7* for more details). As the procedure is invasive, post-baseline assessments should be performed for confirmation of CR/sCR or, if clinically indicated, at time of suspected disease progression or end of treatment.

Plasma Cell Count in Bone Marrow

A bone marrow (BM) aspirate/biopsy for plasma cell quantification will be collected at screening and as clinically indicated to qualify for CR (see *Table 7.3*) and the percentage of plasma cells will be determined by using cytological/histological examination. In the event a fresh screening biopsy/aspirate cannot be collected, use non-decalcified diagnostic tissue (ie, bone marrow aspirate, touch preparation, or clot selection) or formalin-fixed paraffin embedded [FFPE] block (clot selection only, no bone marrow biopsy) from a sample taken within 42 days from C1D1.

Clonal plasma cell will be determined by either flow cytometry or immunohistochemistry or immunofluorescence in order to qualify for sCR (when CR criteria are met and a normal serum FLC ratio is also observed). Either BM aspirate or biopsy can be used for this assessment, but the same method should be used throughout the study. Bone marrow aspirate is required for MRD and flow cytometry assessment.

Table 7.2: Bone Marrow Testing

	Local Testing	Central Testing
Screening	• Plasma cell count (morphology) • Cytogenetics by FISH (if possible to perform locally)	• MRD (baseline) • Cytogenetics by FISH (if not possible to perform locally) • Biomarkers (baseline)
Suspected CR, sCR	• CR Confirmation: Plasma Cell Quantification (morphology) • sCR Confirmation: immunohistochemistry, immunofluorescence (requires kappa/lambda ratio from analysis of ≥100 cells) or 2- to 4-color flow cytometry.	• MRD • Biomarkers
Maintained CR, sCR	Not applicable	• MRD: For subjects who maintain CR/sCR, an additional bone marrow aspirate will be obtained at 6, 12, 18, 24, and thereafter every 12 months (yearly assessments ±3 months), until PD is observed
Disease Progression	Not applicable	• Biomarkers: **If feasible**, a bone marrow aspirate may be collected from subjects **at disease progression** to evaluate mechanisms of daratumumab resistance.

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

7.1.1.5 Assessment of Soft Tissue Plasmacytoma (STP)

Clinical Assessment by Investigator

The investigator should perform a clinical exam to assess the presence of STP at screening and baseline, on Day 1 of each cycle, at end of treatment, and during post-treatment follow-up.

If presence of a STP is suspected during the study, a computed tomography (CT) or MRI must be performed immediately to confirm and document the lesions' dimensions.

- CT/MRI
  - Screening: A CT/MRI will be performed at screening within 28 days prior to start of study treatment. Any imaging assessments already completed during the regular work-up of the subject within 42 days prior to start of treatment can be considered as the baseline assessment.
  - Post-baseline: Assessments should be performed using the same imaging technique used at baseline.
    - If STP is present at baseline, a CT/MRI should be performed every 12 weeks (+/ 7 days) until disappearance of STP or disease progression.
    - If STP is not present at baseline, but there is a suspicion of STP and/or disease progression (based on clinical exam or symptoms), a CT/MRI should be performed promptly to confirm suspicion.

Lesion size will be measured as the sum of the products of the longest diameter and longest perpendicular diameter for all measurable lesions.

All tumor measurements must be made in millimeters. Measurable disease are lesions that can be accurately measured in 2 dimensions and both diameters must be ≥20 mm when evaluated by standard CT scanning or ≥10 mm when evaluated by spiral CT scanning or MRI. At baseline, lesions of smaller dimensions will not be considered measurable and will not be followed for disease evaluation except for assessment of disease progression (when the lesion size increases and becomes measurable as per the above guidance).

7.1.1.6 Skeletal Survey

A skeletal survey is to be performed by conventional radiography for osteolytic disease within 28 days prior to randomization in all subjects. Results from the skeletal survey which have been performed as routine follow-up within 42 days before C1D1, may be used without these tests being repeated. The survey will be performed during the study if clinically indicated. Use of conventional or low-dose CT scan (ie, of the spine) or MRI is acceptable. If imaging is performed on treatment for assessment of progression, the same imaging technique as the one used at screening must be used. The number and location of skeletal lesions and whether they are lytic should be recorded on the eCRF. On-treatment survey, if clinically indicated, it should be recorded whether there is an increase in the number or size of lytic lesions (as described in Appendix 2).

7.1.1.7 Minimal Residual Disease (MRD)

Minimal Residual Disease assessment by next-generation sequencing (NGS) is an effective tool in the assessment of patients with MM (*Ladetto et al 2014*). Several studies have demonstrated that MRD status is correlated with PFS and OS (*Martinez-Lopez et al 2014*; *Kumar et al 2016*; *Munshi et al 2017*). MRD will be analyzed at a central laboratory when BM aspirate sample is obtained at screening to establish the baseline clone and at the time of suspected CR/sCR and 6, 12, 18, 24, and every 12 months (yearly assessments ±3 months) post CR/sCR in subjects who maintain CR or sCR, until PD is observed.

Following the CCO for the final OS analysis, MRD testing will be performed according to the standard of care for subjects without disease progression (see *Appendix 12*).

If a fresh bone marrow aspirate cannot be collected at screening, use non-decalcified diagnostic tissue (ie, bone marrow aspirate, touch preparation, or clot selection) or FFPE block (clot selection only, no bone marrow biopsy) from a sample taken within 42 days from C1D1.

7.1.1.8 Corrected Calcium

Corrected calcium in serum for determination of hypercalcemia as part of response assessment will be evaluated at screening/baseline and on Day 1 of each cycle until disease progression using the following formula:

Corrected Calcium, mg/dL = (0.8 x [normal Albumin, g/dL - Subject's Albumin, g/dL] + Serum Ca, mg/dL) (Appendix 5).

7.1.1.9 Cytogenetics by Means Of Fluorescence In Situ Hybridization (FISH)

A cytogenetic analysis of BM cells will be performed at screening through FISH at local laboratory, if available, or at the Erasmus laboratory for del17p, 1q amp, t(4;14), and t(14;16).

7.1.2 Safety Assessments

Safety evaluations include assessments of AEs, clinical laboratory tests, vital sign measurements, physical examination, assessment of ECOG performance status score, and ECG (at Screening and when clinically indicated), and FEV1 (at Screening for subjects with COPD).

7.1.2.1 Adverse Events

Monitoring for AEs will take place continuously throughout the study, starting from informed consent until 30 days after last study treatment. Expected progression of disease should not be considered an AE (or SAE). However, if determined by the investigator to be more likely related to the study treatment than the underlying disease, the clinical signs or symptoms of progression and the possibility that the study treatment is enhancing disease progression, should be reported per the usual reporting requirements. See *Section 8* for details.

7.1.2.2 Clinical Laboratory Tests

Laboratory assessments to be performed according to standard clinical practice and medicinal products' SmPCs are listed below. See *Table 7.3* for a schedule of assessments.

Hematology and clinical chemistry tests may be performed up to 3 days before the study treatment administration day. The results from these tests must be evaluated before each study drug administration. At C1D1, these tests do not need to be repeated if they have been performed within 7 days.

- Hematology panel: hemoglobin; red blood cell (RBC) count; platelet count; white blood cell count with absolute neutrophils and lymphocytes
- Clinical chemistry: sodium; potassium; total protein; albumin; calcium and albumin-adjusted calcium; alkaline phosphatase; γGT; ALT; AST; total bilirubin; BUN, uric acid; creatinine; glucose; calculated creatinine clearance based (same methodology should be used for individual subject)
- Urine or serum pregnancy test in women who can be pregnant
- Serum β 2-microglobulin and LDH (at Screening only)
- Blood type, Rh, and Indirect Antiglobulin Test (IAT)

Blood type, Rh, and IAT

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

Daratumumab interferes with the IAT, which is a routine pre-transfusion test performed to identify a patient's antibodies to minor antigens so that suitable donor blood can be given for transfusion. Daratumumab does not interfere with ABO/RhD typing. CD38 is expressed at very low levels on erythrocytes. Daratumumab binds to the CD38 on erythrocytes, which results in a positive IAT (Indirect Coombs Test). This positive result masks the detection of antibodies to minor antigens and may prevent or delay blood banks from issuing donor blood for transfusion. This effect occurs during daratumumab treatment and for up to 6 months after treatment ends. Subjects will receive a patient identification wallet card for the study that includes the blood profile (ABO, Rh, and IAT or phenotyping) determined before the first infusion of daratumumab along with information on the IAT interference for healthcare providers/blood banks. Subjects are to carry this card throughout the treatment period and for at least 6 months after treatment ends. Blood banks can eliminate the daratumumab interference with IAT by treating reagent RBCs with dithiothreitol (DTT) (*Chapuy et al 2015*; *Chapuy et al 2016*).

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

- Providing ABO/RhD compatible, phenotypically (standard or extended phenotyping) or genotypically matched units, and
- 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*.

In case of an urgent need for a blood transfusion, a blood sample should be obtained before the first infusion of daratumumab and the subject's blood type (ABO, Rh, and IAT) determined. Subjects should be provided a blood type card, which they will carry with them throughout the treatment period.

7.1.2.3 Vital Signs

Vital signs (body temperature, seated blood pressure, and heart rate) will be recorded as outlined in *Table 7.3*. Blood pressure and heart rate should be measured after the subject has been seated quietly for at least 5 minutes prior to dosing.

Subjects receiving Dara IV will have vital signs monitored also prior to, during, and after the infusion period.

7.1.2.4 Physical Examination

Physical examinations will be performed according to the visit schedule outlined in *Table 7.3*. A full physical examination will be performed at Screening visit, whereas targeted exams will occur during the treatment and post-treatment periods according to the investigator's observations and/or subject complaints on new or changed conditions.

Significant findings that were present prior to the signing of informed consent must be included in the Medical History eCRF page. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event page of the eCRF.

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Status

Eastern Cooperative Oncology Group Performance Status score will be evaluated as indicated in *Table 7.3* using the criteria described in Appendix 3. The assessment should be completed prior to any study-related procedures or assessments.

7.1.2.6 Cardiac Assessments

An ECG will be performed at screening within 28 days of randomization, throughout the study as clinically indicated, and at the EOT visit.

7.1.2.7 Biomarker Assessments

Daratumumab functions through multiple immune-mediated mechanisms and these cells may be utilized to examine natural killer (NK) cells or other pertinent immune cells (eg, regulatory T cells, myeloid derived suppressor cells [MDSC], cytotoxic T cells, dendritic cells, macrophages) important for daratumumab response. An evaluation of the immunomodulatory effects of daratumumab on T cells may be performed by molecular and phenotypic studies and comparisons between treatment arms.

Bone Marrow

Baseline BM aspirate samples may be subjected to DNA and RNA sequencing in order to identify potential neoantigens specific to the subject's MM cells, T cell receptor repertoire diversity, and may also be used to classify subjects into high-risk molecular subgroups and novel biomarkers of response/resistance to therapy. A BM aspirate will be taken at suspected CR (together with the bone marrow samples for CR/sCR confirmation and MRD assessments) for identification of biomarkers of response to therapy and if feasible at the time of PD for identification of biomarkers of resistance to therapy.

Whole Blood

In addition to planned BM aspirate assessments, whole blood samples will be collected from subjects as outlined in the Schedule of Events (*Table 7.3*). These samples may be used to evaluate specific subsets of immune cells such as T cell populations (CD4+, CD8+, and activation markers). Cells may also be used for additional phenotypic, molecular, and functional profiling.

Biomarker analyses are dependent upon the availability of appropriate biomarker assays and may be deferred or not performed if, during or at the end of the study, it becomes clear that the analysis will have no scientific value, or if there are not enough samples or not enough responders to allow for adequate biomarker evaluation. In the event the study is terminated early or shows poor clinical efficacy, completion of biomarker assessments is based on justification and intended utility of the data. Samples for biomarker evaluations will be collected as specified in the Schedule of Events (*Table 7.3*).

7.1.3 Patient Reported Outcome Measures

Patient-reported outcome measures will be administered on Day 1 of each treatment cycle prior to receiving treatment or any other assessment. Post-treatment, PRO measures will be administered every 4 weeks for subjects who discontinue treatment for reasons other than disease progression, death, lost to follow-up, or withdrawal of consent.

EQ-5D-5L

The EQ-5D-5L is a generic measure of health status. For purposes of this study, the EQ-5D-5L will be used to generate utility scores for use in cost effectiveness analyses. The EQ-5D-5L is a 5-item questionnaire that assesses 5 domains, including: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression plus a visual analog scale rating "health today" with anchors ranging from 0 (worst imaginable health state) to 100 (best imaginable health state) (*Herdman et al 2011)*. The scores for the 5 separate questions are categorical and cannot be analyzed as cardinal numbers. However, the scores for the 5 dimensions are used to compute a single utility score ranging from zero (0.0) to 1 (1.0), with higher values representing better general health status of the individual. Administration time for the EQ-5D-5L is less than 10 minutes.

EORTC QLQ-C30

The EORTC QLQ-C30 Item is a cancer-specific PRO measure. It includes 30 items resulting in 5 functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), 1 Global Health Status scale, 3 symptom scales (fatigue, nausea and vomiting, and pain), and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Scores are transformed to a 0 to 100 scale. A higher score for the global health status scale represents higher quality of life, a higher score for the functional scales represents higher level of functioning, and a higher score for symptom scales/items represent higher level of symptomatology/problems. Reliability, validity, and clinically meaningful change of the EORTC QLQ-C30 have been demonstrated in MM patients (*Wisloff et al 1996*; *Wisloff & Hjorth 1997*). The recall period is 1 week (the past week), and the questionnaire takes approximately 15 minutes to complete.

EORTC QLQ-MY20

The EORTC QLQ-MY20 Multiple Myeloma Module is an MM PRO measure to be used in conjunction with the EORTC QLQ-C30 for assessing HRQoL in patients with MM (*Cocks et al 2007*). It includes 20 items resulting in 2 symptom scales (disease symptoms and side effects of treatment), 1 function scale (future perspective), and a single item on body image. Items are scored on a 4-point scale ranging from "not at all" to "very much" and scores are transformed to a 0 to 100 scale. A higher score represents higher level of symptoms, higher functioning, and better body image. The recall period is 1 week (the past week), and the questionnaire takes less than 15 minutes to complete.

7.1.4 Pharmacokinetics and Immunogenicity

7.1.4.1 Evaluations

For subjects who have opted to continue to receive daratumumab by IV administration or who have not switched to Dara SC, samples to assess both the serum concentration (pharmacokinetics) of daratumumab and the generation of antibodies to daratumumab (immunogenicity) will be obtained from DaraPomDex subjects according to Appendix 10.

For subjects who receive daratumumab by SC administration starting from the first dose, samples to assess the serum concentration (pharmacokinetics) of daratumumab, the generation of antibodies to daratumumab (immunogenicity), and the generation of antibodies to rHuPH20 will be obtained from DaraPomDex subjects according to the schedule in *Table 7.3.1*.

For subjects who received daratumumab initially by IV then switched to SC after Amendment 1, samples to assess the serum concentration (pharmacokinetics) of daratumumab, the generation of antibodies to daratumumab (immunogenicity), and the generation of antibodies to rHuPH20 will be obtained from DaraPomDex subjects according to the schedule in Appendix 9.

For all subjects, 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.

After the positive primary analysis, a limited schedule of PK and immunogenicity assessment will be implemented (refer to *Section 7.2.4*).

7.1.4.2 Analytical Procedures

Serum samples will be analyzed to determine concentrations of daratumumab or generation of antibodies to daratumumab and plasma samples will be analyzed for generation of antibodies to rHuPH20 using validated immunoassay methods.

7.1.4.3 Pharmacokinetic Parameters

The pharmacokinetic parameters are defined as:

C_{max} Maximum observed concentration

C_{min} Minimum observed concentration

For daratumumab, the pharmacokinetic evaluations include C_{min} and C_{max}. The C_{min} and C_{max} will be determined based on collection timepoint. If sufficient data are available, population pharmacokinetic analysis of serum concentration-time data of daratumumab may be performed using nonlinear mixed-effects modeling. If population pharmacokinetic analysis is conducted, it may include data from other clinical studies; details will be provided in a population pharmacokinetic analysis plan and results will be presented in a separate report.

7.1.4.4 Immunogenicity Assessments

Serum from venous blood samples will be assessed for the generation of antibodies to daratumumab (immunogenicity) and plasma samples will be collected and assessed for antibodies to rHuPH20 (SC treatment, only) according to the Schedule of Events (*Table 7.3, Table 7.3.1*), Appendix 9 or Appendix 10). Additionally, blood samples to assess daratumumab and rHuPH20 immunogenicity should also be collected at the final visit for subjects who discontinue treatment. Subjects who discontinue treatment will also be asked to return for immunogenicity evaluation during the Follow-up Phase.

All samples collected for daratumumab immunogenicity analysis will also be evaluated for daratumumab serum concentration to ensure appropriate interpretation of immunogenicity data. When both serum daratumumab concentration and daratumumab 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.

Samples will be screened for antibodies binding to daratumumab or rHuPH20 and serum/plasma 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.

In addition, 2 separate blood samples should be obtained, if possible, for the assessment of antibodies to daratumumab and rHuPH20 any time an infusion-related reaction is reported in a subject receiving Dara SC (according to *Table 7.3.1* and the laboratory manual) in association with the second administration or beyond. Daratumumab serum concentration will also be determined from the daratumumab infusion reaction sample for the purpose of interpreting immunogenicity data.

7.1.4.5 Pharmacokinetic/Pharmacodynamic Evaluations

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

7.2 STUDY SCHEDULE

Table 7.3 lists all of the assessments and indicates the visits when they are performed. See *Section 7.1* for details concerning each assessment. All data obtained from these assessments must be supported in the subject's source documentation. Baseline is defined as C1D1 after randomization and prior to start of study treatment. For assessments that are not performed on C1D1, the screening results will be considered as baseline.

At each visit, study assessments should be completed before administration of the study treatment, unless otherwise stated. All visit-specific PRO assessments should be completed before any study procedures for that visit to prevent influencing the subject's perceptions.

Post-baseline disease evaluations may be conducted ± 3 days from the scheduled (based on C1D1) visit date, if necessary. At the following visit, the subject should return to the original planned schedule.

7.2.1 Screening

Following signature of the ICF, most screening assessments will be performed within 28 days of randomization.

A subject who has a laboratory result that does not satisfy eligibility criteria may have the test repeated when the investigator believes the re-test result is likely to be within the acceptable range to satisfy the entrance criteria, but should be completed within the 28-day window before C1D1. If the BM sample collected at screening (aspirate) is inadequate for genetic assessments (FISH) and/or evaluation of percentage of plasma cells, it should be repeated within 28 days of the original collection date prior to randomization. Serum M-protein, urine M-protein, and serum FLC baseline disease evaluations must be performed within 14 days before C1D1. It is not mandatory to collect these samples again at the C1D1 visit. Results from the skeletal survey or the radiologic assessments for extramedullary plasmacytomas, which have been performed as routine follow-up within 42 days before C1D1, may be used without these tests being repeated. Subjects who sign an ICF but who are not randomized for any reason will be considered screening failures. The reason for not being randomized will be entered on the eCRF. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screening failure subjects. No other data will be entered into the clinical database unless the subject experienced an SAE during the Screening period. Subjects who are screening failures may be rescreened if their condition changes. Rescreening must be discussed and approved by the Sponsor on a case by case basis. Subjects who are determined eligible for rescreening must sign a new ICF.

Subject Demographics and Other Baseline Characteristics

The following data are to be recorded on the eCRF during the screening period:

- Demography (date of birth, sex, information on childbearing status of female subjects, race, ethnicity).
- Medical history / current medical conditions.
- Diagnosis of MM and extent of the disease, including staging at study entry according to the International Staging System (ISS) (Appendix 1).
- Bone marrow aspirate/biopsy for cytogenetics (FISH) at local laboratory, if available, or at the Erasmus laboratory.
- All prior anti-neoplastic therapies including surgical interventions and chemo-, biologic-, immunologic- and radiation-therapies and stem cell transplants provided as treatment for MM.
- All concomitant medications and significant non-drug therapies including transfusions of blood products administered within 14 days prior to first dose.
- The following assessments must be performed and recorded for all randomized subjects:
    - Complete physical examination including height and weight.
    - Vital signs (temperature, heart rate, diastolic and systolic blood pressure).
    - Eastern Cooperative Oncology Group (ECOG) Performance Status score.
    - Electrocardiogram.
    - FEV1 in subjects with known or suspected COPD.

    - Serum pregnancy test performed in WOCBP (2 pregnancy tests, one 10-14 days prior to start of study drug and one within 24 hours prior to start of study drug. Urine tests must have a sensitivity ≥25 mIU/mL).
    - Local laboratory evaluations (hematology, clinical chemistry, creatinine clearance).
    - Serum β2-microgloblin and LDH.
- Disease assessments
    - In serum:
        - M-protein by PEP and IFE
        - FLC protein assessment
        - corrected calcium
    - In urine (24-h urine collection required):
        - M-protein by PEP and IFE;
    - Local plasma cell count in BM
    - MRD performed at central laboratory
    - Clinical and CT/MRI assessment of soft tissue plasmacytomas (STP)
    - Local full body skeletal survey by X-ray and/or CT/MRI

7.2.2 Treatment Period

After randomization, subjects will be treated in 28-day cycles until disease progression, unacceptable toxicity, death, or discontinuation from the study treatment due to other reason (see *Section 5.3*). See *Table 7.3* for the assessment schedule, *Section 7.1* for details about assessments, and *Section 6.1* for information about treatment.

The general visit window during the treatment period is +/- 3 days. Subjects should start study treatment within 3 days after randomization.

7.2.3 Follow-up Period

Post-treatment Follow-up

Subjects who discontinue treatment for reasons other than documented disease progression, death, lost to follow-up, or withdrawal of consent should continue to be followed for response assessments every 4 weeks as in *Table 7.3*. The reason for completion/discontinuation should be recorded on the eCRF.

If a subject starts new anti-myeloma therapy prior to disease progression, every attempt should be made to perform tumor evaluations until documented disease progression. In addition, all new anti-neoplastic therapy administered starting from the last dose of the study treatment until death, lost to follow-up, or withdrawal of consent will be recorded in the eCRFs.

Survival Follow-up

Subjects will be followed every 12 weeks, or more frequently, after disease progression for survival and subsequent myeloma therapy.

7.2.4 Updated Assessments Following the Positive Primary Analysis of PFS

Following the positive primary analysis of PFS, subjects remaining in the study will continue to be monitored as follows until the final analysis (ie, when approximately 166 deaths have occurred or 5 years after the last subject was randomized). Subjects benefiting from the study treatment can continue receiving the study drugs after the end of data collection until the study drugs are commercially available and reimbursable, available from another source (eg, via a dedicated long-term extension study), or until study completion, whichever comes first.

Subjects who have had Disease Progression

For subjects whose disease has progressed, every-12 week follow-up contacts should continue to be performed to capture the following:

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

Data may be collected directly from subject or indirectly (eg, from medical correspondence or remote/telephone visits).

Subjects who Have not had Disease Progression

Following the positive primary analysis of PFS, disease evaluations are to be performed locally per the site's standard of care. All subjects must still meet IMWG criteria for progression prior to initiation of subsequent anti-myeloma therapy.

Pharmacokinetic and Immunogenicity Assessments for DPd arm

After the positive primary analysis, a limited schedule of PK and immunogenicity assessment will be implemented to reduce the burden of blood sampling in subjects. For subjects who receive daratumumab by SC administration starting from the first dose and subjects who received daratumumab initially by IV then switched to SC, samples are to be collected for PK and immunogenicity assessments at EOT and 8 weeks after the last dose of daratumumab, regardless of whether there has been confirmed disease progression. No subjects remain on daratumumab IV at the time of positive primary analysis and beyond. In addition, 2 separate blood samples should be obtained, if possible, for the assessment of antibodies to daratumumab and rHuPH20 any time an infusion-related reaction is reported in a subject receiving Dara SC in association with the second administration or beyond. Daratumumab serum concentration will also be determined from the daratumumab infusion reaction sample for the purpose of interpreting immunogenicity data.

Study procedures

The remainder of the study procedures remain unchanged (please refer to *Table 7.3* for the complete schedule of events).

7.2.5 Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form. If blood samples are collected via an indwelling cannula, an appropriate amount (1 mL) of serosanguineous fluid slightly greater than the dead space volume of the lock will be removed from the cannula and discarded before each blood sample is taken. Refer to the Schedule of Events (*Table 7.3*) for the timing and frequency of all sample collections.

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

Table 7.3: Schedule of Events

Following the positive primary analysis some of the below procedures have been adjusted (PD evaluation, PK/Immunogenicity). For more details on the updated procedures, please refer to *Section 7.2.4*.

Note: Refer to *Appendix 12* for a description of study procedures for subjects who continue to receive study treatment after the CCO for the final OS analysis until subjects meet treatment discontinuation criteria (see *Section 5.3.1*) or until study treatment is available through another source such as commercial availability with reimbursement, continued access through a long-term extension study, a patient access program, or after the last subject transitions into the long-term extension phase of the study up to 30 September 2024, whichever occurs first. No eCRF data will be collected after the CCO for the final OS analysis.

	Screening	**Treatment: visit window during the treatment period is +/- 3 days**												**End of treatment EOT[12]**	**Post-treatment FU Every 4 weeks[5]**	**8 weeks After Last Dose**	**Survival follow-up Every 12 weeks**
		Cycles 1 and 2				**Cycles 3-6**				**Cycles 7 and beyond**							
Day of Cycle (28-days)	**Days -28 to 1**	**Day 1 Baseline**	**Day 8**	**Day 15**	**Day 22**	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 1**	**Day 8**	**Day 15**	**Day 22**				
Demographic/baseline Assessments																	
Informed consent	X																
Demography	X																
Inc./Exc. criteria	X																
Medical history	X																
MM diagnosis/history	X																
Internal Staging System (ISS)*****	X																
Cytogenetics (FISH) at study entry****	X																
Randomization	X																
Safety Assessments																	
Physical examination	X	Symptom-directed physical examination												X	X		
Vital signs	X	X	X	X	X	X		X		X				X	X		
Weight	X	X	X	X	X	X		X		X				X	X		
Performance status score (ECOG)	X	X				X				X				X			
Adverse Events	Continuously until 30 days after last study treatment																
Concomitant medication, transfusions	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
FEV1**	X																
ECG	X	As clinically indicated												X			
Lab Assessments****																	

Day of Cycle (28-days)	Screening	Treatment: visit window during the treatment period is +/- 3 days												End of treatment EOT[12]	Post-treatment FU Every 4 weeks[5]	8 weeks After Last Dose	Survival follow-up Every 12 weeks
		Cycles 1 and 2				Cycles 3-6				Cycles 7 and beyond							
	Days -28 to 1	Day 1 Baseline	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22				
Blood Type, Rh, and Indirect Antiglobulin Test (IAT) (DaraPomDex group only)[8]		Prior to dosing on C1D1 only															
Hematology[9]	X	X	X	X	X	X		X		X				X			
Clinical chemistry[9]	X	X		X		X				X				X			
Creatinine clearance	X	X				X				X				X			
Pregnancy test[1]	X	X				X				X				X			
Serum β2-microglobulin, LDH	X																
Hepatitis B serology[14]	X																
HBV-DNA testing[15]	X	Every 12 weeks (window ±7 days)														X	
Daratumumab PK and Immunogenicity (DaraPomDex group only)	**For subjects receiving daratumumab via subcutaneous administration refer to *Section 7.3.1*; for subjects who started daratumumab via IV infusion and switched to daratumumab subcutaneous administration, refer to Appendix 9; for subjects who receive Dara IV, only, refer to Appendix 10**																
Efficacy Assessments																	
Efficacy / Disease Assessment required to confirm response or disease progression should be performed as soon as possible after response or disease progression is suspected[16] – see *Section 7.1* for details) After the primary clinical cut-off date (21 JUL 2020), subject monitoring will be conducted as per *Section 7.2.4*																	
SPEP, UPEP[2, 10]	X	X				X				X				X	X		
sIFE, uIFE[3, 10]	X	X			.	X				X				X	X		
		To confirm CR regardless of whether measurable M-protein was present at baseline. See *Section 7.1.1.1*															
sFLC assay, κ/λ ratio[4, 10]	X	X				X				X				X	X		
		Analyzed only when serum M-protein or urine M-protein or both assessed by PEP is/are non-measurable and to identify sCR in case CR criteria are met. See *Section 7.1.1.2*.															
DSIFE *		To confirm a CR or better in subjects with IgG kappa myeloma when daratumumab interference is suspected based on SPEP- and sIFE results. See *Section 7.1.1.3*.															
Plasma cell count in bone marrow	X	Plasma cell count during the study as clinically indicated to qualify for CR. See *Section 7.1.1.4*.															
Bone marrow aspirates (Biomarker analysis)	X	At suspected CR and at PD (if feasible).															
MRD*[, 13]	X	At suspected CR and, 6, 12, 18, 24 months post CR/sCR and every 12 months (yearly assessments ± 3 months) thereafter in subjects with CR until PD. Assessment done by NGS. See *Section 7.1.1.7*.															
Whole blood for biomarker assessments		X	Whole blood for plasma, PBMCs and immunophenotyping may be collected predose at C3D1, C6D1, C12D1 and at suspected CR and at PD.														
Corrected calcium[6, 10]	X	X				X				X				X	X		
Skeletal survey	X	As clinically indicated; CT/MRI in case of newly symptomatic areas with no X-ray finding. See *Section 7.1.1.6*.															

Day of Cycle (28-days)	Screening	Treatment: visit window during the treatment period is +/- 3 days												End of treatment EOT[12]	Post-treatment FU Every 4 weeks[5]	8 weeks After Last Dose	Survival follow-up Every 12 weeks
		Cycles 1 and 2				Cycles 3-6				Cycles 7 and beyond							
	Days -28 to 1	Day 1 Baseline	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22				
Assessment of extramedullary soft tissue plasmacytoma (STP)	X	Clinical assessment on Day 1 of each cycle at the End of treatment and at Post-treatment follow-up every 12 weeks. CT or MRI at screening if plasmacytoma identified by imaging only will be done every 12 weeks. See *Section 7.1.1.5*.															
Response assessment by Investigator		X				X				X				X	X		
PRO s assessments (EQ-5D-5L, EORTC QLQ-C30, EORTC QLQ-MY20)		X				X				X				X	X		
Treatment																	
Daratumumab [12]		X	X	X	X	X		X		X							
Pre- and post-infusion medications for daratumumab subjects		X	X	X	X	X		X		X							
Pomalidomide		4 mg PO on days 1-21 of each 28-day cycle															
Dexamethasone		X	X	X	X	X	X	X	X	X	X	X	X				
		40 mg (20 mg for subjects ≥75 years of age) orally, weekly															
Other anti-neoplastic therapies		Not permitted												X	X		X
Survival follow-up* **																	X

Note: Pharmacokinetic/immunogenicity sample collection times for subjects receiving daratumumab via subcutaneous administration is provided in *Table 7.3.1*; for subjects who started daratumumab via IV infusion and switched to daratumumab subcutaneous administration, refer to Appendix 9; for subjects who receive Dara IV, only, refer to Appendix 10.

Note: The majority of screening assessments are to be performed within 28 days of C1D1.

[1] For WOCBP only, 2 pregnancy tests, one 10 - 14 days prior to start of study drug and one within 24 hours prior to start of study drug. Urine tests must have a sensitivity of ≥ 25 mIU/mL. WOCBP must have a pregnancy test 28 days after end of treatment.

[2] M-protein by electrophoresis in serum (SPEP) and urine (UPEP). Serum on Day 1 of each cycle until disease progression. 24-hour urine sample can be collected within ± 7 days of visit.

[3] M-protein by immunofixation in serum (sIFE) and urine (uIFE). A daratumumab-specific IF (DSIFE) is to be used when daratumumab interference is suspected based on SPEP and sIFE results.

[4] Free light chain protein assessment (sFLC).

[5] Subjects who discontinue treatment for reasons other than disease progression, death, lost to follow-up, or withdrawal of consent should continue to be followed for response assessments every 4 weeks. Note, however, that **all patients receiving Daratumumab** must attend for visits at 4 and 8 weeks post discontinuation of treatment (regardless of discontinuation reason) in order to undergo PK sampling as per *Table 7.3.1*.

[6] Corrected calcium will be also performed as clinically indicated to confirm disease progression.

[7] Sample must be sent to central laboratory.

[8] It is required that, in addition to ABO and Rh blood typing, the indirect antiglobulin test (also known as Indirect Coombs Test) be performed and that the subject carries an identification wallet card with these results at all times during the study. These tests will be conducted at the local laboratory. Blood type, Rh, and IAT should be done before the first dose of daratumumab. Subject RBC phenotyping (standard or extended) is an alternative option to the IAT test, if locally required. Either method must be completed prior to first daratumumab infusion.

*Examinations to be performed at central laboratory.

**Subjects with known or suspected COPD must have an FEV test during Screening.

***Subjects to be followed for 5 years for secondary primary malignancies.

****Examination to be performed at local laboratory, if available, or at the Erasmus laboratory.

***** For sites where β2-microglobulin is measured locally, the local assessment of serum albumin (instead of the one measured centrally) will be used to determine the ISS stage.

****** Unless otherwise stated, all blood and urine samples must be obtained before administration of study treatment.

[9] Hematology and clinical chemistry tests may be performed up to 3 days before the study treatment administration day. Laboratory assessments do not need to be repeated if done within 7 days of C1D1. Complete blood counts should be monitored at baseline, weekly for the first 8 weeks and monthly thereafter.

[10] Disease assessments SPEP, UPEP, and serum calcium corrected for albumin, should be collected every cycle for the first 14 months of the study and every other month thereafter. After Cycle 1, IFE should only be done when endogenous M-protein is 0 or nonquantifiable. For subjects who are followed by FLC only, these assessments are performed every other cycle after 14 months.

[11] Every effort should be made to follow the planned dosing schedule; however, doses within 3 days of the scheduled dose will be permitted. Subjects should start study treatment within 3 days after randomization. The dose does not need to be recalculated for weight changes that are <10% from baseline.

[12] EOT visit to occur 4 weeks after the last dose of study treatment or as soon as possible before the start of subsequent therapy.

[13] In the event a fresh screening biopsy/aspirate cannot be collected, use non-decalcified diagnostic tissue (ie, bone marrow aspirate, touch preparation, or clot selection) or formalin-fixed paraffin embedded (FFPE) block (clot selection only, no bone marrow biopsy) from a sample taken within 42 days from C1D1.

[14] All subjects will be tested at screening for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), hepatitis B core antibody (anti-HBc).

[15] Only in subjects who are positive for antibodies to hepatitis B core antigen [antiHBc] and/or antibodies to hepatitis B surface antigen [antiHBs]. Subjects with serologic findings suggestive of HBV vaccination (antiHBs positivity as the only serologic marker) AND a known history of prior HBV vaccination do not need to be tested for HBV-DNA by PCR.

[16] Following the positive primary analysis of PFS, disease evaluations are to be performed locally per the site's standard of care. All subjects must still meet IMWG criteria for progression prior to initiation of subsequent anti-myeloma therapy. Notification of PD and approval by the Sponsor is no longer required.

Table 7.3.1: Schedule of Events: Pharmacokinetic/Immunogenicity Sample Collection Times for Subcutaneous Daratumumab Subjects

Days of Cycle (28-days)	Cycle 1		Cycle 3		Cycle 5	Cycle 7	Cycle 12	Follow-up	
Day	**1**	**4**	**1**	**4**	**1**	**1**	**1**	**Post-treatment Week 4**	**Post-treatment Week 8**
Visit Window	0	+/- 1 day	+/- 1 day	+/- 1 day	+/- 3 days	+/- 3 days	+/- 3 days	+/- 7 days	+/- 7 days
Daratumumab PK (serum)	X (Predose) [1]	X	X (Predose) [1]	X	X (Predose) [1]	X (Predose) [1]	X (Predose) [1]	X	X
Daratumumab Immunogenicity (serum)	**No additional sample required; taken from Daratumumab PK Sample**								
	X (Predose) [1, 2]				X (Predose) [1, 2]	X (Predose) [1, 2]	X (Predose) [1, 2]	X	X
rHuPH20 immunogenicity (plasma)	X (Predose) [1, 2]				X (Predose) [1, 2]	X (Predose) [1, 2]	X (Predose) [1, 2]	X	X

rHuPH20=recombinant human hyaluronidase.
[1] On dosing days, sample collection may occur up to 2 hours before but not after the start of drug administration. Samples collected on dosing days with visit windows must be collected on the actual day of study drug administration. Samples collected on non-dosing days should be collected within ±4 hours of the time of day the drug administration was started on the most recent dosing day.
[2] In addition, samples for assessment of antibodies to daratumumab and rHuPH20 should be drawn, if possible, any time an infusion-related reaction is reported (according to laboratory manual and *Section 7.1.4.4*) in association with the second administration or beyond.

7.3 CONCOMITANT MEDICATIONS, TREATMENTS, AND PROCEDURES

Systemic use of the following concomitant medications will be collected in the eCRF and recorded in the source documents beginning with signing of the ICF to 30 days after the last dose of the last study treatment or until the start of subsequent anticancer treatment, if earlier: growth factors, transfusions, anti-infectives (antibacterials, antivirals, and antimycotics), steroids, anti-arrhythmics and other cardiac supportive therapy, anti-epileptics, centrally acting psychiatric medication, antihistamines, and other medications targeting post-infusion systemic reactions, bisphosphonates, and any anticancer therapy (including radiation).

7.3.1 Pre-infusion Medication

Pre-infusion medications for all subjects receiving daratumumab will be administered as described in the Schedule of Events (*Table 7.3*). On daratumumab infusion days, subjects will receive the following medications approximately 1 hour prior to daratumumab infusion:

- Dexamethasone 20 mg IV (preferred) or PO (an equivalent of long-acting corticosteroid may substitute [Appendix 8]);
- Paracetamol (acetaminophen) 650 to 1000 mg IV or PO; and
- An antihistamine (diphenhydramine 25 to 50 mg IV or PO, or equivalent, but avoid IV use of promethazine) (Appendix 7).
- Leukotriene inhibitor (optional) on C1D1: montelukast 10 mg PO.

If necessary, oral pre-infusion medications may be administered outside of the clinic on the day of the infusion, provided they are taken within 1 to 3 hours prior to the infusion.

7.3.2 Post-infusion Medication in High-Risk Subjects

For subjects with a higher risk of respiratory complications (ie, subjects with COPD who have an FEV1 <80% of predicted normal, or subjects with mild asthma [see Appendix 4]), the following post-infusion medications should be considered:

- Antihistamine (diphenhydramine or equivalent) on the first and second days after all infusions
- Short-acting β2 adrenergic receptor agonist such as salbutamol aerosol
- Control medications for lung disease (eg, inhaled corticosteroids ±long-acting β2 adrenergic receptor agonists for subjects with asthma; long-acting bronchodilators such as tiotropium or salmeterol ±inhaled corticosteroids for subjects with COPD)

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

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

Any post-infusion medication will be administered after the infusion has completed.

7.3.3 Other Concomitant Medications

Infection Prophylaxis: Prophylactic use of antibiotics is highly recommended due to the susceptibility of patients with multiple myeloma to infections. Prophylactic administration of levofloxacin (500 mg P.O. daily; dose adjusted for renal function) during the first 3 cycles of treatment is recommended as it has shown to significantly reduce febrile episodes and deaths without increasing healthcare associated infections or carriage of key nosocomial pathogens (*Drayson et. al 2017*).

Prophylaxis for Herpes Zoster Reactivation: Prophylaxis for herpes zoster reactivation is recommended during the Treatment Phase. Acceptable antiviral therapy includes acyclovir (eg, 400 mg given orally 3 times a day, or 800 mg given orally 2 times a day or per institutional standards), famciclovir (eg, 125 mg given orally, twice a day or per institutional standards), or valacyclovir (eg, 500 mg given orally, twice a day or per institutional standards), initiated within 1 week after the start of study drug.

Prevention of Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE): Pomalidomide has been associated with an increased incidence of DVT and PE. Therefore, prophylaxis with aspirin or low molecular weight heparin is strongly recommended for all subjects (*Palumbo et al 2008*). The injection should be handled according to local practice.

Bisphosphonate Therapy: For subjects who have not previously received bisphosphonates, bisphosphonates are recommended for all subjects with evidence of lytic destruction of bone or with osteopenia. Bisphosphonate therapy is recommended to be continued per treatment guidelines (*NCCN 2014; Moreau et al 2013)*. Commercially available IV bisphosphonates (pamidronate and zoledronic acid) are preferred, when available, and should be used according to the manufacturer's recommendations, as described in the prescribing information, for subjects with osteolytic or osteopenic myelomatous bone disease. Oral bisphosphonates may be used as alternatives if IV bisphosphonates are not available at the study site. Investigators should use the same route of bisphosphonate therapy for all subjects at their sites.

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

7.3.4 Prohibited Medications, Treatments, and Procedures

Concomitant administration of any other anti-neoplastic therapy for the intention of treating multiple myeloma is prohibited, including medications that target CD38. Continuation of the study drug and components of the backbone regimens during or after emergency orthopedic surgery or radiotherapy because of the subject's benefit may occur only in the absence of disease progression and after consultation with and approval by the Sponsor. Such emergency radiotherapy may consist of localized radiotherapy for pain control or for stabilization of an extensive bone lesion at high risk of pathologic fracture or damage to surrounding tissues in a subject in whom delay of systemic therapy is not appropriate. Such radiotherapy is

to occur within the first 2 cycles of treatment and the absence of evidence of disease progression is to be reviewed and approved by the Sponsor. Concomitant administration of investigational agents is prohibited. Administration of commercially available agents with activity against or under investigation for multiple myeloma, including systemic corticosteroids (>10 mg prednisone per day or equivalent) (other than those given for IRRs as described in *Section 7.3*) should be avoided. Nonsteroidal anti-inflammatory agents should be avoided to prevent myeloma-related kidney disease. Typically, IV contrast is NOT used in CT scanning of the subjects with secretory multiple myeloma because of the risk to the kidney. If administration of IV contrast is necessary, then adequate precautions including hydration are indicated. The Sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

No interaction studies have been performed with daratumumab. Guidelines for the selection and use of other concomitant medications should be derived from pomalidomide and dexamethasone prescribing information.

7.3.5 Rescue Medications, Treatments, and Procedures

See *Section 6.1.5* for guidelines for managing IRRs.

7.3.6 Subject Access to Study Treatment at Study Closure

Subjects will be provided with study treatment until disease progression, death, lost to follow-up, or withdrawal of consent. The Sponsor may terminate access to study drug if the study is terminated due to safety concerns. At the Sponsor's discretion, if the decision is made to terminate the study early, subjects who benefit with daratumumab may transition to receive commercially available drug product or daratumumab from another source. In these circumstances, the Sponsor and investigator will support transition of the subject to ensure that treatment continues and remains uninterrupted.

7.3.7 End of Study Definition

The end of the study is defined as the timepoint at which all subjects who are still receiving study treatment have access through another source such as commercial availability with reimbursement, continued access through a long-term extension study, a patient access program, or when all subjects have discontinued study treatment after the CCO for the final OS analysis up to 30 September 2024, whichever occurs first.

8 SAFETY MONITORING AND REPORTING

Refer to *Appendix 12* for guidance regarding safety monitoring and reporting for subjects continuing on study treatment after the CCO for the final OS analysis.

8.1 ADVERSE EVENTS

8.1.1 Definition

According to the International Conference on Harmonisation (ICH), an AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated

with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product. Pre-existing conditions that worsen during a study are to be reported as AEs.

The occurrence of AEs should be sought by non-directive questioning of the subject during screening, after signing the ICF, and at each visit during the study. Adverse events also may be detected when they are volunteered by the subject or through physical examination, laboratory test, or other assessments.

Death should not be recorded as an AE or SAE, but as the outcome of an AE. The AE that resulted in death should be reported as an SAE.

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

Laboratory abnormalities that constitute an AE should be recorded on the Adverse Event eCRF. Whenever possible, a diagnosis rather than a symptom should be provided (eg, anemia instead of low hemoglobin).

Laboratory abnormalities, that do not meet the definition of an AE, should not be reported as AEs. A Grade 3 or 4 event (severe), per CTCAE, does not automatically indicate an SAE unless it meets the definition of serious as defined below.

8.1.2 Definition of Serious Adverse Events (SAEs)

An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or Sponsor, it results in any of the following outcomes: death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Events not considered as SAEs are hospitalizations for: a standard procedure for therapy administration, routine treatment or monitoring of the study indication, hospitalization or prolongation of hospitalization for technical/practical or social reasons in absence of an AE, or a procedure which is planned. A prolongation of such a hospitalization for a complication remains a reportable SAE.

8.2 CLASSIFICATION OF AN ADVERSE EVENT

8.2.1 Severity of Event

Intensity: all AEs will be graded according to the CTCAE (Version 4.03) as follows (a semi-colon [;] indicates 'or' within the description of the grade):

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

8.2.2 Relationship to Study Treatment(s)

For all collected AEs, the clinician who examines and evaluates the subject will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Possibly Related –** There is some evidence to suggest a causal relationship (eg, the event occurred within a reasonable time after administration of the study medication). However, other factors may have contributed to the event (eg, the subject's clinical condition, other concomitant events). Although an AE may be rated only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.
- **Unlikely to be related –** A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (eg, the event did not occur within a reasonable time after administration of the study medication) and in which other drugs or chemicals or underlying disease provide plausible explanations (eg, the subject's clinical condition, other concomitant treatments).
- **Not Related –** The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.2.3 Expectedness

The Sponsor will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the applicable product information (eg, Investigator's Brochure or SmPC of the study agents).

8.3 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study subject presenting for medical care, or upon review by a study monitor. All AEs, including local and systemic reactions, regardless of seriousness, severity, or presumed relationship to study treatment, will be captured on the eCRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the subject is screened will be considered as baseline and not reported as an AE. However, if the study subject's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. Adverse Events characterized as intermittent require documentation of onset and duration of each episode.

The investigator will record all reportable events with start dates occurring any time after informed consent is obtained until 30 days after the last day of study treatment. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.4 REPORTING PROCEDURES

8.4.1 Adverse Event Reporting

All identified AEs (related and unrelated) must be recorded and described on the AE page of the eCRF.

8.4.2 Serious Adverse Event Reporting

Every SAE, regardless of suspected causality, occurring after the subject has provided informed consent and until at least 30 days after the subject has stopped study treatment must be reported to the Sponsor within 24 hours of site awareness.

Any SAE experienced after this 30-day period should only be reported to the Sponsor if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information.

Information about all SAEs will be recorded on the SAE Report Form (in the eCRF). In case of technical difficulties, SAE notification can be carried out by contacting a Pharmacovigilance Officer via email at *all_phv@opis.it* or by fax using the following number: Fax: +39 0362 633622 (or updated contact information supplied by the Sponsor if the email address and/or fax number change during the conduct of the study).

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the study Sponsor and should be provided as soon as possible. The Study Sponsor will be responsible for notifying Health Authorities of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the Sponsor's initial receipt of the information.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

8.4.3 Events of Special Interest

Safety events of special interest include, but are not limited to:

- Secondary Primary Malignancies
- Infusion-Related Reactions
- Medication Error
- Abuse/Misuse/Overdose
- Occupational Exposure
- Drug-Drug Interaction
- Suspected Transmission of Infectious Agents
- Intravascular Hemolysis

All events of special interest should be monitored and recorded in the eCRF. Any event that meets the criteria of a serious adverse event should be recorded on the eCRF. In addition, any events of secondary primary malignancies and suspected transmission of infectious agents will follow the same SAE reporting timelines and procedures outlined in *Section 8.4.2*.

8.4.4 Pregnancy

A female subject will be instructed to immediately inform the investigator if she becomes pregnant during the study. The investigator shall report all pregnancies within 24 hours to the Sponsor using the Pregnancy Reporting Form (in the eCRF). In case of technical difficulties, pregnancy notification can be carried out by contacting a Pharmacovigilance Officer via email at *all_phv@opis.it* or by fax using the following number: Fax: +39 0362 633622 (or updated contact information supplied by the Sponsor if the email address and/or fax number change during the conduct of the study).

Any female subject who becomes pregnant during the study must discontinue treatment with pomalidomide. The subject should be referred to a physician experienced in teratology for evaluation and advice on her pregnancy and the possible effects on the fetus.

There are no human or animal data to assess the risk of daratumumab use during pregnancy. IgG1 monoclonal antibodies are known to cross the placenta after the first trimester of pregnancy. Therefore, daratumumab should not be used during pregnancy unless the benefit of treatment to the woman is considered to outweigh the potential risks to the fetus. The investigator will therefore inform the subject of the potential risks to the fetus and discuss with the Sponsor as well as the subject if it is in the subject's best interest to continue or stop treatment with daratumumab.

Monitoring of the subject should continue until conclusion of the pregnancy. Pregnancies occurring up to 90 days after the completion of the study medication must also be reported to the investigator.

The effect of daratumumab on sperm is unknown. Therefore, pregnancy occurring in the partner of a male subject participating in the study should also be reported to the investigator and the Sponsor.

Investigators should comply with the local label for pomalidomide for guidance on subject education and ensure that all subjects adhere to the local Pomalidomide REMS program. When no local pomalidomide REMS program exists, subjects must adhere to the pomalidomide Global Pregnancy Prevention Plan.

8.4.5 Product Quality Complaint

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 effect on the safety and efficacy of the product; therefore, the timely, accurate, and complete reporting and analysis of PQC information are crucial for the protection of subjects, investigators, and the Sponsor.

All PQCs must be reported to the Sponsor using a PQC form (in the eCRF) within 24 hours upon awareness, regardless if the relevant defect is combined with an (S)AE or not. Where possible, a sample of the suspected product should be maintained for further investigation if requested by the Sponsor.

8.4.6 Annual Safety Report

An annual safety report will be submitted to the Competent Authorities and Ethics Committees once a year, according to the relevant local regulations.

8.5 SAFETY OVERSIGHT

Safety data will be reviewed by the study Independent Data Monitoring Committee (IDMC) approximately every 6 months (after first randomized subject started Dara SC administration). The IDMC will no longer review study data after the primary PFS analysis has been completed.

9 CLINICAL MONITORING

Clinical site monitoring will be conducted to ensure that the rights and well-being of human subjects are protected, that the reported study data are accurate, complete, and verifiable, and that the conduct of the study complies with the currently approved protocol, with GCP, and with applicable regulatory requirements.

Monitoring for this study will be performed by a Contract Research Organization (CRO).

Details of clinical site monitoring are documented in a Clinical Monitoring Plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

Independent audits may be conducted to ensure monitoring practices are performed consistently across all participating sites and that monitors are following the CMP.

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL AND ANALYTICAL PLANS

The primary analysis of PFS will be performed when the targeted number of PFS events required has been reached. Analysis will use response or progression status as derived by a validated computer algorithm in accordance with modified IMWG response criteria.

10.2 STATISTICAL HYPOTHESES

The primary efficacy endpoint is PFS as assessed by the computer algorithm.

The distribution of PFS will be estimated using the Kaplan-Meier method. The median PFS, along with 95% CIs, will be presented by treatment group. The primary efficacy analysis will be the comparison of the distribution of PFS between the 2 treatment groups using a stratified log-rank test at one-sided 2.5% level of significance, i.e.,

H_0: $S_{DaraPomDex}(t) = S_{PomDex}(t)$

will be tested against the one-sided alternative hypothesis

H_{a1}: $S_{DaraPomDex}(t) > S_{PomDex}(t)$ for all t with strictly inequality for some t.

where $S_{DaraPomDex}(t)$ is the survival distribution function of PFS in the DaraPomDex, and $S_{PomDex}(t)$ is the survival distribution function of PFS in the PomDex arm. A stratified Cox proportional hazard model will be used to estimate the HR of PFS, along with 95% CI (see *Section 10.4.2*).

The primary analysis will be performed when at least 188 PFS events have been documented.

10.3 ANALYSIS DATASETS

Intent-to-Treat Analysis Set

The intent-to-treat (ITT) Analysis Set comprises all subjects to whom study treatment has been assigned by randomization. Subjects who already began treatment with daratumumab for IV infusion (Dara IV) prior to Amendment 1 approval will be offered the option to switch to SC dosing through study end, and they will be included as part of the ITT population.

Safety Analysis Set

The safety analysis set consists of all subjects who received at least 1 dose of study medication. Subjects who have been randomized and did not take at least 1 dose of study medication will not be included in the safety set. Subjects will be analyzed according to the study treatment they actually received.

Pharmacokinetic Analyses

Pharmacokinetic analyses will be performed on the pharmacokinetic-evaluable population, defined as subjects who have received 1 dose of daratumumab and have at least 1 postdose pharmacokinetic sample. All serum concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration data presentation. Concentrations below the lowest quantifiable concentration will be treated as zero in the summary statistics. All subjects and samples excluded from the analysis will be clearly documented in the study report.

Descriptive statistics will be used to summarize daratumumab serum concentrations at each sampling time point and pharmacokinetic parameters of daratumumab such as C_{min} and C_{max}.

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

Immunogenicity Analyses

The incidence of antibodies to daratumumab (immunogenicity) and rHuPH20 will be summarized separately for all subjects who receive a dose of daratumumab and have appropriate samples for detection of antibodies to daratumumab and rHuPH20. A listing of any subjects positive for antibodies to daratumumab and rHuPH20 will also be presented.

Pharmacokinetic/Pharmacodynamic Analyses

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

10.4 DESCRIPTION OF STATISTICAL METHODS

10.4.1 General Approach

All data collected in this study will be listed and summarized as appropriate as described below. Data from all sites will be pooled and summarized.

Continuous data will be summarized by mean, standard deviation (SD), median, first and third quartiles, and minimum and maximum. Categorical data will be presented by absolute and relative frequencies (n and %) or contingency tables.

One-sided alpha level 0.025 will be used for the primary endpoint, PFS. Hierarchical testing of secondary endpoints will be specified in the Statistical Analysis Plan (SAP) to strongly control the family-wise Type I error rate at one-sided alpha of 0.025.

10.4.2 Analysis of the Primary Efficacy Endpoint(s)

The efficacy analysis will be performed based on the ITT analysis set.

Progression Free Survival (PFS)

Progression free survival is defined as the time, in months, from the date of randomization to the date of the first documented disease progression or death due to any cause, whichever comes first. Clinical deterioration will not be considered progression. For subjects who neither progress nor die, the PFS time will be censored at the date of their last adequate disease assessment. For subjects who start a new anti-MM treatment, PFS time will be censored at the date of last adequate assessment before the start of the new treatment. For a randomized subject who does not have any post-baseline disease assessments and who has not died, PFS time will be censored at the randomization date.

Progression free survival will be compared between treatment groups using a stratified log-rank test with a one-sided $\alpha = 0.025$ level. The distribution of PFS for each treatment group will be estimated using the Kaplan-Meier product-limit method. Median and two-sided CIs for median PFS will be computed by treatment group. Kaplan-Meier plots of PFS will be presented.

A stratified Cox proportional hazard model for PFS with treatment arm as single factor will be used to estimate the HR of DaraPomDex to PomDex and its corresponding 95% CI. The stratification factor will be the same as that used in the randomization process.

Absolute frequencies and proportions of subject with disease progression or all-cause death will also be provided.

A sensitivity analysis of PFS may be conducted by excluding those subjects who already began treatment with Dara IV prior to Amendment 1.

10.4.3 Analysis of the Secondary Endpoint(s)

All secondary efficacy analyses will be performed based on the ITT analysis set.

Overall Response Rate (ORR)

Overall response rate is defined as the proportion of randomized subjects who achieve a best response of PR or better using modified IMWG criteria (Appendix 2).

Overall response rate will be compared between arms using a stratified Cochran Mantel-Haenszel (CMH) chi-square test with a two-sided $\alpha = 0.05$ level. The response rate, along with its exact two-sided 95% CI, will be computed within each treatment group. A two-sided 95% CI for difference of response rate between the treatment groups will also be computed.

A sensitivity analysis of ORR may be conducted by excluding those subjects who already began treatment with Dara IV prior to Amendment 1.

Very Good Partial Response (VGPR) or Better Rate, CR or Better Rate, MRD Negativity Rate

Very good partial response (VGPR) or better rate is defined as the proportion of randomized subjects who achieve a best response of VGPR or better using modified IMWG criteria.

Complete response (CR) or better rate is defined as the proportion of randomized subjects who achieve a best response of CR or better using modified IMWG criteria.

Minimal residual disease (MRD) negativity rate is defined as the proportion of randomized subjects who achieve a negative result of MRD. Subjects without MRD assessment will be considered as having MRD-positive results.

These categorical endpoints will be analyzed similarly to ORR.

Time to Response

Time to response is defined for subjects who achieve a confirmed response as the time between the date of randomization and the first efficacy evaluation that the subject has met all criteria for PR or better.

Descriptive statistics will be used to summarize time to response.

Duration of Response (DoR)

Duration of response will be restricted to the randomized subjects who achieve a best response of PR or better. It is measured from the time, in months, that the criteria for response are first met until the date of a progression event (according to the primary definition of PFS). A subject with response who does not have a progression event will be censored at the same time they were censored under the primary definition of PFS.

The DoR for each treatment group will be estimated descriptively using the Kaplan-Meier product-limit method.

Time to Next Therapy

Time to next therapy will be defined as the time, in months, from the date of randomization to the date of subsequent antimyeloma therapy or death from any cause, whichever comes first. For subjects who neither start a new antimyeloma therapy nor die, survival time will be censored at the date of their last available follow-up date. For a randomized subject who does not have any post-baseline follow-up assessments and who has not died, survival time will be censored at the randomization date.

Time to next therapy will be analyzed similarly to PFS.

Overall Survival (OS)

Overall survival is defined as the time, in months, from the date of randomization to the date of death from any cause. If a subject is not known to have died, survival time will be censored at the date of last contact ("last known date alive"). Overall survival will be analyzed similarly to PFS.

Patient Reported Outcomes Measures

EORTC QLQ-C30, EORTC QLQ-MY20 scale and single-item scores, and EQ-5D-5L visual analog scale and utility values will be summarized at each time point. Treatment effect will be assessed by change from baseline at each time point summarized by treatment group.

10.4.4 Safety Analyses

Safety analyses will be conducted on the safety set and will be reported by actual treatment group.

Adverse Events

Adverse events will be assessed according to the CTCAE (Version 4.03).

The incidence of AEs will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term (PT). The incidence of AEs will also be summarized by SOC, PT, and severity (based on CTCAE grades).

The same analysis will be repeated for SAEs regardless of drug relationship, for drug-related SAEs, AEs with CTCAE Grade 3 or 4, and for drug-related AEs. AEs for which relationship to study drug is not specified will be considered treatment-related.

Deaths reportable as SAEs will be listed by subject and tabulated by type of AE.

Laboratory Parameters

Categorization of laboratory values will be assigned programmatically as per NCI CTCAE Version 4.03 or according to normal ranges for those parameters without available CTCAE grading. The calculation of CTCAE grades will be purely based on the observed laboratory values, clinical assessments will not be taken into account.

A CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

For laboratory tests where grades are not defined by CTCAE Version 4.03, results will be graded by the low/normal/high (low and high) classifications based on laboratory normal ranges.

The following by-treatment summaries will be generated separately for hematology, biochemistry, and urinary laboratory tests:

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each subject will be counted only once for the worst grade observed post-baseline.
- Shift tables using CTCAE grades to compare baseline to the worst on-treatment value.
- Shift tables using the low/normal/high/ (low and high) classification to compare baseline to the worst on-treatment value, for laboratory tests where CTCAE grades are not defined.

Listings of all laboratory data with values flagged to show the corresponding CTCAE grades, and the classifications relative to the laboratory normal ranges will also be generated.

Other Safety Data

Electrocardiograms, vital signs, and ECOG PS will be listed and summarized by treatment arm.

ECG

- Shift table baseline to worst on-treatment result
- Listing of ECG evaluations for all subjects with at least 1 abnormality
- Change from baseline QTcF

Vital Signs

- Table with descriptive statistics at baseline, 1 or several post-baseline time points and change from baseline to this/these post-baseline time points

ECOG Performance Status

- Shift tables comparing the baseline PS with the worst post-baseline result

10.4.5 Baseline Descriptive Statistics

All data regarding subject demographics and baseline characteristics will be summarized on the ITT, overall and by treatment group, by means of summary descriptive statistics.

A complete description of subject disposition will be provided, overall and by treatment group specifying the number of randomized subjects, discontinued subjects, and the reason for the discontinuation.

The analysis populations will be described and the reasons for excluding the subject from any analysis set will be provided with the number of protocol violators per each criterion.

Medical history data will be presented by MedDRA SOC and PT.

10.4.6 Treatments (Study Treatment, Concomitant Therapies)

The Safety set will be used for the following analyses.

Investigational Treatment

Duration of study treatment, cumulative dose, average daily dose, actual dose intensity, and relative dose intensity of each of the components of study treatment will be summarized by treatment arm and for every 28-day cycle. The number of subject with dose changes/interruptions will be presented by treatment group, along with the reasons for the dose change/interruptions.

Concomitant Treatments

Concomitant medications or procedures and significant non-drug therapies taken concurrently with the study treatment will be listed and summarized by World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) Class, PT, and treatment arm. These summaries will include medications starting on or after the start of study treatment (defined as C1D1) or medications starting prior to the start of study treatment and continuing after the start of study treatment. Any prior medication or significant non-drug therapy starting and ending prior to the start of study treatment will be listed.

For the analyses of transfusions, only transfusions received after start of study treatment and up to 30 days after last dose will be considered. The number of subjects with transfusions and number of transfusions per subject will be analyzed.

10.4.7 Planned Interim Analyses

An interim analysis will be performed by the IDMC, consisting of 2 clinicians and 1 statistician who are independent experts not otherwise participating in the study, when 113 PFS events arising from both DaraPomDex and PomDex arms, which is 60% of the total planned events, have been accumulated. The purpose of this interim analysis is to evaluate cumulative interim safety and efficacy data. The significance level at this interim analysis to establish the superiority of DaraPomDex over PomDex with regard to PFS will be determined based on the observed number of PFS events at the interim analysis, using the O'Brien-Fleming boundaries as implemented by the Lan-DeMets alpha spending method (ie, 0.0038 if observing exactly 113 events). If the stopping boundary is crossed at the interim analysis, the IDMC may recommend early stopping for superiority, as well as cross-over of subjects who have disease progression on PomDex alone, based on their unblinded review of the efficacy and safety data.

10.4.8 Additional Sub-group Analyses

Additional sub-group analyses will be detailed in the SAP.

10.4.9 Multiple Comparison/Multiplicity

Unless stated otherwise, one-sided alpha level 0.025 will be considered. Strong control of family-wise Type I error rate will be controlled at a one-sided significance level of 0.025 for the following major secondary endpoints: OS, ORR, VGPR or better rate, CR or better rate, and MRD negativity rate. A hierarchical testing procedure will be used. Details about this procedure will be specified in the SAP for this study.

10.4.10 Exploratory Analyses

Additional exploratory analyses will be detailed in the SAP.

10.5 SAMPLE SIZE

Based on the primary endpoint PFS, at a one-sided significance level of 0.025, assuming exponential survival distribution with a HR of 0.621, a total of 280 evaluable subjects (140 per arm) are required to observe 188 events to test the hypothesis with 90% power. Assuming a 7% rate for permanent early censoring before the study cutoff, approximately 302 subjects will need to be randomized (151 per arm).

The primary analysis of PFS will occur after approximately 188 PFS events have been observed. The actual timing of the analysis will depend on the event rates in both control and treatment arms and will be monitored during the study. Long-term survival follow-up will continue until approximately 166 deaths have been observed. Therefore, this study will achieve approximately 70% power to detect a 34% reduction in the risk of death (HR=0.66) with a log-rank test (one-sided alpha=0.025).

10.6 MEASURES TO MINIMIZE BIAS

10.6.1 Enrollment/ Randomization/ Masking Procedures

Subject Numbering

Each subject is identified in the study by a Subject Number (Subject No.), that is assigned when the subject is first enrolled for screening and is retained as the primary identifier for the subject throughout his/her entire participation in the study. The investigator or designated staff will contact the Interactive Web Response System (IWRS) and provide the requested information for the subject to register them into the system. Once assigned, the Subject No. must not be reused for any other subject and the Subject No. for that individual must not be changed. If the subject fails to be randomized for any reason, then the reason will be entered into the Screening Disposition page.

Treatment Assignment/Randomization

Subjects will be assigned to 1 of the treatments (ie, DaraPomDex vs. PomDex) in a 1:1 ratio stratified by number of lines of prior therapy (1 vs. 2-3 vs. ≥4) and ISS stage (1, 2, 3). Subjects who already began treatment with daratumumab for IV infusion (Dara IV) prior to Amendment 1 approval will be offered the option to switch to SC dosing through study end, and they will be counted toward a total of 302 subjects.

The randomization numbers will be generated using procedures that ensure that treatment assignment is unbiased. A subject randomization list will be produced by the IWRS provider using a validated system that automates the random assignment of subject numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers.

Prior to dosing, all subject who fulfill all inclusion/exclusion criteria will be randomized via IWRS to 1 of the treatment arms. The investigator or his/her delegate will log on to the IWRS and confirm that the subject fulfills all the inclusion/exclusion criteria. The IWRS will assign a randomization number to the subject, which will be used to link the subject to a treatment arm and will specify a unique medication number for the first package of study treatment to be dispensed to the subject.

10.6.2 Blinding - Unblinding

Since this is an open-label study, the treatment will be open to subject, investigator staff, and personnel performing the assessments.

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Each participating site will maintain appropriate medical and research records for this study, in compliance with ICH E6 and regulatory and institutional requirements for the protection of confidentiality of subject. Each site will permit authorized representatives of Regulatory Agencies to examine (and when permitted by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress, and data validity.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medical-technical departments involved in the clinical study.

The eCRF will not be the only record of the subject's participation in the study in order to ensure that anyone who accessed the subject's medical record would have adequate knowledge that the subject is participating in the study.

Inclusion/Exclusion Criteria Source Documentation Requirements

The minimum source documentation requirements for the Inclusion/Exclusion criteria that specify a need for documented medical history (see *Section 5.1* and *Section 5.2*) are the following:

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

12 QUALITY ASSURANCE AND QUALITY CONTROL

Following written Standard Operating Procedures, the monitors will verify that the clinical study is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (eg, Good Laboratory Practices [GLP], Good Manufacturing Practices [GMP]).

The investigational site will provide direct access to all study-related sites, source data/documents, and reports for the purpose of monitoring and auditing by the Sponsor, and inspection by local and regulatory authorities.

13 ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1 ETHICAL STANDARDS

This clinical study shall be implemented and reported in accordance with the ICH Guidelines for GCP, all applicable local regulations, and with the ethical principles laid down in the Declaration of Helsinki.

13.2 INSTITUTIONAL REVIEW BOARD (IRB)/INDEPENDENT ETHICS COMMITTEE (IEC) AND COMPETENT AUTHORITY (CA)

The protocol, ICF(s), recruitment materials, and all subject materials will be submitted to the relevant Institutional Review Board (IRB)/IEC and CA for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRB/IEC and or CA before the changes are implemented to the study. All changes to the consent form will be IRB/IEC and/or CA approved; a determination will be made regarding whether previously consented subject need to be re-consented.

13.3 INFORMED CONSENT PROCESS

13.3.1 Consent/Assent and Other Informational Documents Provided to Subject

Consent forms describing in detail the study agent, study procedures, and risks are given to the subject and written documentation of informed consent is required prior to enrollment in the study and before any study-related procedure takes place.

13.3.2 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the subjects and their families. Consent forms will be IRB/IEC-approved and the subject will be asked to read and review the document. The investigator will explain the research study to the subject and answer any questions that may arise. All subjects will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research subjects. Subjects will have the opportunity to carefully review the written consent form and ask questions prior to signing. The subjects should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The subject will sign the ICF prior to any procedures being done specifically for the study. The subject may withdraw consent at any time throughout the course of the study. A copy of the ICF will be given to the subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

13.4 SUBJECT AND DATA CONFIDENTIALITY

Subject confidentiality is strictly held in trust by the participating investigators, their staff, and the Sponsor and their representatives. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to subjects. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Sponsor.

The study monitor, other authorized representatives of the Sponsor, representatives of the IRB/IEC or pharmaceutical company supplying study product(s) may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subject in this study. The clinical study site will permit access to such records.

The study subject's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB/IEC and institutional regulations.

Study subject research data, which is for purposes of statistical analysis and scientific reporting, will not include the subject's contact details or identifying information. Rather, individual subjects and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites will be secured and password protected.

13.4.1 Research Use of Stored Human Samples, Specimens or Data

Samples and data collected under this protocol will be used to study MM. Bone marrow, blood, and urine samples will be analyzed at a central or local laboratory depending on the type of test. All samples will be labeled appropriately with the subject identification code, date of collection, and site details.

Detailed instructions for sample collection and shipment will be provided to investigators in a separate laboratory guidance document/manual.

13.5 FUTURE USE OF STORED SPECIMENS

The samples obtained for this study will be used only for research purposes strictly related to this protocol. All samples will be stored only for the time necessary to perform the tests related to this protocol and will be destroyed upon completion of the study.

13.6 INSURANCE

Prior to the start of the study, the Sponsor will ensure that adequate insurance for subjects is in place covering losses due to death or injury resulting from the study, in accordance with applicable laws and regulations in each country where the study is conducted. In addition, the Sponsor will ensure that adequate insurance is in place for both investigator(s) and Sponsor to cover liability pertaining to death or injury resulting from the study. The investigator(s) will remain responsible towards the Sponsor of any fault or misconduct regarding the performance of the study.

14 DATA HANDLING AND RECORD KEEPING

Refer to *Appendix 12* for guidance regarding data handling and record keeping for subjects continuing on study treatment after the CCO for the final OS analysis.

14.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data Collection

Designated investigator staff will enter the data required by the protocol into the eCRF using fully validated software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the Electronic Data Capture system until they are trained.

Web-based software will be used and no installation procedure is needed. Each site will be authorized by the administrator to access the eCRF. Each site-qualified personnel will be allowed to access the eCRF by means of a ‘login mask’ requiring user ID and password and may read, modify, and update only the information he/she previously reported. Each page reports site code and subject code.

On-line validation programs will check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer to the CRO working on behalf of the Sponsor. The investigator will certify that the data entered into the eCRF is complete and accurate.

After database lock, the investigator will receive a CD-ROM of subject data for archiving at the investigational site.

Database Management and Quality Control

The CRO working on behalf of the Sponsor will review the data entered into the eCRF by investigational staff for completeness and accuracy and instruct site personnel to make any necessary corrections or additions. The Data Manager will perform the cleaning session by reviewing the warning messages raised by on-line checks and by running post-entry checks by means of validation programs and data listings specific for the study. If clarifications are needed, the Data Manager will raise queries by means of data query forms through the web application. Designated investigator site staff will be required to respond to queries and the Data Manager will make the correction to the database according to the responses.

Data collection and query flows, as well as the on-line and off-line checks, are detailed in the Data Management Plan and Data Validation documents.

Concomitant medications and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the ATC classification system. Medical history/current medical conditions and AEs will be coded using MedDRA.

Randomization codes and data about the study drug are tracked using the eCRF. The system is supplied by CRO, who also manages the database.

The occurrence of any protocol deviations will be checked and the database will be locked and made available for data analysis after these actions have been completed and the database has been declared complete and accurate.

14.2 STUDY RECORDS RETENTION

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for a period of not less than twenty-five (25) years from the completion of the study unless the Sponsor provides written permission to dispose of them earlier or requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines. The subjects' medical files will be archived in accordance with the national laws.

14.3 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical study protocol or GCP requirements. The noncompliance may be on the part of the subject, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, Sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, Section 5.1.1
- 5.20 Noncompliance, Sections 5.20.1, and 5.20.2.

It is the responsibility of the site to use continuous vigilance to identify and report deviations. All deviations must be addressed in study source documents.

14.4 PUBLICATION AND DATA SHARING POLICY

This study will ensure that the public has access to the published results of the research.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or subjects, including pharmacokinetic measures and AEs. The ICMJE policy requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies.

14.5 END OF STUDY REPORT

The Sponsor will notify the accredited IEC and the CA for the end of study within a period of 90 days. The end of the study is defined as the timepoint at which all subjects who are still receiving study treatment have access through another source such as commercial availability with reimbursement, continued access through a long-term extension study, a patient access program, or when all subjects have discontinued study treatment after the CCO for the final OS analysis up to 30 September 2024, whichever occurs first. In case the study is ended prematurely, the Sponsor will notify the accredited IEC and the CA within 15 days, including the reasons for the premature termination.

The Sponsor will submit the Clinical Study Report with the final results of the study to the accredited IEC and the CA within 1 year after the end of study.

15 STUDY ADMINISTRATION

15.1 STUDY LEADERSHIP

The Scientific Committee will govern the conduct of the study and will be composed of the Sponsor Representative, the Co-ordinating Investigator, and the Scientific Co-Ordinating Investigator. The Scientific Committee will meet at least annually.

16 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this study will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the study. The study leadership has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest. Financial disclosures shall be provided by study personnel who are directly involved in the treatment or evaluation of subjects at the site - prior to study start.

17 LITERATURE REFERENCES

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APPENDICES

Appendix 1: The International Staging System (ISS) For Multiple Myeloma

Stage	Criteria	Median Survival (Months)
Stage 1	Serum β 2-microglobulin <3.5 mg/L Serum albumin ≥3.5 g/dL	62
Stage 2	Not stage I or III (There are 2 categories for stage II) serum β2-microglobulin <3.5 mg/L but serum albumin <3.5 g/dL OR β2-microglobulin 3.5 to <5.5 mg/L irrespective of the serum albumin level	44
Stage 3	Serum β2-microglobulin ≥5.5 mg/L	29

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Appendix 2: Modified International Myeloma Working Group (IMWG) Uniform Response Criteria for Multiple Myeloma

Response	*IMWG criteria*
Stringent complete response (sCR)	CR as defined below plus normal FLC ratio and absence of clonal cells in bone marrow[1] by immunohistochemistry or immunofluorescence.[2]
Complete response (CR)	Negative immunofixation on serum and urine and disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow.[1]
Very good partial response (VGPR)	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥90% reduction in serum M-protein plus urine M-protein level <100 mg/24 h
Partial response (PR)	≥50% reduction of serum M-protein and reduction in 24 hours urinary M-protein by ≥90% or to <200 mg/24 h. If serum and urine M-protein are unmeasurable, [3] a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. If serum and urine M-protein are not measurable, and serum free light assay is also not measurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥30%. In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required.
Minor (Minimal) Response (MR)	25-49% reduction of serum M-protein and reduction in 24-hour urine M-protein by 50-89%, which still exceeds 200 mg per 24 hours. In addition, if present at baseline, 25-49% reduction in the size of soft tissue plasmacytomas is also required. No increase in the size or number of lytic bone lesions (development of compression fracture does not exclude response).
No change/Stable disease	Not meeting criteria for CR, VGPR, PR, or progressive disease.
Progressive disease (PD)[3]	Any of the following: • Increase of ≥25% from lowest response value in any one or more of the following: o Serum M-component and/or (the absolute increase must be ≥0.5 g/dL)[4] o Urine M-component and/or (the absolute increase must be ≥200 mg/24 h) o Only in patients without measurable serum and urine M-protein levels; the difference between involved and uninvolved FLC levels. The absolute increase must be >10 mg/dL o Bone marrow plasma cell percentage; the absolute percentage must be ≥10%[5] • Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas (≥50% increase from nadir in SPD[7] of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in the short axis). • Development of hypercalcemia (corrected serum calcium >11.5 mg/dL or 2.87 mmol/L) that can be attributed solely to the plasma cell proliferative disorder

Response	***IMWG criteria***
Relapse	Clinical relapse requires one or more of: Direct indicators of increasing disease and/or end organ dysfunction (CRAB features).[4] It is not used in calculation of time to progression or progression-free survival but is listed here as something that can be reported optionally or for use in clinical practice • Development of new soft tissue plasmacytomas or bone lesions • Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion • Hypercalcemia (>11.5 mg/dL) [2.87 mmol/L] • Decrease in hemoglobin of ≥2 g/dL [1.24 mmol/L] • Rise in serum creatinine by 2 mg/dL or more [177 μmol/L or more]
Relapse from CR[3] (To be used only if the end point studied is DFS)[6]	Any one or more of the following: • Reappearance of serum or urine M-protein by immunofixation or electrophoresis • Development of ≥5% plasma cells in the bone marrow[5] • Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcemia)

Note: A clarification to IMWG criteria for coding CR and VGPR in patients in whom the only measurable disease is by serum FLC levels: CR in such patients is defined as a normal FLC ratio of 0.26–1.65 in addition to CR criteria listed above. VGPR in such patients is defined as a >90% decrease in the difference between involved and uninvolved free light chain (FLC) levels.

[1] Confirmation with repeat bone marrow biopsy not needed.

[2] Presence/absence of clonal cells is based upon the kappa/lambda ratio. An abnormal kappa/lambda ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is kappa/lambda of > 4:1 or < 1:2.

[3] All relapse categories require 2 consecutive assessments made at any time before classification as relapse or disease progression and/or the institution of any new therapy. In the IMWG criteria, CR patients must also meet the criteria for PD shown here to be classified as progressive disease for the purposes of calculating time to progression and PFS. The definitions of relapse, clinical relapse and relapse from CR are not to be used in calculation of time to progression or PFS.

[4] For progressive disease, serum M-component increases of ≥1 g/dL are sufficient to define relapse if starting M-component is ≥5 g/dL.

[5] Relapse from CR has the 5% cutoff versus 10% for other categories of relapse.

[6] For purposes of calculating time to progression and PFS, CR patients should also be evaluated using criteria listed above for progressive disease.

[7] SPD = sum of the products of the maximal perpendicular diameters of measured lesions

Appendix 3: ECOG Performance Status Scale

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, 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, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.
Credit to: the Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

Appendix 4: Guidelines for Asthma Eligibility Criteria

Components of Severity		Classification of Asthma Severity ≥12 years of age			
			Persistent		
		Intermittent	Mild	Moderate	Severe
Impairment Normal FEV_1/FVC: 8–19 yr 85% 20 –39 yr 80% 40 –59 yr 75% 60 –80 yr 70%	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤2x/month	3–4x/month	>1x/week but not nightly	Often 7x/week
	Short-acting $beta_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not daily, and not more than 1x on any day	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	• Normal FEV_1 between exacerbations • FEV_1 >80% predicted • FEV_1/FVC normal	• FEV_1 >80% predicted • FEV_1/FVC normal	• FEV_1 >60% but <80% predicted • FEV_1/FVC reduced 5%	• FEV_1 <60% predicted • FEV_1/FVC reduced >5%
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year (see note)	≥2/year (see note) →		
		← Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category. Relative annual risk of exacerbations may be related to FEV_1.			
Recommended Step for Initiating Treatment		Step 1	Step 2	Step 3 and consider short course of oral systemic corticosteroids	Step 4 or 5
(See figure 4–5 for treatment steps.)		In 2–6 weeks, evaluate level of asthma control that is achieved and adjust therapy accordingly.			

Appendix 5: Serum Calcium Corrected for Albumin

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

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

Source: Burtis CA, Ashwood ER. Tietz textbook of clinical chemistry, 3rd ed. Philadelphia; WB Saunders, 1998.

Appendix 6: Calculated Creatinine Clearance

Cockcroft-Gault formula:

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

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

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

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

Formula to measure creatinine clearance:

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

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

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

Appendix 7: The Family of Antihistamine Medications

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

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

  * The IV use of promethazine should be avoided.

Appendix 8: Conversion Table for Glucocorticoid Dose

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

Appendix 9: Schedule of Events: Pharmacokinetic / Immunogenicity Sample Collection Times for Subcutaneous Daratumumab Subjects Who Switched from Intravenous Infusion to Subcutaneous Administration

Days of Cycle (28-days)	First SC Dose[3]	Second SC Cycle	Third SC Cycle	Follow-up	
Day	**1**	**1**	**1**	**Post-treatment Week 4**	**Post-treatment Week 8**
Visit Window	0	+/- 1 day	+/- 1 day	+/- 7 days	+/- 7 days
Daratumumab PK (serum)	X (Predose) [1]	X (Predose) [1]	X (Predose) [1]	X	X
Daratumumab Immunogenicity (serum)	**No additional sample required; taken from Daratumumab PK Sample**				
	X (Predose) [1, 2]			X	X
rHuPH20 immunogenicity (plasma)	X (Predose) [1, 2]			X	X

rHuPH20=recombinant human hyaluronidase

[1] On dosing days, sample collection may occur up to 2 hours before but not after the start of drug administration. Samples collected on dosing days with visit windows must be collected on the actual day of study drug administration. Samples collected on non-dosing days should be collected within ±4 hours of the time of day the drug administration was started on the most recent dosing day.

[2] In addition, samples for assessment of antibodies to daratumumab and rHuPH20 should be drawn, if possible, any time an infusion-related reaction is reported (according to laboratory manual and *Section 7.1.4.4*) in association with the second administration or beyond.

[3] Subjects who switch from IV infusion to SC administration should receive the first SC dose on Day 1 of any cycle starting with Cycle 3 or later.

Appendix 10: Schedule of Events: Pharmacokinetic / Immunogenicity Sample Collection Times for Subjects receiving Daratumumab via Intravenous Administration, ONLY

	Screening	Treatment: visit window during the treatment period is +/- 3 days												End of treatment EOT[3]	Post-treatment	Survival follow-up Every 12 weeks
		Cycles 1 and 2				Cycles 3-6				Cycles 7 and beyond						
Day of Cycle (28-days)	**Days -28 to 1**	**Day 1 Baseline**	**Day 8**	**Day 15**	**Day 22**	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 1**	**Day 8**	**Day 15**	**Day 22**			
PK and Immunogenicity: Daratumumab Intravenous Only																
Daratumumab PK (DaraPomDex group only)[1,2]		C1D1 Predose; C1D1 End of Infusion (EOI)				C3D1 Predose/EOI				C7D1 Predose/EOI					4 and 8 weeks after last dose (+/- 7 days)	
Daratumumab Immunogenicity (DaraPomDex group only)[1]		**No additional sample required; taken from PK Sample (see *Section 7.1.4*)**														
		C1D1 Predose								C7D1 Predose					4 and 8 weeks after last dose (+/- 7 days)	

[1] Sample must be sent to central laboratory.

[2] For C1, C3, C7, 1 sample is to be collected before (up to 2 hours before, but not after the start of infusion) and 1 sample immediately after (up to 2 hours after, but not before the end of infusion) daratumumab administration. For additional information please refer to *Section 7.1.4*.

[3] EOT visit to occur 4 weeks after the last dose of study treatment or as soon as possible before the start of subsequent therapy.

Appendix 11: Prior Multiple Myeloma Therapy Lines

In order to achieve a uniform stratification of all subjects, the number of prior lines of therapy will be derived according to the following definition:

An administered regimen is considered as a **New Line of Therapy** when EITHER:

- There is a six-month treatment-free interval since the last regimen

  OR

- Patient has documented evidence of PD since the last regimen

Appendix 12: Continuation of Treatment After Clinical Cutoff for the Final OS Analysis to End of Study

Protocol Amendment 5 allows those subjects who are benefitting from study treatment at the time of the CCO date for the final OS analysis to continue to receive study treatment. For these subjects, study treatment will be available through continued access within the current study until it is available through another source such as commercial availability with reimbursement, continued access through a long-term extension study, a patient access program, or after the last subject transitions into the long-term extension phase of the study up to 30 September 2024, whichever occurs first. The following limited schedule is applicable.

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

Dosage and Administration
Study treatment will be administered according to the regimen established prior to Amendment 5 (see *Section 6.1.4*).

Treatment Period
Once the Sponsor has notified investigators that the CCO for the final OS analysis has been achieved (end of eCRF data collection), subjects may continue to receive study treatment through continued access within the current study until it is available through another source such as commercial availability with reimbursement, continued access through a long-term extension study, a patient access program, or after the last subject transitions into the long-term extension phase of the study up to 30 September 2024, whichever occurs first. The long-term extension phase of this study will begin at the time of the CCO for the final OS analysis and is intended to provide ongoing access to study treatment for subjects who continue to benefit from such treatment. For subjects who continue treatment after the CCO for the final OS analysis, post-treatment follow-up as defined in the protocol is not applicable; however, it will be monitored by the investigator per standard of care. HBV DNA monitoring will be performed in accordance with the local label.

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

Safety Reporting
For subjects continuing study treatment after the CCO date for the final OS analysis, SAEs that occur while the subject is receiving study treatment and within 30 days after the last dose of study treatment will be collected on paper-based SAE forms and reported to the Sponsor's global medical safety database with the same information that has been collected on the eCRF, however, SAE notification can be carried out by contacting a Pharmacovigilance Officer via email at *all_phv@opis.it* or by fax using the following number: Fax: +39 0362 633622 (or updated contact information supplied by the Sponsor if the email address and/or fax number change during the conduct of the study). SAEs that occur between the 30-day post-dose period and completion of the study should be reported using the same process if considered by the investigator to be related to study treatment. SAEs should also be documented in the subject file/source notes.

Pregnancy reporting should continue as described in *Section 8.4.4*. The pregnancy should be documented in the subject file/source notes.

Sample Collection and Handling
For subjects continuing study treatment after the CCO date for the final OS analysis, there will be no study-related assessments performed during this treatment period, and any sample collection or test for safety or disease evaluation performed by the sites for patient management should comply with standard local institution practice.

Case Report Form Completion
No data will be collected in the eCRF during this treatment period.

Source Documentation
At a minimum, the type and level of detail of source data collected should include: subject and study identification, study discussion, documentation of the informed consent process including the date, dates of visits, drug dispensing/return records, study treatment administration information, and study treatment discontinuation information (including date and reason for discontinuation).

Appendix 13: Signatures

I. SPONSOR'S SIGNATURE

Study title: A Phase 3 Study Comparing Pomalidomide and Dexamethasone With or Without Daratumumab in Subjects With Relapsed or Refractory Multiple Myeloma Who Have Received at Least One Prior Line of Therapy With Both Lenalidomide and a Proteasome Inhibitor: The APOLLO Study

Protocol No: EMN14/54767414MMY3013 Amendment 5

Version: 6.0

Date: 04 March 2024

Sponsor Representative:

Signature: .....

07 Mar 2024
Date (DD Mmm YYYY)

Prof. Pieter Sonneveld
Office No-822
Dr. Molewaterplein 40
3015 GD Rotterdam
Zuid-Holland, Netherlands

II. CO-ORDINATING INVESTIGATORS SIGNATURE

Study title: A Phase 3 Study Comparing Pomalidomide and Dexamethasone With or Without Daratumumab in Subjects With Relapsed or Refractory Multiple Myeloma Who Have Received at Least One Prior Line of Therapy With Both Lenalidomide and a Proteasome Inhibitor: The APOLLO Study

Protocol No: EMN14/54767414MMY3013 Amendment 5

Version: 6.0

Date: 04 March 2024

I have read all pages of this clinical study protocol and I agree that it contains all the information required to conduct this study.

Signature: .....

05. MAR. 2024
Date (DD Mmm YYYY)

Prof. Evangelos Terpos
Department of Clinical Therapeutics, National and Kapodistrian University of Athens School of Medicine, General Hospital of Athens "ALEXANDRA"
80 Vas. Sofias Ave & Lourou Str., PC 11528, Athens, Greece

-Confidential- 117

III. SCIENTIFIC CO-ORDINATING INVESTIGATORS SIGNATURE

Study title: A Phase 3 Study Comparing Pomalidomide and Dexamethasone With or Without Daratumumab in Subjects With Relapsed or Refractory Multiple Myeloma Who Have Received at Least One Prior Line of Therapy With Both Lenalidomide and a Proteasome Inhibitor: The APOLLO Study

Protocol No: EMN14/54767414MMY3013 Amendment 5

Version: 6.0

Date: 04 March 2024

I have read all pages of this clinical study protocol and I agree that it contains all the information required to conduct this study.

Signature:

.....

05 Mar 2024

Prof. Meletios Athanasios Dimopoulos
Department of Clinical Therapeutics, National and Kapodistrian University of Athens School of Medicine, General Hospital of Athens "ALEXANDRA"
80 Vas. Sofias Ave & Lourou Str., PC 11528, Athens, Greece

Date (DD Mmm YYYY)

IV. PRINCIPAL INVESTIGATOR SIGNATURE

Study title: A Phase 3 Study Comparing Pomalidomide and Dexamethasone With or Without Daratumumab in Subjects With Relapsed or Refractory Multiple Myeloma Who Have Received at Least One Prior Line of Therapy With Both Lenalidomide and a Proteasome Inhibitor: The APOLLO Study

Protocol No: EMN14/54767414MMY3013 Amendment 5

Version: 6.0

Date: 04 March 2024

I have read all pages of this clinical study protocol and agree to conduct the study as outlined in the protocol and to comply with all the terms and conditions set out therein. I confirm that I will conduct the study in accordance with ICH GCP guidelines and applicable local regulations. I will also ensure that Sub-investigator(s) and other relevant members of my staff have access to copies of this protocol and the ICH GCP guidelines to enable them to work in accordance with the provisions of these documents.

Principal Investigator:

Signature: .....

<Insert name and qualifications of the Investigator> Date (DD Mmm YYYY)

Printed Name: .....

Address: .....

.....