

Janssen Scientific Affairs, LLC*

Clinical Protocol

**Daratumumab plus Cyclophosphamide, Bortezomib and Dexamethasone (Dara-CyBorD)
in Previously Untreated and Relapsed Subjects with Multiple Myeloma**

Dara-CyBorD

**Protocol 54767414MMY2012; Phase 2
Amendment 2
JNJ-54767414 (daratumumab)**

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

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Prepared by: Janssen Scientific Affairs, LLC

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

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PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	16 June 2016
Amendment 1	29 August 2016
Amendment 2	2 May 2017

Amendment INT-2 (2 May 2017)

This amendment is considered 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 is to end enrollment in the relapsed multiple myeloma arm, add a third interim safety analysis, and add several clarifications to entry criteria and assessments.

Edits and additions to original text are noted in bold, and deletions are noted in strikeout.

Applicable Sections	Description of Changes
	Rationale: Due to approval of daratumumab in combination with bortezomib and dexamethasone for the treatment of subjects with multiple myeloma after at least one prior line of therapy, subjects and physicians are not opting to enroll in the relapsed multiple myeloma arm of this study. Because of this, enrollment in the relapsed multiple myeloma arm is being stopped.
Synopsis, Overview of Study Design (second paragraph)	Approximately 100 subjects will be enrolled into this study with at least 40 previously untreated multiple myeloma subjects. The relapsed multiple myeloma arm is closed to enrollment as of Amendment 2.
Synopsis, Statistical Methods (third paragraph)	To ensure that an adequate number of subjects in each cohort (previously untreated and relapsed) are enrolled, it is planned that at least 40 subjects will be enrolled in the previously untreated each disease cohort. As of Amendment 2, enrollment of subjects in the relapsed cohort is closed and expected not to exceed 15 subjects. No inferential statistics will be performed for the relapsed cohort. If the number of relapsed multiple myeloma subjects enrolled provides inadequate power, no statistical comparisons will be reported; rather, descriptive summaries will be reported.
3.1, Overview of Study Design Overview (first paragraph)	Approximately 100 subjects will be enrolled into this study with at least 40 previously untreated multiple myeloma subjects, and at least 40 subjects with relapsed multiple myeloma following one prior line of therapy. Due to slow enrollment of and at least 40 subjects with relapsed multiple myeloma following one prior line of therapy, this cohort is closed to enrollment in Amendment 2.
4.1, Inclusion Criteria #4	Have previously untreated myeloma or relapsed myeloma (enrollment of subjects with relapsed myeloma closed in Amendment 2) with one prior line of therapy including....
11.2, Sample Size Determination (third paragraph)	If the number of relapsed multiple myeloma subjects enrolled provides inadequate power, no statistical comparisons will be reported; rather, descriptive summaries will be reported.
	With the planned enrollment of 100 subjects, with a minimum of 40 newly diagnosed multiple myeloma subjects and at least 40 subjects with relapsed multiple myeloma following one prior line of therapy, at least 80% power will be achieved to detect an absolute 20% increase in each of these the untreated cohorts at the 5% 1-sided significance level. In Amendment 2, enrollment of subjects in the relapsed cohort is closed and expected not to exceed 15 subjects. No inferential statistics will be performed for the relapsed cohort.

11.3, Efficacy Analyses (second paragraph)	The proportion of subjects will be analyzed using a normal approximation to the binomial distribution comparing the observed proportion to a reference of 0.60 for previously untreated subjects. and a reference value of 0.30 for relapsed subjects.
Rationale: Text regarding 1 additional interim safety analysis after at least 50 subjects complete Cycle 1 of study treatment (or discontinue before the end of Cycle 1) was added in order to evaluate infusion-related reactions during Cycle 1.	
Synopsis, Statistical Methods (last paragraph)	Two Three interim safety analyses are planned. The first interim safety analysis will occur after the first at least 20 subjects are treated for at least 1 cycle of study treatment (or discontinue before the end of Cycle 1), and the second will occur after at least 50 subjects are treated for at least 4 cycles. The second interim safety analysis will occur after at least 50 subjects complete cycle 1 of study treatment (or discontinue before the end of Cycle 1) with a focus on infusion related reactions during cycle 1. The third interim safety analysis will occur after at least 50 subjects are treated for at least 4 cycles (or discontinue before the end of Cycle 4).
3.1, Overview of Study Design (ninth paragraph)	An Internal Data Monitoring Review Committee will review interim data at 23 predetermined interim safety analyses. The first safety analysis will occur after at least 20 subjects are treated for at least 1 cycle of study treatment (or discontinue before the end of Cycle 1), and the second will occur after at least 50 subjects are treated for at least 4 cycles. The second interim safety analysis will occur after at least 50 subjects complete Cycle 1 of study treatment (or discontinue before the end of Cycle 1) with a focus on infusion related reactions during Cycle 1. The third interim safety analysis will occur after at least 50 subjects are treated for at least 4 cycles (or discontinue before the end of Cycle 4).
11.5, Interim Analysis (first paragraph)	Two Three interim safety analyses are planned for the main study. The interim safety analyses will occur after the first 20 subjects are treated for at least 1 cycle of study treatment (or discontinue before the end of Cycle 1), and the second will occur after at least 50 subjects are treated for at least 4 cycles. The first interim safety analysis will occur after at least 20 subjects are treated for at least 1 cycle of study treatment (or discontinue before the end of Cycle 1). The second interim safety analysis will occur after at least 50 subjects complete Cycle 1 of study treatment (or discontinue before the end of Cycle 1) with a focus on infusion-related reactions during Cycle 1. The third interim safety analysis will occur after at least 50 subjects are treated for at least 4 cycles (or discontinue before the end of Cycle 4).
Rationale: Introductory text was added regarding the recent marketing approvals for daratumumab, and results for Study MMY3004, daratumumab in combination with bortezomib and dexamethasone.	
1, Introduction (second paragraph)	Daratumumab by intravenous (IV) injection is approved in the United States (US), European Union, and other countries for the treatment of patients with multiple myeloma who have received at least 3 prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD) or who are double-refractory to a PI and an IMiD. On 21 November 2016, the US Food and Drug Administration (FDA) approved daratumumab in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy.
1.1.2.2, Studies of Daratumumab in Combination with Other Backbone Chemotherapy Regimens in Relapsed/Refractory Multiple Myeloma (second, third paragraphs)	In Study MMY3004, daratumumab in combination with bortezomib and dexamethasone (DVd), the primary analysis showed a significant improvement in PFS for subjects in the DVd group, compared with the bortezomib/dexamethasone (Vd) group. This represents a 61% reduction in the risk of disease progression or death for the DVd group compared with the Vd group. The 12-month PFS rate was 61% for the DVd group and 27% for the Vd group.

	<p>Among 243 DVd-treated subjects, the most common AEs were thrombocytopenia (60%), peripheral sensory neuropathy (49%), diarrhea (34%), upper respiratory tract infection (30%), anemia (28%), and cough (27%). SAEs were reported in 49% of subjects, with the most common being pneumonia (9%); anemia, bronchitis, thrombocytopenia, atrial fibrillation, and upper respiratory tract infection (each in 3%); and pyrexia (2%). Deaths were reported in 14 subjects; 12 deaths were due to AEs and 2 were due to disease progression. The safety profile for DVd was similar to that for the Vd comparator group.</p>
<p>Rationale: The entry criterion defining multiple myeloma was edited slightly for clarity. Positron emission tomography (PET)/computed tomography (CT) fusion studies were removed for assessing lytic bone disease and extramedullary plasmacytomas since this method is unlikely to be used.</p>	
<p>4.1, Inclusion Criteria #2</p>	<p>Have documented multiple myeloma as defined by the IMWG 2015 criteria below:</p> <ul style="list-style-type: none"> - Clonal bone marrow plasma cells $\geq 10\%$ or biopsy-proven bony or extramedullary plasmacytoma* and any one or more of the following CRAB (calcium level, renal dysfunction, anemia, and destructive bone lesions) features and myeloma defining events. <p style="text-align: center;">Myeloma defining events: In addition, the subject must meet one of the criteria in either 2a or 2b.</p> - a. Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically: <ul style="list-style-type: none"> o Hypercalcemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL) o Renal insufficiency: creatinine clearance <40 mL per min or serum creatinine >177 μmol/L (>2 mg/dL) o Anemia: hemoglobin value of >20 g/L below the lower limit of normal, or a hemoglobin value <100 g/L o Bone lesions: one or more osteolytic lesions on skeletal radiography, or CT (computed tomography)**, or positron emission tomography (PET) CT. - b. Any one or more of the following: <ul style="list-style-type: none"> o Clonal bone marrow plasma cell percentage* $\geq 60\%$ o Involved:uninvolved serum FLC ratio*** ≥ 100 o >1 focal lesions on MRI (magnetic resonance imaging) studies; Each focal lesion must be 5 mm or more in size.
<p>Rationale: The exclusion criterion for human immunodeficiency virus and hepatitis was clarified, with additional assessments for hepatitis C reactivation.</p>	
<p>4.2, Exclusion Criteria, #6</p>	<p>Subjects who completed treatment for hepatitis C at least 6 months prior to screening and have no detectable circulating hepatitis C virus (HCV) by hepatitis C RNA polymerase chain reaction (PCR) at screening, may participate in the study. Such subjects will be required to undergo regular assessment for HCV reactivation during their participation in the study. Subjects who test positive for HCV at any time during these assessments will be withdrawn from the study.</p>
<p>Time and Events Schedule (Laboratory assessments/ footnote j)</p>	<p>HCV viral load to be assessed only for subjects who completed treatment for hepatitis C at least 6 months prior to screening and have no detectable circulating HCV at screening. Such subjects will be required to undergo regular assessment for HCV reactivation through 6 months after their last daratumumab administration. Subjects who test positive for HCV at any time during these assessments will be withdrawn from the study. [To be checked every 3 months through 6 months after their last daratumumab administration]</p>

9.3.2, Clinical Laboratory Tests	Hepatitis C viral load testing by hepatitis C RNA PCR – for reactivation of HCV for any subjects who had prior, treated hepatitis C and no detectable circulating HCV at study entry.
10.2 Discontinuation of Study Treatment (sixth bullet)	<ul style="list-style-type: none"> A subject with a history of HCV who completed treatment at least 6 months prior to screening, who does not agree to undergo regular assessment for HCV reactivation during their participation in the study.
10.2 Withdrawal From the Study (third bullet)	<ul style="list-style-type: none"> Had a history of HCV and completed treatment at least 6 months prior to screening but test positive for HCV at any time during the regular assessments
Rationale: An item was added to the exclusion criterion for prior multiple myeloma treatment, for completeness.	
4.2, Exclusion Criterion #2	<p>Diagnosed or treated for malignancy other than multiple myeloma, except:</p> <ul style="list-style-type: none"> Adequately treated non-melanoma skin cancer, lentigo maligna or in situ malignancies (eg, cervical, breast) without evidence of disease
Rationale: Wording regarding spirometry/FEV1 testing was clarified.	
Time and Events Schedule row; and footnote f	<p>Pulmonary functions testing Spirometry (FEV1)</p> <p>For subjects with chronic obstructive pulmonary disease or asthma, FEV1 should be measuredPulmonary function testing (spirometry) is required only for subjects with chronic obstructive pulmonary disease or asthma. FEV1 should be measured.</p>
Rationale: Text was corrected regarding enrollment of previously untreated subjects since this may not be accurate.	
3.2, Study Design Rationale	<p>Since the total subject population will likely consist of at least 50% previously untreated subjects who may undergo consolidation therapy with an autologous transplant, The duration of follow-up needs to will be at least 36 months to capture median long-term outcomes such as progression-free survival.</p>
Rationale: Clarification was made regarding language for “study drug” and “study treatment”, and dose adjustments due to change in weight.	
6, Dosage and Administration	<p>In this protocol, the term “study drug” refers to daratumumab, and “study treatment” refers to Dara-CyBorD. In this study, daratumumab is the study drug. The CyBorD medications are considered standard of care and will be commercially available drugs.</p> <p>If a subject’s weight changes by more than 10% after C1D1, the dose of daratumumab and the other weight-based treatments (cyclophosphamide, bortezomib) will be re-calculated. Otherwise, dose modification of daratumumab is not permitted (see Section 6.2, Dose Delay and Modification).</p>
Rationale: Correction was made for duration to withhold the daratumumab dose.	
Table 3: Daratumumab Administration Schedule and Dose Delay Instructions for Cycles 7+	Dose Held: $>7 \geq 14$ days (if induction or maintenance)
Rationale: Correction was made to dexamethasone dose administration for Cycle 2.	
6.1.4.1, Preinfusion Medication; Dexamethasone	3. Cycle 2 Day 1, 8, 15, and 22: dexamethasone 40 mg IV

Rationale: Clarification was made regarding cyclophosphamide dose modifications.	
6.4, Cyclophosphamide (first paragraph)	Cyclophosphamide will be given as 300 mg/m ² on Days 1, 8, 15 and 22 of each cycle (continuous) by mouth (PO), for up to 8 cycles. Dose modification may be made due to myelotoxicity (excluding anemia) and cystitis during any treatment cycle .
Rationale: Rescreening is allowed once and corresponding instructions were added.	
9.1.1, Screening Phase	Subjects who fail to meet the inclusion and exclusion criteria (ie, screen failures) may be rescreened once if their condition changes. Rescreening must be discussed with and approved by the sponsor on a case-by-case basis. Subjects who are determined to be eligible for rescreening must sign a new ICF and will then be assigned a new screening number.
Rationale: Wording for the bone marrow aspirate at screening was clarified.	
9.2.3, Bone Marrow Examination	A reasonable attempt to obtain a fresh bone marrow aspirate is required at screening. A fresh bone marrow aspirate at screening is required, if at all possible.
Rationale: Wording about laboratory results prior to dosing was clarified.	
Time and Events Schedule, footnote j; 9.3.2, Clinical Laboratory Tests	Results of local hematology and chemistry tests must be evaluated before each study drug administration Day 1 of each cycle to guide treatment decisions, but do not need to be reported in the eCRF unless they result in a dose delay.
Rationale: Clarifications were made for safety event reporting.	
12.3.1, All Adverse Events (first paragraph)	All adverse events and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until 30 days after the last dose of study treatment – completion of the subject's last study related procedure, which may include contact for follow up of safety. Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study treatment drug, must be reported using the Serious Adverse Event Form.
(New second paragraph)	During the stem cell mobilization and transplantation procedures (in eligible subjects), adverse events related to stem cell mobilization and transplantation do not need to be reported in the CRF; however, any toxicity related to study treatment will continue to be reported.
Rationale: The “Data Monitoring Committee” is now referred to as the Data Review Committee to align with current Sponsor conventions.	
	Changed everywhere relevant.
Rationale: An Anticipated Event Review Committee was erroneously referred to in the previous version of the protocol and this is being deleted as there is no need for this committee.	
Attachment 6, Anticipated Events	<p>Anticipated Event Review Committee (ARC)</p> <p>An Anticipated Event Review Committee (ARC) will be established to perform reviews of pre-specified anticipated events at an aggregate level. The ARC is a safety committee within the sponsor's organization that is independent of the sponsor's study team. The ARC will meet to aid in the recommendation to the sponsor's study team as to whether there is a reasonable possibility that an anticipated event is related to the study drug.</p>

Amendment INT-1 (29 August 2016)

This amendment is not considered substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: The overall reason for the amendment is to add clarifications for a few of the assessments being done in this study.

Edits and additions to original text are noted in bold, and deletions are noted in strikeout.

Applicable Section(s)	Description of Change(s)
Rationale: The inclusion criterion pertaining to diagnosis of multiple myeloma is being edited to align with the most recent IMWG criteria.	
4.1, Inclusion Criteria; #2 (first sentence and bullet related to bone lesions)	<p>1. Have documented multiple myeloma as defined by the IMWG 2015 criteria below:</p> <p>Clonal bone marrow plasma cells $\geq 10\%$ or biopsy-proven bony or extramedullary plasmacytoma* and any one or more of the following CRAB (calcium level, renal dysfunction, anemia, and destructive bone lesions) features and myeloma defining events:</p> <ul style="list-style-type: none"> • Myeloma defining events: <ul style="list-style-type: none"> – Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically: <ul style="list-style-type: none"> ○ Bone lesions: one or more osteolytic lesions.... If bone marrow has <10% clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement

Rationale: The details for recording daratumumab administration are being simplified.

7 Treatment Compliance	Daratumumab will be administered as an IV infusion by qualified study-site personnel and the details of each administration will be recorded in the case report form (CRF) (including date, start and stop times of the IV infusion, volume infused, and weight of IV infusion bag, including the infusion line, before and after the completion of the IV infusion) .
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Rationale: The FISH testing is being corrected to note that it is only being done at screening (for risk stratification analyses whereby patients will be grouped by high, intermediate, or standard risk for time to progression analyses).

The exploratory objective based on FISH results is being corrected to reflect the most important genetic biomarkers.

Treatment and Events Schedule; Sections 9.1.1.2 Bone Marrow Biopsy, Serum and Urine Tests; 9.1.2.3 Maintenance Therapy with Daratumumab; and 9.1.3 Post-treatment Phase (Follow-Up)	FISH was removed as an assessment to be done any time after screening.
Exploratory Objective (Synopsis; Sections 2.1.1 Objectives; 2.1.2 Endpoints)	An exploratory objective is to evaluate the clinical efficacy of Dara-CyBorD in molecular subgroups, including: del17p, del13, t(4;14), t(11;14), t(14;16) t(14;20), gain of 1q, del1p, hypodiploid status.
Rationale: A clarification is being made for the hematology and chemistry laboratory tests to make it clear they are to be done both locally and centrally except at screening (where are to be done centrally, to determine eligibility). Further, creatinine clearance was added to the serum chemistry panel, for clarity.	
Time and Events Schedule;	The rows for Hematology and Chemistries (laboratory tests) were combined, and now clarify that these are to be done by both the Central Laboratory and Local Laboratory. Footnotes were corrected accordingly.
Section 9.1.2.3, Maintenance Therapy with Daratumumab (second paragraph);	On Day 1 of every therapy cycle, a physical examination, vital signs, weight, ECOG performance status, and laboratory tests (central and local assessment of hematology, chemistry, and local assessment of pregnancy [with urine sample] if applicable) should be performed.
Section 9.3.2, Clinical Laboratory Tests (second and fifth paragraphs)	Tests being performed by the central laboratory include the hematology and chemistry tests listed below and serum pregnancy testing.....
	Results of local hematology and chemistry tests must be evaluated before each study drug administration to guide treatment decisions, but do not need to be reported in the eCRF unless they result in a dose delay.
	Creatinine clearance (added to assessments under Serum Chemistry Panel).

Rationale: Corrections are being made to delete karyotyping from the assessments to be done in an effort to limit the assessments only to those needed.

Time and Events Schedule; Sections 9.1.1.2, Bone Marrow Biopsy, Serum and Urine Tests; 9.1.2.3, Maintenance Therapy with Daratumumab	karyotype (deleted)
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Rationale: Corrections are being made to clarify that karyotyping is not being performed (as stated above), and to note quantitative immunoglobulin assessment is not part of the biopsy procedure.

Section 9.1.3, Post-treatment Phase (Follow-Up) Once the end of treatment visit has occurred, subjects will be asked to return to the study site every 12 weeks so that, if suspected CR, suspected sCR, or PD, bone marrow biopsy with Flow cytometry, ~~quantitative Ig, karyotype and myeloma FISH panel~~ can be performed. **Quantitative Ig will also be measured.**

Rationale: The procedure for assessing baseline creatinine clearance is being clarified.

4.2, Exclusion Criteria, #10 for creatinine clearance • Creatinine clearance ≤ 20 mL/min; ~~please note that the creatinine clearance can be either measured by 24 hour urine study, or estimated using a validated equation, such as the Modification of Diet in Renal Disease, Chronic Kidney Disease Epidemiology Collaboration (CKD epi), or Cockcroft-Gault; see Attachment 1~~

Rationale: Details regarding testing of bone marrow samples are being clarified.

9.2.3, Bone Marrow Examination Bone marrow aspirate or biopsy will be performed at Screening for clinical characterization (morphology, immunohistochemistry [IHC], or immunofluorescence or ~~2 to 4 color~~ flow cytometry, and cytogenetics),.... Additional bone marrow aspirates or biopsies (or both) will be performed to confirm sCR, CR, or disease progression ~~(only one analysis is required, with either IHC or immunofluorescence or 2 to 4 color flow cytometry included in the analysis)~~.

Rationale: Details for daratumumab compliance reporting are being corrected.

7 TREATMENT COMPLIANCE Daratumumab will be administered as an IV infusion by qualified study-site personnel and the details of each administration will be recorded in the case report form (CRF) ~~(including date, start and stop times of the IV infusion, volume infused, and weight of IV infusion bag, including the infusion line, before and after the completion of the IV infusion)~~.

SYNOPSIS

Study Title: Daratumumab plus Cyclophosphamide, Bortezomib and Dexamethasone (Dara-CyBorD) in Previously Untreated and Relapsed Subjects with Multiple Myeloma

BACKGROUND

Daratumumab (JNJ-54767414) is a first-in-class, fully human immunoglobulin G (IgG)1κ monoclonal antibody that binds with high affinity to CD38-expressing malignant cells, inducing tumor cell death through diverse mechanisms of immune-mediated actions (complement dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, and antibody-dependent cell phagocytosis), as well as induction of apoptosis and modulation of CD38 enzyme activities. CD38 is overexpressed on myeloma cells, but is expressed at relatively low levels on normal lymphoid and myeloid cells and in some tissues of non-hematopoietic origin, making it a relevant target for the treatment of multiple myeloma.

High response rates have been noted in subjects with previously untreated multiple myeloma when treated with the combination of cyclophosphamide, bortezomib, and dexamethasone (CyBorD), now a standard of care. Due to the safety, tolerability, and response profile for daratumumab, its combination with CyBorD has the potential to bring higher response rates.

OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

Objectives

Primary Objective

The primary objective is to evaluate complete response + very good partial response (CR+VGPR) rate following 4 cycles of induction therapy with daratumumab plus CyBorD (Dara-CyBorD), in previously untreated subjects, and in relapsed subjects with multiple myeloma, as defined by the International Myeloma Working Group (IMWG) criteria.

Secondary Objectives

The secondary objectives are to evaluate, in previously untreated subjects and in relapsed subjects with multiple myeloma:

- Overall response rate (CR+VGPR+partial response [PR], ORR)
 - Following 4 cycles of Dara-CyBorD induction therapy
 - At the end of 4 to 8 cycles of Dara-CyBorD induction therapy
 - Post-transplant (in subjects who undergo high dose therapy and autologous stem cell transplantation)
 - At the end of 12 cycles of daratumumab maintenance therapy
- Time to VGPR or better
- Time to PR or better
- Progression-free survival (PFS) rate: at 1 year and 3 years
- Overall survival (OS) rate: at 1 year and 3 years
- Safety and tolerability of Dara-CyBorD
- Safety profile of split-dose initial infusions of daratumumab administered as 8 mg/kg on Cycle 1 Day 1 (C1D1) and cycle 1 Day 2 (C1D2)

Exploratory Objective

An exploratory objective is to evaluate the clinical efficacy of Dara-CyBorD in molecular subgroups, including: del17p, del13, t(4;14), t(11;14), t(14;16).

Endpoints

Primary Endpoint

The primary endpoint is the proportion of subjects achieving CR+VGPR response following 4 cycles of induction therapy with Dara-CyBorD, in previously untreated subjects and in relapsed subjects with multiple myeloma, as defined by the IMWG criteria.

Secondary Endpoints

The secondary efficacy endpoints include:

- ORR - the proportion of subjects achieving CR+VGPR+PR response following 4 cycles of induction therapy with Dara-CyBorD, in previously untreated subjects, and in relapsed subjects with multiple myeloma, as defined by the IMWG criteria at the following timepoints:
 - Following 4 cycles of induction therapy
 - At the end of Dara-CyBorD induction therapy
 - Post-transplant (in subjects who undergo high dose therapy and autologous stem cell transplantation)
 - At the end of all (12 cycles) maintenance therapy
- Time to VGPR or better - the duration from the date of start of induction therapy to the date of initial documentation of VGPR or better, which was confirmed by a repeated measurement as required by the IMWG criteria*
- Time to PR or better - the duration from the date of start of induction therapy to the date of initial documentation of PR or better, which was confirmed by a repeated measurement as required by the IMWG criteria*
- Duration of response - defined as the duration from the date of initial documentation of a response (PR or better) according to the IMWG criteria to the date of first documented evidence of progressive disease according to the IMWG criteria
- PFS - defined as the duration from the date of start of induction therapy to the date of first documented evidence of progressive disease or death, whichever comes first. PFS rate at 1 year and 3 years will be estimated.
- OS measured from the date of start of induction therapy to the date of the subject's death. OS rate at 1 year and 3 years will be estimated.

The safety endpoints are:

- Safety and tolerability of the combination of Dara-CyBorD as assessed by the incidence of adverse events and laboratory test abnormalities
- Infusion reaction profile of split-dose infusions of daratumumab administered as 8 mg/kg on C1D1 and C1D2 by tabulating the incidence of infusion-related reactions by System-Organ Class and Preferred Term

* Predefined data censoring rules will be applied for time to event analyses.

Exploratory Endpoint

Clinical efficacy of Dara-CyBorD in high-risk molecular subgroups including: del17p, del13, t(4;14), t(11;14), t(14;16).

Hypothesis

The primary hypothesis of this study is that CR+VGPR rate following 4 cycles of induction therapy with Dara-CyBorD in previously untreated subjects is higher than 60%, and in relapsed subjects with multiple myeloma is higher than 30%, as defined by the IMWG criteria.

OVERVIEW OF STUDY DESIGN

This is a multicenter, single-arm, open-label, Phase 2 study evaluating the combination of daratumumab and oral cyclophosphamide, bortezomib, and dexamethasone (Dara-CyBorD) in subjects with previously untreated multiple myeloma, irrespective of eligibility for high-dose chemotherapy (HDT) and autologous stem cell transplant (ASCT), or relapsed multiple myeloma following one prior line of therapy. Relapsed multiple myeloma following one line of therapy is defined as having achieved at least a PR with first-line therapy before progression.

Approximately 100 subjects will be enrolled into this study, with at least 40 previously untreated multiple myeloma subjects. The relapsed multiple myeloma arm is closed to enrollment as of Amendment 2.

Treatment phases consist of induction therapy with 4 to 8 cycles of Dara-CyBorD (this range allows for local standard of care and physician discretion), consolidation therapy with HDT/ASCT for eligible subjects, and maintenance therapy. Following induction and/or consolidation therapy with ASCT, subjects will receive maintenance therapy with daratumumab alone for 12 cycles (of 28 days each), or until disease progression (whichever occurs first). The follow-up period for each subject, after completion of maintenance therapy with daratumumab, will continue through 36 months following the start of induction therapy.

Throughout the study, subjects will be monitored closely for adverse events, laboratory abnormalities, and clinical response. Disease response and progression will be based on assessments from IMWG Guidelines. Efficacy assessments include: M-protein measurements (serum and urine), immunofixation (serum and urine), serum free light chains, serum calcium corrected for albumin, serum immunoglobulins, examination of bone marrow aspirate or biopsy, and skeletal survey/documentation of extramedullary plasmacytomas.

A Data Review Committee will be commissioned for this study.

SUBJECT POPULATION

Participants in this study are to be at least 18 years of age and have documented multiple myeloma, measurable disease, previously untreated myeloma or relapsed myeloma with one prior line of therapy, and an Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2.

DOSAGE AND ADMINISTRATION

Approximately 100 subjects will be assigned to receive Dara-CyBorD as induction on a 28-day cycle length. All subjects will receive 4 to 8 cycles of oral cyclophosphamide 300 mg/m² on Days 1, 8, 15, and 22; subcutaneous (SC) bortezomib 1.5 mg/m² on Days 1, 8, and 15; and oral or intravenous (IV) dexamethasone 40 mg weekly. Subjects will concurrently receive daratumumab on 28-day cycles. The initial dose of daratumumab will be given as a “split dose” of 8 mg/kg IV on C1D1 and C1D2. Starting Cycle 1 Day 8 through the completion of Cycle 2, daratumumab will be given weekly at 16 mg/kg IV. For Cycle 3 to Cycle 6, subjects will receive daratumumab 16 mg/kg IV once every 2 weeks. From Cycle 7 on, subjects will receive daratumumab 16 mg/kg IV once every 4 weeks, whether in the last

induction cycles with CyBorD, or alone during the maintenance phase. All eligible subjects are to receive 12 cycles of maintenance therapy with daratumumab monotherapy, given on 28-day cycles.

The induction regimen is the same dose, schedule and cycle length for all subjects in both study populations (previously untreated myeloma or relapsed myeloma with one prior line of therapy), although the number of induction cycles may vary from 4 to 8, based on local standard of care and physician discretion. Regardless of the number of induction cycles given, all subjects will receive maintenance therapy with daratumumab 16 mg/kg on Day 1 of a 28-day cycle for 12 cycles.

EFFICACY EVALUATIONS

Disease response and progression will be assessed based on IMWG Guidelines. Daratumumab detection on serum immunofixation (IFE) has been demonstrated in subjects treated with 16 mg/kg, and may interfere with the traditional IMWG criteria of negative serum IFE for CR or stringent CR (sCR). To mitigate this interference, the sponsor has developed a reflex assay that utilizes anti-idiotype antibody to bind daratumumab and confirm its interference on IFE. For all subjects with VGPR and a negative M-protein by serum M-protein quantitation by electrophoresis (SPEP), reflex IFE testing will be performed to confirm the presence of daratumumab on IFE. In addition, for subjects who have an SPEP ≤ 0.2 g/dL and detectable IgG kappa myeloma during the study, reflex testing will also be performed to determine whether the para-protein identified on SPEP/IFE is monoclonal daratumumab or the subject's endogenous myeloma protein.

Disease evaluations must be performed on Day 1 of each cycle during the induction phase with Dara-CyBorD. Disease evaluation should be performed following ASCT, on Day 1 of the first maintenance cycle dose, for subjects who undergo ASCT. For all subjects, disease evaluation will be done on Day 1 of the maintenance phase with daratumumab and then on Day 1 of every other cycle (approximately every 56 days) or, if there are concerns for relapse, sooner.

SAFETY EVALUATIONS

Safety evaluations will include adverse event monitoring, clinical laboratory testing (hematology and serum chemistry), pregnancy testing, electrocardiogram monitoring, vital sign measurements, physical examinations, and ECOG performance status.

Since daratumumab interferes with the indirect antiglobulin test (IAT), subjects will receive a subject identification wallet card for the study that includes the blood profile (ABO, Rh, and IAT) determined before the first infusion of daratumumab along with information on the IAT interference for healthcare providers/blood banks.

STATISTICAL METHODS

The historical CR+VGPR rate after 4 cycles of CyBorD induction therapy is 60% in previously untreated multiple myeloma subjects.¹⁷ Thirty-three (33) enrolled subjects will provide 80% power at a 5% 1-sided significance level to detect an absolute 20% increase over 60% with Dara-CyBorD.

The historical CR+VGPR rate after 4 cycles of CyBorD induction therapy is 30% in previously relapsed multiple myeloma subjects.²⁰ Thirty-five (35) enrolled subjects will provide 80% power at a 5% 1-sided significance level to detect an absolute 20% increase over 30% with Dara-CyBorD.

It is planned that at least 40 subjects will be enrolled in the previously untreated cohort. As of Amendment 2, enrollment of subjects in the relapsed cohort is closed and expected not to exceed 15 subjects. No inferential statistics will be performed for the relapsed cohort.

The primary analysis will be performed after all enrolled subjects have completed 4 cycles of induction therapy disease evaluation, or have been discontinued from study treatment by this timepoint. A final data cutoff and analysis, to update secondary endpoints and safety, will occur at the end of study when all

subjects have completed 36 months of follow-up after the start of induction therapy (on Cycle 1 Day 1 [C1D1]), or until death or withdrawal of consent for study participation, whichever occurs first.

Response to study treatment and progressive disease will be evaluated by a validated computer algorithm to calculate IMWG response. The primary endpoint, rate of CR+VGPR achieved after 4 cycles of induction therapy for previously untreated and relapsed subjects, will be tabulated. Other binary endpoints, including overall CR, sCR, ORR, VGPR or better rate following induction, consolidation, and maintenance will be analyzed similarly. Time-to-event efficacy endpoints, including duration of CR, sCR, time to progression, PFS, and OS, will be descriptively summarized using the Kaplan-Meier method.

The CR+VGPR rate and its 2-sided 95% confidence interval will be provided. Other binary endpoints, including overall CR, sCR, ORR, VGPR or better rate following induction, consolidation, and maintenance will be analyzed similarly. Time-to-event efficacy endpoints, including duration of CR, sCR, time to progression, PFS, and OS, will be descriptively summarized using the Kaplan-Meier method.

For safety, treatment-emergent adverse events will be analyzed as the percentage of subjects who experience at least 1 occurrence of the given event.

Laboratory data will be summarized by type of laboratory test. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point. Change from baseline to the worst adverse event grade experienced by the subject during the study will be provided as shift tables.

Descriptive statistics of vital signs and electrocardiogram results, and changes from baseline will be summarized at each scheduled time point and the percentage of subjects with values beyond clinically important limits will be summarized.

An internal Data Review Committee will be established to review the interim data. Three interim safety analyses are planned. The first interim safety analysis will occur after at least 20 subjects are treated for at least 1 cycle of study treatment (or discontinue before the end of Cycle 1). The second interim safety analysis will occur after at least 50 subjects complete cycle 1 of study treatment (or discontinue before the end of Cycle 1) with a focus on infusion related reactions during cycle 1. The third interim safety analysis will occur after at least 50 subjects are treated for at least 4 cycles (or discontinue before the end of Cycle 4).

TIME AND EVENTS SCHEDULE

Study procedures	Screening phase (up to 28 days)	Induction ^a (4 to 8 28-day cycles of Dara-CyBorD)	+- HDT/ ASCT ^b	Maintenance Therapy ^a (12 months; approximately 12 cycles of daratumumab)	EOT ^c	Follow-up: Through 36 months after Cycle1Day1 ^d
Informed consent ^e	X					
Eligibility criteria	X					
Medical history and demographics	X					
Physical examination	X	Prior to dose on Day 1 of each cycle		Prior to dose on Day 1 of each cycle	X	
ECOG performance status	X	Day 1 of each cycle		Day 1 of each cycle	X	
Spirometry (FEV1) ^f	X					
Height	X					
Weight ^g	X	Prior to dose on Day 1 of each cycle		Prior to dose on Day 1 of each cycle		
Vital signs ^h	X	Prior to and after each dose		Prior to and after each dose		
Screening serology tests	X					
12-lead ECG	X					
Myeloma FISH panel	X					
Blood type/indirect coombs test ⁱ	X	C1D1 only				
Clinical Laboratory Assessments						
Hematology and Chemistries ^j (to be performed at central laboratory and local laboratory)	X (central laboratory only)	Prior to dose on Day 1 of each cycle		Prior to dose on Day 1 of each cycle	X	
Hepatitis C viral load testing ^j	X	Every 3 months		Every 3 months		
Serum pregnancy test (done at central laboratory)		Within 28 days before first dose on C1D1.				
Urine pregnancy test (done at local laboratory)		Within 24 hours before first dose on C1D1 and prior to dose on Day 1 of each cycle		Prior to dose on Day 1 of each cycle		
Disease Evaluation (to be performed at the central laboratory)						
Bone marrow biopsy w/ Flow cytometry	X	At suspected CR, suspected sCR, or PD		At suspected CR, suspected sCR, or PD		
SPEP ^k	X	Day 1 of each cycle		Day 1 of every other cycle		Q12wks until PD
Serum quantitative immunoglobulins ^l	X	Day 1 of each cycle		Day 1 of every other cycle		Q12wks until PD
24-hour urine (UPEP) ^m	X	Day 1 of each cycle		Day 1 of every other cycle		Q12wks until PD
Beta-2 microglobulin	X					

Study procedures	Screening phase (up to 28 days)	Induction ^a (4 to 8 28-day cycles of Dara-CyBorD)	+/- HDT/ ASCT ^b	Maintenance Therapy ^a (12 months; approximately 12 cycles of daratumumab)	EOT ^c	Follow-up: Through 36 months after Cycle1Day1 ^d
Albumin (central laboratory)	X					
Imaging						
Chest x-ray ⁿ	X					
Assessment of lytic lesions	X	As clinically indicated, using the same methodology as used at screening		As clinically indicated, using the same methodology as used at screening		
Extramedullary plasmacytomas ^o	X	To be performed/evaluated locally every 4 weeks (by physical exam) for subjects with a history of plasmacytomas or as clinically indicated until confirmed CR or PD. If assessment can only be performed radiologically, may be done every 12 weeks.		To be performed/evaluated locally every 4 weeks (by physical exam) for subjects with a history of plasmacytomas or as clinically indicated until confirmed CR or PD. If assessment can only be performed radiologically, may be done every 12 weeks.		
Drug Administration						
Daratumumab		8 mg/kg IV on C1D1, C1D2; 16 mg/kg IV on Cycle 1, Days 8, 15, 22; Cycle 2, Days 1, 8, 15, 22; Cycles 3-6, Days 1,15; Cycles 7-8, Day 1		16 mg/kg IV Day 1 of each cycle; can be administered within 14 days of planned date		
Cyclophosphamide		300 mg/m ² PO, Days 1, 8, 15, 22 of each cycle				
Bortezomib		1.5 mg/m ² SC Days 1, 8, 15 of each cycle				
Dexamethasone		C1D1 and C1D2: 20 mg IV; C1Day 3, 4 mg PO. C1 Days 8, 15, and 22: 20 mg IV; C1 Days 9, 16, and 23: 20 mg PO. C2 Days 1, 8, 15, and 22: 40 mg IV/PO. C3-8 (if with CyBorD), Days 1, 8, 15, and 22: 40 mg IV/PO		Day 1: 12 mg IV/PO		

Study procedures	Screening phase (up to 28 days)	Induction ^a (4 to 8 28-day cycles of Dara-CyBorD)	+/- HDT/ ASCT ^b	Maintenance Therapy ^a (12 months; approximately 12 cycles of daratumumab)	EOT ^c	Follow-up: Through 36 months after Cycle1Day1 ^d
Ongoing Subject review						
Concomitant medications		Continuous from the time of signing of ICF until 30 days after last dose of any component of the study treatment in the maintenance phase				
Adverse event monitoring		Continuous from the time of signing of ICF until 30 days after last dose of any component of the study treatment in the maintenance phase				

ASCT = autologous stem cell transplantation; C = cycle; CR = complete response; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end-of-treatment; FISH = fluorescence in situ hybridization; FLC = free light chain; HDT = high-dose chemotherapy;

ICF = informed consent form; IV = intravenous; PD = progressive disease; PO = oral; Q12wks = every 12 weeks; sCR = stringent CR; SPEP = serum M-protein quantitation by electrophoresis; UPEP = M-protein quantitation by electrophoresis.

- a) Induction cycles are 28 days in duration. Maintenance therapy cycles are 28 days in duration. See [Table 3](#) for acceptable dosing windows for daratumumab.
- b) Stem cell mobilization, HDT, and ASCT will be performed according to institutional standards.
- c) Subjects will receive study treatment through completion of the maintenance phase, or until confirmed disease progression, discontinuation of study treatment due to an unacceptable drug toxicity, or other reasons. Unless a subject withdraws consent for study participation, or is lost to follow-up, an EOT visit is to be scheduled 30 days after the last dose of all components of the study treatment have been discontinued, or as soon as possible before the start of next-line therapy. The EOT visit should be performed 30 days after all other study treatment is permanently discontinued.
- d) Subjects will be followed through 36 months after the start of induction therapy, or until death, withdrawal of consent for study participation, or the end of study definition is met.
- e) Must be signed before any study-related procedures are performed.
- f) Pulmonary function testing (spirometry) is required only for subjects with chronic obstructive pulmonary disease or asthma. FEV1 should be measured.
- g) If a subject's weight changes by more than 10% from C1D1, the dose of all study treatments will be re-calculated.
- h) Temperature and respiratory rate; and pulse/heart rate and blood pressure measured in sitting position. For all infusions except C1D1 and C1D2, measured immediately before the start of and at the end of daratumumab infusion. For C1D1 and C1D2 only: immediately before the start of daratumumab infusion; at 0.5, 1, 1.5, 2, and 3.5 hours after the start of the infusion and then every 2 hours through duration of infusion; at end of infusion; and 0.5 and 1 hour after the end of the infusion. For all other daratumumab infusions, vital signs should be measured before the start of infusion and at the end of the infusion.
- i) To be performed prior to dosing with daratumumab. For C1D1, there is no need to repeat the tests if they have been performed within the past 3 days. Does not need to be performed on C1D1 if no blood transfusions between screening and C1D1. A wallet card with the subject's blood type will be provided to subjects.
- j) Results of local hematology and chemistry tests must be evaluated before Day 1 of each cycle to guide treatment decisions, but do not need to be reported in the eCRF unless they result in a dose delay. HCV viral load to be assessed only for subjects who completed treatment for hepatitis C at least 6 months prior to screening and have no detectable circulating HCV at screening. Such subjects will be required to undergo regular assessment for HCV reactivation through 6 months after their last daratumumab administration. Subjects who test positive for HCV at any time during these assessments will be withdrawn from the study. Hematology and chemistry panels: see Section [9.3.2](#).
- k) Serum IFE and serum FLC assay will be performed at screening and thereafter when a CR or sCR is suspected (when SPEP or UPEP is 0 or nonquantifiable) or maintained. For subjects with light chain multiple myeloma, serum FLC assay will be performed routinely.
- l) All subject's samples will be tested for IgG, IgA, and IgM. Subjects with IgE or IgD myeloma will have samples tested for IgE or IgD.
- m) Urine IFE test will be performed at screening and thereafter when a CR or sCR is suspected (when SPEP UPEP are 0 or nonquantifiable) or maintained.
- n) To be done locally; acceptable for screening if performed as part of standard of care within 28 days before C1D1.
- o) For subjects with history of plasmacytoma; assessed by physical exam or radiologic imaging, repeat assessment on C1D1 if not done within 14 days prior to C1D1.

ABBREVIATIONS

ADCC	antibody-dependent cell mediated cytotoxicity
ADCP	antibody-dependent cell phagocytosis
AE	adverse event
ALT	alanine aminotransferase
ASCT	autologous stem cell transplantation
AST	aspartate aminotransferase
BSA	body surface area
C	Cycle
CDC	complement dependent cytotoxicity
C1D1, C1D2	Cycle 1 Day 1, Cycle 2 Day 2
CR	complete response
CrCl	creatinine clearance
CRF	case report form
CT	computed tomography
CyBorD	cyclophosphamide, bortezomib, and dexamethasone
D	Day; dexamethasone
Dara-CyBorD	daratumumab with cyclophosphamide, bortezomib, and dexamethasone
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eDC	electronic data capture
EOT	end of treatment
FEV1	forced expiratory volume in 1 second
FDA	United States Food and Drug Administration
FISH	fluorescence in situ hybridization
FLC	free light chain
GCP	Good Clinical Practice
HCV	hepatitis C virus
HDT	high-dose chemotherapy
IAT	Indirect Antiglobulin Test
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFE	immunofixation
Ig	immunoglobulin
IHC	immunohistochemistry
IMID	immunomodulatory drug
IMWG	International Myeloma Working Group
IRB	Institutional Review Board
IRR	infusion-related reaction
ISS	International Staging System
IV	Intravenous
IWRS	interactive web response system
MedDRA	Medical Dictionary for Regulatory Activities
M-protein	Monoclonal immunoglobulin (protein)
MRI	Magnetic Resonance Imaging
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
nCR	near complete response
ORR	overall response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PI	proteasome inhibitor
PO	Oral

PQC	Product Quality Complaint
PR	partial response
Q12wks	every 12 weeks
RBC	red blood cell(s)
Rd	lenalidomide + dexamethasone
SC	subcutaneous
sCR	stringent complete response
SPEP	serum M-protein quantitation by electrophoresis
SUSAR	suspected unexpected serious adverse reaction
ULN	upper limit of normal
UPEP	24-hour urine test M-protein quantitation by electrophoresis
US	United States
VGPR	very good partial response
WBC	white blood cell(s)

1. INTRODUCTION

Daratumumab (JNJ-54767414) is a first-in-class, fully human immunoglobulin G (IgG)1κ monoclonal antibody that binds with high affinity to CD38-expressing malignant cells, inducing tumor cell death through diverse mechanisms of immune-mediated actions (complement dependent cytotoxicity [CDC], antibody-dependent cell-mediated cytotoxicity [ADCC], and antibody-dependent cell phagocytosis [ADCP]), as well as induction of apoptosis and modulation of CD38 enzyme activities. CD38 is overexpressed on myeloma cells, but is expressed at relatively low levels on normal lymphoid and myeloid cells and in some tissues of non-hematopoietic origin, making it a relevant target for the treatment of multiple myeloma.

Daratumumab by intravenous (IV) injection is approved in the United States (US), European Union (EU), and other countries for the treatment of patients with multiple myeloma who have received at least 3 prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD) or who are double-refractory to a PI and an IMiD. On 21 November 2016, the US Food and Drug Administration (FDA) approved daratumumab in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy.

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

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

1.1. Background

Multiple myeloma, a malignant disorder of the plasma cells, is characterized by uncontrolled and progressive proliferation of a plasma cell clone. Patients with multiple myeloma produce a monoclonal protein, also known as paraprotein (comprising monoclonal protein [M-protein] and free light chain [FLC]), which is an Ig or a fragment of one that has lost its function. The proliferation of myeloma cells causes displacement of the normal bone marrow. Normal Ig levels are compromised, leading to susceptibility to infections. Hypercalcemia, renal insufficiency or failure, and neurological complications are frequently reported side effects of the disease.¹³

There are numerous treatment options for subjects with previously untreated multiple myeloma. A treating physician selects a regimen based not only upon age, performance status, comorbidity, and aggressiveness of the disease, but also their personal understanding of and comfort level with myeloma regimens. The agents included in a regimen may include corticosteroids, DNA alkylators (oral melphalan, oral or intravenous cyclophosphamide, bendamustine), proteasome inhibitors (PIs: bortezomib), immunomodulatory drugs (IMiDs: thalidomide, lenalidomide, and pomalidomide), monoclonal antibodies (daratumumab and elotuzumab), and high-dose chemotherapy (HDT, typically melphalan) with stem cell support. In the past, newly diagnosed subjects with multiple myeloma were categorized into 2 subpopulations based on transplant eligibility. Using this characterization younger subjects typically received an induction regimen avoiding oral melphalan followed by consolidation treatment with HDT and autologous stem cell

transplantation (ASCT). For those not considered suitable for HDT and ASCT, regimens typically included an alkylating agent (oral melphalan) and a PI or IMiD in combination with corticosteroids.

This stratification remained unchallenged until the FIRST trial which randomized newly diagnosed transplant-ineligible subjects to 1 of 3 therapeutic options: melphalan, prednisone, and thalidomide for 12 months; lenalidomide and dexamethasone (Rd) for 18 months; or continuous Rd until progression.¹ The median progression-free survival for the continuous Rd arm, Rd for 18 months, and the melphalan, prednisone, and thalidomide arm were 25.5 months, 20.7 months, and 21.2 months, respectively. Therefore, in current practice even newly diagnosed transplant-ineligible patients are treated with regimens omitting oral melphalan and are thus eligible for clinical trials exploring non-melphalan based approaches.

1.1.1. Nonclinical Studies

Based on preclinical data, daratumumab may utilize multiple effector cell functions, resulting in immune-mediated killing of tumor cells. In ex vivo experiments utilizing human bone marrow stromal cells co-cultured with primary multiple myeloma cells, CDC, ADCC, and ADCP have all been shown to lead to multiple myeloma cell lysis. The precise role of some or all of these effector functions in reducing tumor burden is unknown.^{3,12}

The binding of daratumumab to CD38 on the surface of tumor cells and engagement/ligation of the Fc domains of bound antibodies led to multiple biologic effects, including CDC, ADCC, ADCP, tumor cell apoptosis, and modulation of CD38 enzymatic activity in patient-derived cells and cell lines expressing human CD38. The in vivo efficacy of daratumumab was investigated by engrafting Daudi-luc lymphoma cells into severe combined immunodeficiency mice by intravenous (IV) injection, followed by treatment with daratumumab either immediately (preventive) or after the tumor was established (therapeutic). Treatment with daratumumab effectively reduced growth of human lymphoma cells in severe combined immunodeficiency mice, both in the preventive setting and in the therapeutic setting. In the preventive setting, the estimated half maximal effective concentration was calculated to be 0.065 µg/kg of body weight. When daratumumab was administered to mice bearing established disease, therapeutic activity was observed at a dose as low as 10 µg per mouse, corresponding to approximately 0.5 mg/kg body weight (see Investigator Brochure for details).

Importantly, daratumumab-induced ADCC and CDC do not appear to be affected by the presence of bone marrow stromal cells, indicating that daratumumab can effectively induce the killing of multiple myeloma tumor cells in a tumor-preserving bone marrow microenvironment. In vivo studies have shown that daratumumab is highly active and interrupts xenograft tumor growth at low doses.

In toxicology studies in chimpanzees, the major observed toxicities were infusion reactions and thrombocytopenia. Infusion reactions occurred during the first, but not subsequent, daratumumab infusions. Milder infusion reactions were observed after implementation of a 10 mg pre-dose 24 hours prior to the first infusion. The binding of daratumumab is ≥15-fold higher for

chimpanzee platelets than for human platelets, suggesting that thrombocytopenia may have limited clinical relevance. In cynomolgus monkeys treated with another anti-CD38 antibody, a decrease in red blood parameters was observed. The other anti-CD38 antibody binds strongly to cynomolgus monkey red blood cells, while daratumumab shows only a low level of binding to human red blood cells. This suggests that the anemia observed in the cynomolgus monkey has limited clinical relevance in patients. The effect on platelets and red blood cells in monkeys was reversible as daratumumab was cleared.

1.1.2. Clinical Studies

1.1.2.1. Single-agent Studies of Daratumumab in Relapsed/Refractory Multiple Myeloma

The GEN501 study had a 2-part design that investigated the safety and tolerability of daratumumab. Part 1 included the first-in-human study of daratumumab as part of a dose-escalation study. Part 2 of the study was a dose-expansion phase which investigated the 8 and 16 mg/kg dose of daratumumab with a primary endpoint of safety and secondary endpoints including pharmacokinetics and response. The median age of subjects was 64 years, with a median of 4 prior lines of therapy, 76% received prior ASCT, and 79% were refractory to the last line of therapy. In Part 1 of the study no maximum tolerated dose was found and the most common adverse events in Part 2 of the study was the occurrence of infusion-related reactions in 71% of subjects which were most commonly Grade 1-2 and dependent on the rate of infusion. Grade 3-4 adverse events included pneumonia and thrombocytopenia in >5% of subjects. The overall response rate (ORR) in Part 2 on the study was 36% in the cohort which was administered 16 mg/kg of daratumumab and 10% in the cohort administered 8 mg/kg of daratumumab.⁹

The MMY2002 study is an open-label, Phase 2, multicenter trial in subjects with relapsed/refractory myeloma who had previously received at least 3 lines of therapy or were refractory to both a PI and an IMiD. In Part 1 of the study, subjects were randomized 1:1 to receive 8 or 16 mg/kg of daratumumab and the dose that appeared most effective was to be evaluated further in the second part of the study. At the first interim analysis, the 18 subjects randomized to the 8 mg/kg dose cohort had an ORR of 11.1%, therefore, this dose was determined to be suboptimal. An additional 25 subjects were enrolled in the 16 mg/kg dose cohort and following a second interim analysis, the 16 mg/kg dose was selected to be studied in Part 2 of the study which included an additional 65 subjects. The median age was 63.5 years with 45% of subjects aged 65 years or older, and 11% \geq 75 years. The median time from diagnosis was 4.8 years (1.1 – 23.8 years), with subjects having a median of 5 prior lines of therapy. All subjects had prior exposure to a PI and an IMiD with 95% being refractory to both a PI and an IMiD, and 80% received prior ASCT. In total, 106 subjects were treated with 16 mg/kg of daratumumab which resulted in an ORR of 29.2% including 3 subjects (2.8%) experiencing a stringent complete response (CR) and 10 subjects (9.4%) attaining very good partial response (VGPR). The median time to response was 1 month and the median duration of response was 7.4 months. Grade 3 or higher adverse effects included anemia (24%), thrombocytopenia (19%), neutropenia (12%), fatigue (3%) and back pain (3%). The most common adverse effect was

infusion-related reactions which occurred in 42% of subjects and were mostly Grade 1-2, however, 5% of subjects had a Grade 3 infusion-related reaction.¹⁰

The clinical efficacy of the 148 subjects treated with single agent daratumumab 16 mg/kg in the GEN501 and MMY2002 trials were studied by Usmani et al.²⁰ The ORR was 31% with 2% stringent complete response (sCR), 1% CR, and 11% VGPR. The 1-year overall survival (OS) was 69% and the median OS was 19.9 months in this cohort of relapsed/refractory subjects.

1.1.2.2. Studies of Daratumumab in Combination with Other Backbone Chemotherapy Regimens in Relapsed/Refractory Multiple Myeloma

There are 7 ongoing and planned studies of daratumumab in combination with other backbone chemotherapy regimens in subjects, including 4 in subjects with relapsed or refractory multiple myeloma (the Phase 1 Study MMY1001, the Phase 1/2 Study GEN503, and the Phase 3 Studies MMY3003, MMY3004) and 3 in subjects with newly diagnosed multiple myeloma (MMY3006, MMY3007, and MMY3008).

In Study MMY3004, daratumumab in combination with bortezomib and dexamethasone (DVd), the primary analysis showed a significant improvement in PFS for subjects in the DVd group, compared with the bortezomib/dexamethasone (Vd) group. This represents a 61% reduction in the risk of disease progression or death for the DVd group compared with the Vd group. The 12-month PFS rate was 61% for the DVd group and 27% for the Vd group.

Among 243 DVd-treated subjects, the most common AEs were thrombocytopenia (60%), peripheral sensory neuropathy (49%), diarrhea (34%), upper respiratory tract infection (30%), anemia (28%), and cough (27%). SAEs were reported in 49% of subjects, with the most common being pneumonia (9%); anemia, bronchitis, thrombocytopenia, atrial fibrillation, and upper respiratory tract infection (each in 3%); and pyrexia (2%). Deaths were reported in 14 subjects; 12 deaths were due to AEs and 2 were due to disease progression. The safety profile for DVd was similar to that for the Vd comparator group.

1.1.2.3. Combination Therapy: Bortezomib, Cyclophosphamide, and Dexamethasone

Prior to the era of the novel first generation (bortezomib and lenalidomide) anti-myeloma agents, the standard of care in many institutions was combination chemotherapy with vincristine, doxorubicin and dexamethasone, which was able to induce a partial response in 63% of subjects with 6% in CR/near CR (nCR).⁶ Bortezomib is the first PI to have been approved by the US Food and Drug Administration (FDA) for multiple myeloma and other hematological malignancies (in 2008) and represented a breakthrough in the management of patients with multiple myeloma. Bortezomib was initially dosed at 1.3 mg/m² administered intravenously on a twice weekly schedule and 21-day cycle length in combination with corticosteroids. Subsequent studies revealed that subcutaneous administration and weekly dosing was equivalent to the intravenous twice weekly dosing, and the cycle length increased to 28 days.^{5,11}

Another critical element in the evolution of our understanding in the optimal dosing and administration of the combination of bortezomib and dexamethasone was the results of the

Eastern Cooperative Oncology Group (ECOG) E4A03 study which evaluated high-dose versus low-dose dexamethasone in combination with lenalidomide.¹⁵ This pivotal study addressed the contributions of higher doses of dexamethasone, which was a legacy component of myeloma therapy in the era prior to the first generation anti-myeloma agents. At that time, dexamethasone likely represented one of the most active anti-myeloma agents, even in regimens including multi-agent chemotherapy using alkylators, anthracyclines, and plant-based vinca alkyloids. Therefore, the corticosteroid dose was probably critical in the era prior to the first-generation anti-myeloma agents, as obtaining a response was challenging in itself. However, in the era of first- (bortezomib, lenalidomide), second- (carfilzomib, pomalidomide), and now third- (daratumumab, elotuzumab, ixazomib) generation anti-myeloma agents the role of corticosteroids may be more limited and its role in toxicity more scrutinized. The ECOG E4A03 study confirmed that higher doses of corticosteroids did, in fact, decrease survival in myeloma as compared to a lower dose of corticosteroids, mainly due to the higher incidence of serious infections in the control (higher dose corticosteroids) arm.

Following the FDA approval of bortezomib, the results of several clinical studies were published, describing the use of alkylators or non-cycle specific inhibitors such as cyclophosphamide and the anthracyclines. Although bortezomib was being included in the “Total Therapy 3” VTD-PACE study,²² Kropff et al.⁷ initially described the results of the combination of bortezomib, cyclophosphamide, and “intermediate-dose dexamethasone” in relapsed myeloma.⁷ Fifty-four subjects were treated with 8 cycles of bortezomib 1.3 mg/m² on days 1, 4, 8, and 11 given intravenously, cyclophosphamide 50 mg per day continuous given orally (PO), and dexamethasone 20 mg on the day of bortezomib and then the following day (total 40 mg). This induction was followed by three 5-week cycles of bortezomib 1.3 mg/m². The population was unique in that 67% of subjects had either 1-2 lines of prior therapy, however, only 30% had prior therapy with thalidomide; 20% had no prior autologous transplant but 80% had at least one prior autologous transplant. Grade 3-4 adverse events that occurred in at least 9-10% of subjects consisted of myelosuppression (leukopenia and thrombocytopenia), infections (including herpes zoster), peripheral neuropathy and fatigue. The ORR was 90% including 66% with a partial response (PR) and an impressive 16% with a CR.

Reece et al. presented the Canadian experience in a Phase 1/2 study of 37 subjects with relapsed/refractory multiple myeloma.¹⁶ The Phase 1 portion of the study included 6 dosing levels where the maximum dose of bortezomib was 1.5 mg/m² given intravenously weekly (days 1, 8, and 15), cyclophosphamide 300 mg/m² given continuously, and prednisone 100 mg given every 2 days. There was no maximum tolerated dose of the regimen, thus the Phase 2 portion of the study utilized the above dosing and schedule for 13 subjects in total. A total of 14 Grade 3-4 adverse events were reported that comprised nausea/vomiting, diarrhea, myelosuppression, hypokalemia, hypophosphatemia community acquired pneumonia, increased AST/ALT, and varicella zoster. The ORR was 85% and included CR in 54% of subjects who were, for the most part, treatment naive to the first generation anti-myeloma agents.

Reeder et al described the Mayo Scottsdale experience using the combination of bortezomib, cyclophosphamide and dexamethasone in a Phase 2 study of 33 newly diagnosed subjects with

myeloma.¹⁷ The regimen consisted of bortezomib 1.3 mg/m² given intravenously on days 1, 4, 8, and 11, cyclophosphamide 300 mg/m² given on days 1, 8, 15, and 22, and dexamethasone 40 mg on days 1-4, 9-12, and 17-20 all in a 28-day cycle. Dose modification was allowed only after Cycle 1 in anticipation of the most likely adverse events, eg, myelosuppression and cystitis due to cyclophosphamide, and peripheral neuropathy due to bortezomib. The statistical design of the study utilized the historical response rates from the studies using lenalidomide and dexamethasone and sought to improve the VGPR to >45% which would be supportive of an additional future study. The median age of the population was 60 years, 30% were International Staging System (ISS) III, and on Fluorescence In Situ Hybridization (FISH) panel 13% had deletion 17p and 18% had t(4;14). By intention-to-treat criteria the ORR was 88% with 61% achieving a >VGPR, however, 28 patients completed the 4 planned cycles and their ORR was 96%, among whom 71% had a >VGPR.

The authors commented that as compared to the Mayo experience with lenalidomide plus dexamethasone the depth of response using bortezomib, cyclophosphamide and dexamethasone resulted in significantly higher depths of response (>VGPR of 61% as compared to 44%). All subjects were able to mobilize and collect stem cells using either cytokine alone or chemo-mobilization. Five subjects did not complete the planned 4 cycles of therapy due to: disease progression in 1 patient, adverse effects in 3 patients, and 1 due to unrelated complications from surgery. Grade 3 and 4 adverse events occurred in 48% and 13% of subjects, respectively. Grade 3-4 adverse events were due to myelosuppression (50%: anemia 12%, neutropenia 13%, and thrombocytopenia 25%). Dose reductions of bortezomib were required in 27% of subjects due to peripheral neuropathy and in 21% of subjects due to myelotoxicity secondary to cyclophosphamide. However, consistent with the discussion above, 33% of subjects required a dose reduction of dexamethasone due to toxicities.

Reeder et al. updated their experience in unison with the Canadian group studying weekly bortezomib in 30 newly diagnosed subjects with myeloma.¹⁸ The control regimen was the previously studied twice weekly (days 1, 4, 8, 11) bortezomib regimen. In addition, there was an evaluation of the combination of bortezomib 1.5 mg/m² given intravenously but weekly on days 1, 8, 15, and 22, cyclophosphamide as in the control regimen and dexamethasone with Cycles 1-2 using the control regimen and Cycles 3-4 using once weekly 40 mg of dexamethasone. The ORR of 63 subjects treated with the 2 regimens (twice weekly bortezomib and once weekly bortezomib) was 90% and >VGPR in 60% and 41% in a CR/nCR. The toxicity profile of once weekly bortezomib was better than that of the control regimen and fewer dose reductions were needed of both bortezomib and dexamethasone. Long-term follow-up revealed that 49 subjects (78%) had an autologous stem cell transplant following the planned 4 cycles of therapy with only 29% receiving some form of maintenance therapy.¹⁹ The median PFS for the entire cohort of 63 subjects was 40 months, with a 5-year PFS rate of 42% and an OS rate of 70%. The ORR was similar between standard- and high-risk subjects, however, the median PFS was significantly shorter in the high-risk population (27.6 versus 55.7 months) and this impacted the 5-year OS rate (54% versus 81%).

1.2. Overall Rationale for the Study

The clinical studies described above indicate that the combination of cyclophosphamide, bortezomib, and dexamethasone (CyBorD) is a highly active regimen for subjects with previously untreated and relapsed multiple myeloma. Category 1 recommendations by the National Comprehensive Cancer Network (NCCN) for induction regimens for previously untreated patients with multiple myeloma include bortezomib and dexamethasone; lenalidomide and dexamethasone; bortezomib, doxorubicin and dexamethasone; bortezomib, thalidomide and dexamethasone; and bortezomib, lenalidomide and dexamethasone (<http://www.cancertherapyadvisor.com/multiple-myeloma/multiple-myeloma-treatment-regimens/article/218209/>). The combination of bortezomib, cyclophosphamide and dexamethasone is not currently a Category 1 recommendation; however, it offers an ideal platform for study in combination with daratumumab. As compared to combinations including intravenous doxorubicin the addition of oral cyclophosphamide has no significant cardiac toxicity. Combinations containing IMiDs have the potential to cause additional renal failure in those subjects who present with renal disease either secondary to myeloma or as an underlying co-morbidity which, in addition, may cause unexpected myelotoxicity due to the erratic renal clearance of IMiDs.

The potential benefit of combining daratumumab with multi-drug chemotherapy regimens was evaluated in fresh tumor cells from subjects with multiple myeloma.²¹ Lysis of primary tumor cells was measured directly in bone marrow mononuclear cell isolates obtained from subjects with multiple myeloma. Synergistic tumor cell lysis was demonstrated when daratumumab was combined with lenalidomide and/or bortezomib, even in samples from subjects who were refractory to lenalidomide and bortezomib treatment. Treatment of bone marrow mononuclear cell isolates with lenalidomide or bortezomib resulted in 10% and 18% lysis, respectively. When daratumumab was added to either lenalidomide or bortezomib, a 2-fold increase in lysis was observed compared with lenalidomide or bortezomib alone.

Thus, preliminary studies have shown that daratumumab can be added to multiple myeloma treatment regimens with acceptable tolerability and evidence of additional clinical activity.

We have described the high response rates which patients with previously untreated myeloma experience with the combination of CyBorD. Due to the tolerability and response profile for daratumumab, its combination with CyBorD has the potential to be the standard of care in myeloma. The broad allowance of 4 to 8 cycles of induction therapy is based on local standard of care and physician discretion for treating the subjects in this study. The primary endpoint is being evaluated after 4 weeks of induction therapy since historically, CyBorD and other induction regimens have been evaluated after 4 cycles.

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

2.1. Objectives and Endpoints

2.1.1. Objectives

Primary Objective

The primary objective is to evaluate complete response + very good partial response (CR+VGPR) rate following 4 cycles of induction therapy of daratumumab plus CyBorD (Dara-CyBorD), in previously untreated subjects, and in relapsed subjects with multiple myeloma, as defined by the International Myeloma Working Group (IMWG) criteria.

Secondary Objectives

The secondary objectives are to evaluate, in previously untreated subjects and in relapsed subjects with multiple myeloma:

- Overall response rate (CR+VGPR+partial response [PR], ORR)
 - Following 4 cycles of Dara-CyBorD induction therapy
 - At the end of 4 to 8 cycles of Dara-CyBorD induction therapy
 - Post-transplant (in subjects who undergo high dose therapy and autologous stem cell transplantation)
 - At the end of 12 cycles of daratumumab maintenance therapy
- Time to VGPR or better
- Time to PR or better
- Progression-free survival (PFS) rate: at 1 year and 3 years
- Overall survival (OS) rate: at 1 year and 3 years
- Safety and tolerability of Dara-CyBorD
- Safety profile of split-dose initial infusions of daratumumab administered as 8 mg/kg on Cycle 1 Day 1 (C1D1) and Cycle 1 Day 2 (C1D2).

Exploratory Objectives

An exploratory objective is to evaluate the clinical efficacy of Dara-CyBorD in molecular subgroups, including: del17p, del13, t(4;14), t(11;14), t(14;16).

2.1.2. Endpoints

Primary Endpoint

The primary endpoint is the proportion of subjects achieving CR+VGPR response following 4 cycles of induction therapy with Dara-CyBorD, in previously untreated subjects, and in relapsed subjects with multiple myeloma, as defined by the IMWG criteria.

Secondary Endpoints

The secondary efficacy endpoints include:

- ORR - the proportion of subjects achieving CR+VGPR+PR response following 4 cycles of induction therapy of Dara-CyBorD, in previously untreated subjects, and in relapsed subjects with multiple myeloma, as defined by the IMWG criteria at the following timepoints:
 - Following 4 cycles of induction therapy
 - At the end of Dara-CyBorD induction therapy
 - Post-transplant (in subjects who undergo high dose therapy and autologous stem cell transplantation)
 - At the end of all (12 cycles) maintenance therapy
- Time to VGPR or better - the duration from the date of start of induction therapy to the date of initial documentation of VGPR or better, which was confirmed by a repeated measurement as required by the IMWG criteria.*
- Time to PR or better - the duration from the date of start of induction therapy to the date of initial documentation of PR or better, which was confirmed by a repeated measurement as required by the IMWG criteria.*
- Duration of response - the duration from the date of initial documentation of a response (PR or better) according to the IMWG criteria to the date of first documented evidence of progressive disease according to the IMWG criteria.
- PFS - the duration from the date of start of induction therapy to the date of first documented evidence of progressive disease or death, whichever comes first. PFS rate at 1 year and 3 years will be estimated.
- OS measured from the date of start of induction therapy to the date of the subject's death. OS rate at 1 year and 3 years will be estimated.
- Safety and tolerability of the combination of Dara-CyBorD as assessed by the incidence of adverse events and laboratory test abnormalities.
- Infusion reaction profile of split-dose infusions of daratumumab administered as 8 mg/kg on C1D1 and C1D2 by tabulating incidence of IRRs by System-Organ Class and Preferred Term.

* Predefined data censoring rules will be applied for time to event analyses.

Exploratory Endpoints

Clinical efficacy with Dara-CyBorD in high-risk molecular subgroups including: del17p, del13, t(4;14), t(11;14), t(14;16).

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

2.2. Hypothesis

The primary hypothesis of this study is that CR+VGPR rate following 4 cycles of induction therapy of Dara-CyBorD in previously untreated subjects is higher than 60%, and in relapsed subjects is higher than 30%, as defined by the IMWG criteria.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a multicenter, single-arm, Phase 2 study, evaluating the combination of Dara-CyBorD in subjects with previously untreated multiple myeloma irrespective of eligibility for HDT and ASCT and subjects with relapsed multiple myeloma following one prior line of therapy. Approximately 100 subjects will be enrolled into this study with at least 40 previously untreated multiple myeloma subjects. Due to slow enrollment of subjects with relapsed multiple myeloma following one prior line of therapy, this cohort is closed to enrollment in Amendment 2.

Treatment phases consist of induction therapy with 4 to 8 cycles of Dara-CyBorD, consolidation therapy with HDT/ASCT for eligible subjects, and maintenance therapy ([Figure 1](#)). Following induction and/or consolidation therapy with ASCT, subjects will receive maintenance therapy with daratumumab alone for twelve 28-day cycles or until disease progression (whichever occurs first). Maintenance therapy for subjects who have ASCT should begin approximately 90 days after ASCT. Follow-up for all subjects will continue up until 36 months after the start of induction therapy (C1D1).

Approximately 100 subjects will be assigned to receive Dara-CyBorD as induction on a 28-day cycle length. All subjects will receive 4 to 8 cycles of oral cyclophosphamide 300 mg/m² on Days 1, 8, 15, and 22; subcutaneous (SC) bortezomib 1.5 mg/m² on Days 1, 8, and 15; and oral or IV dexamethasone 40 mg weekly. Subjects will concurrently receive daratumumab on 28-day cycles ([Table 1](#)). The initial dose of daratumumab will be given as a split dose, at a dose of 8 mg/kg IV on consecutive days (C1D1 and C1D2). Starting Cycle 1 Day 8 through the completion of Cycle 2, daratumumab will be given weekly at 16 mg/kg IV. For Cycle 3 to Cycle 6, subjects will receive daratumumab 16 mg/kg IV once every 2 weeks. From Cycle 7 onward, subjects will receive daratumumab 16 mg/kg IV once every 4 weeks, whether in the last induction cycles with CyBorD, or alone during the maintenance phase. Regardless of the number of induction cycles given, all eligible subjects are to receive 12 cycles of maintenance therapy with daratumumab 16 mg/kg IV monotherapy, given on 28-day cycles.

Table 1: Dosing Information for Dara-CyBorD by Cycle

	Cycle 1					Cycle 2	Cycles 3 to 6	Cycles 7 to 8	Maintenance cycles
Drug (dose)	Day 1	Day 2	Day 8	Day 15	Day 22				
Daratumumab (8 mg/kg IV, Cycle 1 Days 1 and 2; 16 mg/kg IV, all others)	X	X	X	X	X	Day 1, 8, 15, 22	Day 1, 15	Day 1	Day 1
Bortezomib (1.5 mg/m ²)	X		X	X		Up to 4 to 8 cycles, Days 1, 8, 15		--	
Cyclophosphamide (300 mg/m ²)	X		X	X	X	Up to 4 to 8 cycles, Days 1, 8, 15, 22		--	
Dexamethasone ^a	X	X	X	X	X	Up to 4 to 8 cycles, Days 1, 8, 15, 22		Day 1	

a: See dexamethasone dosing table ([Table 5](#))

No daratumumab dose modification (increase or decrease) will be permitted. Protocol-specified dose delays for daratumumab have been included in this protocol (refer to Section 6.2.1) and will be implemented as necessary. Subjects will be evaluated for toxicity before each dose of daratumumab is administered, as well as the occurrence of infusion-related reactions (refer to Section 6.1.5). Doses may be held based on the severity of and recovery from a previous toxicity.

Dose adjustments and delays of cyclophosphamide, bortezomib, and corticosteroids will be permitted (refer to Sections 6.3 – 6.5).

Throughout the study, subjects will be monitored closely for adverse events, laboratory abnormalities, and clinical response, as specified in the Time and Events Schedule. The National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE Version 4.03) will be used to grade toxicity throughout the study.

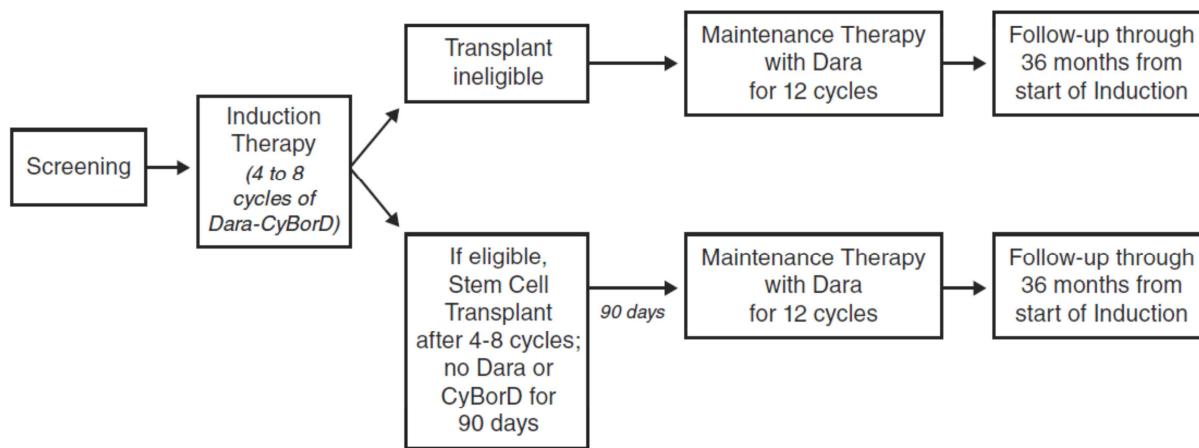
Disease response and progression will be based on assessments from IMWG Guidelines (see [Attachment 5](#)).^{4,8} Efficacy assessments include: M-protein measurements (serum and urine), IFE (serum and urine), serum FLC, serum calcium corrected for albumin, serum immunoglobulins, examination of bone marrow aspirate or biopsy, and skeletal survey/documentation of extramedullary plasmacytomas.

The primary study endpoint will be the CR+VGPR rate following 4 cycles of induction therapy with Dara-CyBorD, in previously untreated subjects and in relapsed subjects with multiple myeloma, as defined by the IMWG criteria. Secondary endpoints include ORR after 4 cycles of induction, at end of induction, after ASCT (if applicable) and at end of maintenance therapy; time to response (VGPR and PR); duration of response; the PFS rate and OS rates at 1 and 3 years; and the safety profile of Dara-CyBorD as well as of split dose infusions of daratumumab on C1D1 and C1D2.

An Internal Data Review Committee will review interim data at 3 predetermined interim safety analyses. The first safety analysis will occur after at least 20 subjects are treated for at least 1 cycle of study treatment (or discontinue before the end of Cycle 1). The second interim safety analysis will occur after at least 50 subjects complete Cycle 1 of study treatment (or discontinue before the end of Cycle 1) with a focus on infusion related reactions during Cycle 1. The third interim safety analysis will occur after at least 50 subjects are treated for at least 4 cycles (or discontinue before the end of Cycle 4).

A diagram of the study design is provided below.

Figure 1: Schematic Overview of the Study



3.2. Study Design Rationale

The present study is designed to evaluate the combination of Dara-CyBorD in subjects with previously untreated multiple myeloma and in subjects with relapsed multiple myeloma following only one line of therapy. The duration of induction therapy is generously broad due to the variability of physician preferences in the community oncology setting. It is anticipated that the median number of induction cycles will be 6 and, from this assumption, we anticipated approximately 12 months of maintenance therapy with daratumumab. The duration of follow-up will be at least 36 months to capture median long-term outcomes such as progression-free survival.

4. SUBJECT POPULATION

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

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

4.1. Inclusion Criteria

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

1. Be at least 18 years of age.
2. Have documented multiple myeloma as defined by the IMWG 2015 criteria below:
Clonal bone marrow plasma cells $\geq 10\%$ or biopsy-proven bony or extramedullary plasmacytoma.* In addition, the subject must meet one of the criteria in either 2a or 2b.
 - a. Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
 - Hypercalcemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL)
 - Renal insufficiency: creatinine clearance <40 mL per min or serum creatinine >177 μ mol/L (>2 mg/dL)
 - Anemia: hemoglobin value of >20 g/L below the lower limit of normal, or a hemoglobin value <100 g/L
 - Bone lesions: one or more osteolytic lesions on skeletal radiography, or CT (computed tomography) **.
 - b. Any one or more of the following:
 - Clonal bone marrow plasma cell percentage* $\geq 60\%$
 - Involved:uninvolved serum FLC ratio*** ≥ 100
 - >1 focal lesions on MRI (magnetic resonance imaging) studies; Each focal lesion must be 5 mm or more in size.

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

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

***These values are based on the serum Freelite assay (The Binding Site Group, Birmingham, UK). The involved FLC must be ≥ 100 mg/L.

3. Have measurable disease as defined by any of the following:
 - Serum M-protein level ≥ 1.0 g/dL or urine M protein level ≥ 200 mg/24 hours; or
 - Immunoglobulins A, D, E or M multiple myeloma: serum M-protein level ≥ 0.5 g/dL or urine M-protein level ≥ 200 mg/24 hours; or
 - Light chain multiple myeloma without measurable disease in the urine: serum Ig FLC ≥ 10 mg/dL and abnormal serum Ig kappa/lambda FLC ratio
4. Have previously untreated myeloma or relapsed myeloma (enrollment of subjects with relapsed myeloma closed in Amendment 2) with one prior line of therapy including an

induction regimen which may be followed by autologous stem cell transplantation and single agent maintenance therapy. For previously untreated subjects an emergency course of steroids (defined as no greater than 40 mg of dexamethasone, or equivalent per day for a maximum of 4 days) is permitted. In addition, radiation therapy is permitted prior to study entry, during screening, and during Cycles 1-2 of study treatment as needed for lytic bone disease.

5. Have an Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2 (refer to [Attachment 2](#)).
6. Before C1D1, a woman must be either:
 - Not of childbearing potential: premenarchal; postmenopausal (>45 years of age with amenorrhea for at least 12 months or any age with amenorrhea for at least 6 months and a serum follicle stimulating hormone level >40 IU/L or mIU/mL); permanently sterilized (eg, bilateral tubal occlusion [which includes tubal ligation procedures as consistent with local regulations], hysterectomy, bilateral salpingectomy, bilateral oophorectomy); or otherwise be incapable of pregnancy,
 - Of childbearing potential and practicing a highly effective method of birth control for 4 weeks before initiating study treatment that is consistent with local regulations regarding the use of birth control methods for subjects participating in clinical studies: eg, established use of oral, injected or implanted hormonal methods of contraception; placement of an intrauterine device or intrauterine system; barrier methods: condom with spermicidal foam/gel/film/cream/suppository or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository; male partner sterilization (the vasectomized partner should be the sole partner for that subject); true abstinence (when this is in line with the preferred and usual lifestyle of the subject)

Note: If the childbearing potential changes after start of the study (eg, woman who is not heterosexually active becomes active, premenarchal woman experiences menarche) a woman must begin a highly effective method of birth control, as described above.

7. A woman of childbearing potential must have 2 negative serum (β human chorionic gonadotropin) or urine pregnancy tests during screening, the first one within 28 days prior to the first dose of study drug and the second within 24 hours prior to the first dose of study drug.
8. A man who is sexually active with a woman of childbearing potential and has not had a vasectomy must agree to use a barrier method of birth control eg, either condom with spermicidal foam/gel/film/cream/suppository or partner with occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository, and all men must also not donate sperm during the study and for 3 months after receiving the last dose of study drug.
9. Subjects must be willing and able to adhere to the prohibitions and restrictions specified in this protocol and referenced in the informed consent form (ICF).
10. Each subject (or their legally acceptable representative) must sign an ICF indicating that he or she understands the purpose of and procedures required for the study and are willing to participate in the study.

4.2. Exclusion Criteria

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

1. Refractory to any PI or the combination of PI and IMiD agents (such as lenalidomide), defined as failure to respond or progression within 60 days of the end of PI therapy
2. Diagnosed or treated for malignancy other than multiple myeloma, except:
 - Malignancy treated with curative intent and with no known active disease present for ≥ 5 years before enrollment
 - Adequately treated non-melanoma skin cancer, lentigo maligna or in situ malignancies (eg., cervical, breast) without evidence of disease
3. Exhibiting clinical signs of or has a known history of meningeal or central nervous system involvement by multiple myeloma
4. Has known chronic obstructive pulmonary disease with a forced expiratory volume in 1 second (FEV1) $<50\%$ of predicted normal

(Note that FEV1 testing is required for subjects suspected of having chronic obstructive pulmonary disease and subjects must be excluded if FEV1 $<50\%$ of predicted normal.)

5. Has known moderate or severe persistent asthma within the past 2 years (see [Attachment 3](#)), or currently has uncontrolled asthma of any classification

(Note that subjects who currently have controlled intermittent asthma or controlled mild persistent asthma are allowed in the study.)

6. Is known to be seropositive for human immunodeficiency virus, known to have hepatitis B surface antigen positivity, or known to have a history of hepatitis C. Subjects who completed treatment for hepatitis C at least 6 months prior to screening and have no detectable circulating hepatitis C virus (HCV) by hepatitis C RNA polymerase chain reaction (PCR) at screening, may participate in the study. Such subjects will be required to undergo regular assessment for HCV reactivation during their participation in the study. Subjects who test positive for HCV at any time during these assessments will be withdrawn from the study.
7. Has any concurrent medical condition or disease (eg, active systemic infection) that is likely to interfere with study procedures or results, or that in the opinion of the investigator would constitute a hazard for participating in this study
8. Has clinically significant cardiac disease, including:
 - Myocardial infarction within 6 months before C1D1, or unstable or uncontrolled disease/condition related to or affecting cardiac function (eg, unstable angina, congestive heart failure, New York Heart Association Class III-IV)
 - Uncontrolled cardiac arrhythmia (NCI-CTCAE Version 4.03 Grade 2 or higher) or clinically significant electrocardiogram (ECG) abnormalities
9. Screening 12-lead ECG shows a baseline QT interval (QTc) >470 msec.

10. Has any of the following laboratory test results during the screening phase:

- Absolute neutrophil count $\leq 1.0 \times 10^9/L$; (granulocyte colony stimulating factor use is permitted)
- Hemoglobin level $\leq 7.5 \text{ g/dL}$ ($\leq 5 \text{ mmol/L}$); blood transfusions to maintain hemoglobin >7.5 are acceptable
- Platelet count $< 75 \times 10^9/L$ for subjects in whom $< 50\%$ of bone marrow nucleated cells are plasma cells; otherwise platelet count $< 50 \times 10^9/L$; no platelet transfusions in the past 7 days are allowed
- Alanine aminotransferase (ALT) level $\geq 2.5 \times$ upper limit of normal (ULN)
- Aspartate aminotransferase (AST) level $\geq 2.5 \times$ ULN
- Total bilirubin level $\geq 1.5 \times$ ULN, (except for Gilbert Syndrome: direct bilirubin $2 \times$ ULN)
- Creatinine clearance $\leq 20 \text{ mL/min}$ estimated using Cockcroft-Gault; see [Attachment 1](#)
- Corrected serum calcium $> 14.0 \text{ mg/dL}$ ($> 3.5 \text{ mmol/L}$) or free ionized calcium $> 6.5 \text{ mg/dL}$ ($> 1.6 \text{ mmol/L}$); see [Attachment 4](#)

11. Has known allergies, hypersensitivity, or intolerance to monoclonal antibodies or human proteins, daratumumab or its excipients (refer to Investigator's Brochure), or known sensitivity to mammalian-derived products

12. Has plasma cell leukemia ($> 2.0 \times 10^9/L$ circulating plasma cells by standard differential), Waldenström's macroglobulinemia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and/or skin changes), or amyloid light-chain amyloidosis

13. Is known or suspected of not being able to comply with the study protocol (eg, because of alcoholism, drug dependency, or psychological disorder) or the subject has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise their well-being) or that could prevent, limit, or confound the protocol-specified assessments

14. Has a contraindication to the use of oral cyclophosphamide, bortezomib, or corticosteroids per local prescribing information

15. Has received an investigational drug (including investigational vaccines) or used an invasive investigational medical device within 4 weeks before C1D1 (except for investigational anti-myeloma agents, which cannot be taken within 2 weeks before C1D1)

16. Is a woman who is pregnant or breast-feeding or planning to become pregnant while enrolled in this study or within 6 months after the last dose of study drug

17. Has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments

18. Has had major surgery within 2 weeks before C1D1, or will not have fully recovered from 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 is not considered a major surgery.)

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's status changes (including laboratory results or receipt of additional medical records) after screening but before C1D1 such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study. Section [17.4](#), Source Documentation, describes the required documentation to support meeting the enrollment criteria.

4.3. Prohibitions and Restrictions

Potential subjects must be willing and able to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation:

1. Refer to Section [8](#) (Prestudy and Concomitant Therapy) for details regarding prohibited and restricted therapy during the study
2. Agree to follow the contraceptive requirements as noted in the inclusion criteria

In addition, during the study and for 3 months after receiving the last dose of daratumumab, a woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction. Women of reproductive potential should use effective contraception during and for 3 months after cessation of daratumumab treatment.

5. TREATMENT ALLOCATION AND BLINDING

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

Subjects who are entered in the study will be registered at Screening. To initiate sponsor registration, study sites will use the interactive web response system (IWRS). After the investigator has verified that all eligibility criteria have been met, the subject will be assigned by IWRS to receive study drug. All subjects will receive the same treatment regimen, single-agent daratumumab.

The IWRS will also be used to assign study drug for the subject throughout the study, per the Time & Events schedule. The requestor will use his or her own user identification and personal identification number when contacting the IWRS, and will then give the relevant subject details to uniquely identify the subject. Details on the use of IWRS will be provided in the IWRS manual.

6. DOSAGE AND ADMINISTRATION

Study site personnel will instruct subjects on how to store pre- and post-infusion medications for at-home use as indicated for this protocol. In this protocol, the term "study drug" refers to daratumumab, and "study treatment" refers to Dara-CyBorD. The CyBorD medications are considered standard of care and will be commercially available drugs.

If a subject's weight changes by more than 10% after C1D1, the dose of daratumumab and the other weight-based treatments (cyclophosphamide, bortezomib) will be re-calculated. Otherwise,

dose modification of daratumumab is not permitted (see Section [6.2](#), Dose Delay and Modification).

6.1. Daratumumab

6.1.1. Preparation

Infusion solution will be prepared as a 500-mL dilution of daratumumab in sterile, pyrogen-free 0.9% NaCl ([Table 2](#)). Preparation of infusion bags should be done on the day of the planned infusion. Daratumumab must be administered as an IV infusion given through a well-functioning IV catheter by using an infusion pump. The study drug must be filtered by using an inline filter (0.2 μ M) during the infusion. Manuals with detailed descriptions for preparation and administration of daratumumab will be supplied to each pharmacy and site.

6.1.2. Treatment Schedule and Administration

Daratumumab will be administered in 28-day cycles. The initial dose of daratumumab will be given as a split dose, at a dose of 8 mg/kg IV on consecutive days on C1D1 and C1D2. Starting Cycle 1 Day 8 through the completion of Cycle 2, daratumumab will be given weekly at 16 mg/kg IV. For Cycle 3 to Cycle 6, subjects will receive daratumumab 16 mg/kg IV once every 2 weeks. From Cycle 7 onward, subjects will receive daratumumab 16 mg/kg IV once every 4 weeks, whether in the last induction cycles with CyBorD, or alone during the maintenance phase. All eligible subjects are to receive 12 cycles of maintenance therapy with daratumumab monotherapy, given on 28-day cycles.

Each subject's dose will be calculated based on the subject's weight rounded to the nearest kilogram. The dose of daratumumab will remain constant throughout the study, unless the subject's weight changes more than 10% from baseline. Subjects will receive preinfusion medications and postinfusion medications as outlined in Sections [6.1.4.1](#) and [6.1.4.2](#), respectively. All infusions will be planned as outpatient visits.

Subjects who have an ASCT will be eligible for maintenance daratumumab beginning approximately 90 days following the re-infusion of autologous stem cells (Day 0). Subjects will receive daratumumab post-ASCT once every 4 weeks until they complete a total of 12 cycles of maintenance therapy with daratumumab, or have disease progression, whichever comes first.

Every effort should be made to keep subjects on the planned dosing schedule. Day 1 of each cycle of daratumumab should correspond to Day 1 of each cycle of CyBorD while subjects are receiving CyBorD. However, doses given within the permitted windows (see [Table 3](#)) are allowed. All induction and maintenance cycles are 28 days. Delays in Day 1 of CyBorD should result in a corresponding delay in Day 1 of daratumumab for that cycle.

6.1.3. Instructions for Preparing and Administering Daratumumab Infusions

The dilution volumes, initial infusion rates, and increment of infusion rates for the first, second, and subsequent doses in the absence of an infusion-related reaction >Grade 1 are provided in [Table 2: Daratumumab Infusion Rates](#). The sponsor may modify the infusion rates or the preinfusion medications prospectively based upon the information collected to date from this and

other studies. Additional details for administration times and rates, as well as preinfusion medications, will be provided in the administration guidelines (study site investigational product and procedures manual).

Infusion rates will be administered as shown in Table 2.

Table 2: Daratumumab Infusion Rates

	Dilution Volume	Initial Infusion Rate (first hour)	Increments of Infusion Rate	Maximum Infusion Rate
First infusion (C1D1, 8 mg/kg)	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Second infusion (C1D2, 8 mg/kg)^a	500 mL	100 mL/hour	50 mL/hour every hour	200 mL/hour
Subsequent infusions (16 mg/kg)^b	500 mL	100 mL/hour	50 mL/hour every hour	200 mL/hour

^a: Escalate only if there were no Grade 1 (mild) or greater infusion reactions during the first 3 hours of the first infusion.

^b: Escalate only if there were no Grade 1 (mild) or greater infusion reactions during a final infusion rate of ≥ 100 mL/hr in the first 2 infusions.

As noted in the Time and Events Schedule, vital signs should be monitored frequently on C1D1 and C1D2, before, during, and after the first infusion of daratumumab (immediately before the start of daratumumab infusion; at 0.5, 1, 1.5, 2, and 3.5 hours after the start of the infusion and then every 2 hours through duration of infusion; at end of infusion; and 0.5 and 1 hour after the end of the infusion). For all other infusions, vital signs should be measured before the start of infusion and at the end of the infusion. If a subject experiences any significant medical event, then the investigator should assess whether the subject should stay overnight for observation. If the subject has not experienced a significant medical event but is hospitalized overnight only for observation, then the hospitalization should not be reported as a serious adverse event.

For this study, any dose of daratumumab greater than 8 mg/kg on C1D1 and C1D2 and 16 mg/kg on all subsequent doses of daratumumab within a 24-hour time period will be considered an overdose.

6.1.4. Guidelines for Prevention and Management of Infusion-related Reactions

The recommended pre- and postinfusion medications listed in the following sections will be provided by the study sites.

6.1.4.1. Preinfusion Medication

On daratumumab infusion days, subjects will receive the following medications approximately 1 hour prior to daratumumab infusion; premedication up to 3 hours before the dose of daratumumab is permitted:

- Dexamethasone (as listed in [Table 5](#)); doses may be give PO unless specified as IV:
 1. C1D1 and C1D2: dexamethasone 20 mg IV
 2. Cycle 1 Day 8, 15 and 22: dexamethasone 20 mg IV
 3. Cycle 2 Day 1, 8, 15, and 22: dexamethasone 40 mg
 4. Cycles 3-6 (if with CyBorD) Days 1, 8, 15, 22: dexamethasone 40 mg
 5. Cycles 7-8 (if with CyBorD), Days 1, 8, 15, 22: dexamethasone 40 mg
 6. Maintenance cycles, Day 1: dexamethasone, 12 mg
- Paracetamol (acetaminophen) 650-1000 mg IV or PO
- An antihistamine (diphenhydramine 25-50 mg IV or PO, or equivalent). Avoid the use of IV promethazine
- Leukotriene inhibitor (optional): montelukast 10 mg PO or equivalent, as per investigator discretion

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

6.1.4.2. Postinfusion Medication

Postinfusion medications are listed below.

- Cycle 1 Day 3: dexamethasone (4 mg PO)
- Cycle 1 Day 9, 16, 23: dexamethasone (20 mg PO)
- No further post-infusion corticosteroids are needed following Cycle 1 if no delayed infusion reactions have occurred. However, dexamethasone 4 mg PO for up to 2 days after each dose of daratumumab may be continued at the investigator's discretion.

For subjects receiving daratumumab and who have a higher risk of respiratory complications (ie, subjects with mild asthma or subjects with chronic obstructive pulmonary disease who have an FEV1 <80% at screening or developed FEV1 <80% during the study without any medical history), the following postinfusion medications should be considered:

- Antihistamine (diphenhydramine or equivalent medication)
- Leukotriene inhibitor (montelukast or equivalent medication)
- Short-acting β 2 adrenergic receptor agonist such as salbutamol aerosol
- Control medications for lung disease (eg, inhaled corticosteroids \pm long-acting β 2 adrenergic receptor agonists for subjects with asthma; long-acting bronchodilators such as tiotropium or salbutamol \pm inhaled corticosteroids for subjects with chronic obstructive pulmonary disease)

In addition, hospitalization for monitoring for up to 2 nights after an infusion should be considered. 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 a serious adverse event. Investigators may prescribe bronchodilators, antihistamines, and corticosteroids that are deemed necessary to provide adequate supportive care in the event that a bronchospasm occurs after subjects are released from the hospital/clinic. If an at-risk subject experiences no major infusion-related reactions, then postinfusion medications may be waived after Cycle 1, at the investigator's discretion.

6.1.5. Management of Infusion-related Reactions

Subjects should be carefully observed during daratumumab infusions. Trained study staff at the clinic should be prepared to intervene in case of an infusion-related reaction (IRR), 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 IRRs of any grade/severity, immediately interrupt the daratumumab infusion and manage symptoms. Management of IRRs may further require reduction in the rate of infusion, or 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, then infusion rate escalation may resume at increments and intervals as outlined in [Table 2](#).
- **Grade 3 (severe):** If the intensity of the reaction decreases to Grade 2 or lower, then consider restarting the infusion at no more than half the rate at which the reaction occurred. If the subject does not experience additional symptoms, then resume infusion rate escalation at increments and intervals as outlined in [Table 2](#).

Immediately interrupt the daratumumab infusion in the renewed event of Grade 3 symptoms. If the intensity decreases to Grade 2 or lower consider restarting the infusion as described above. Permanently discontinue daratumumab upon the third occurrence of a Grade 3 or greater infusion reaction.

- **Grade 4 (life threatening):** Permanently discontinue daratumumab treatment.

6.2. Dose Delay and Modification

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

6.2.1. Toxicity Management

Cycle Delays

On the first day of each new treatment cycle and before each daratumumab dose, 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 Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03. Dose delays will be made based on the toxicity experienced during the previous infusion or newly encountered on Day 1 of a new cycle.

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

The criteria for a dose delay are:

- Grade 4 hematologic toxicity
- Grade 3 or higher thrombocytopenia
- Febrile neutropenia
- Neutropenia with infection
- 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

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

If daratumumab administration does not commence within the prespecified window ([Table 3](#)) of the scheduled administration date, then the dose will be considered a missed dose and it should be skipped.

Administration may resume at the next planned dosing date. A missed dose will not be made up.

Table 3: Daratumumab Administration Schedule and Dose Delay Instructions

Cycles	Frequency	Dose Held	Dosing Re-start
1 and 2 (excluding C1D1 and C1D2 which must be given as planned)	Weekly	>3 days	next planned weekly dosing date
3 to 6	Biweekly (q2wks)	>7 days	next planned biweekly dosing date
7+	Every 4 weeks	>7 days (if induction or maintenance)	next planned every 4 weeks dosing date

Doses of daratumumab may be delayed as listed in [Table 3](#). If Day 1 of a cycle is delayed, Day 1 of subsequent cycles should be adjusted accordingly to maintain the 28-day cycle duration. However, if a within-cycle dose is delayed, then the dates of the subsequent within-cycle doses should not be adjusted.

A daratumumab dose that is held for more than the permitted time from the per-protocol administration date for any reason other than toxicities suspected to be related to daratumumab should be brought to the attention of the Sponsor at the earliest possible time. Subjects whose dose was delayed for more than the prescribed duration, should have study treatment discontinued, unless, upon consultation with the sponsor and the review of safety and efficacy, continuation is agreed upon.

6.3. Bortezomib

Bortezomib will be given as 1.5 mg/m² subcutaneously on Days 1, 8, and 15 of each cycle, for up to 8 cycles (see [Table 1](#)). Dose modification may be made only after the first cycle is completed for the occurrence of peripheral neuropathy and myelotoxicity excluding anemia.

The amount (in mg) of bortezomib to be administered is based on body surface area (BSA) calculations using a standard nomogram or according to institutional policy, as follows:

$$\frac{\text{Bortezomib dose (mg/m}^2\text{)} \times \text{subject BSA (m}^2\text{)}}{2.5 \text{ mg/mL}}$$

= Total bortezomib volume (mL) to be administered

The total calculated dose of bortezomib may be rounded to the nearest decimal point (eg, a calculated dose of 2.47 mg can be rounded to 2.5 mg). Subjects will receive 1.5 mg/m² bortezomib as an SC injection once weekly (Days 1, 8, and 15) during the 28-day induction. For subjects who experience injection-site reactions at the SC administration site, bortezomib may be administered by IV injection (see study site investigational product and procedures manual and bortezomib United States prescribing information). On daratumumab infusion days, bortezomib will be administered at the end of the daratumumab infusion.

6.3.1. Dose Adjustments of Bortezomib

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

Bortezomib should be withheld at the onset of any Grade 3 or 4 non-hematological or Grade 4 hematological toxicity, excluding neuropathy as discussed in Table 4: Recommended Dose Modification for Bortezomib-related Neuropathic Pain and/or Peripheral Sensory or Motor Neuropathy. Once the symptoms of the toxicity have resolved, bortezomib may be reinitiated at a reduced dose as follows:

- Starting dose: 1.5 mg/m²
- Dose level -1: 1.3 mg/m²
- Dose level -2: 1.0 mg/m²

Neurologic Toxicity

If the subject experiences peripheral neuropathy, then dose adjustments should be made according to the recommendations in Table 4.

Table 4: Recommended Dose Modification for Bortezomib-related Neuropathic Pain and/or Peripheral Sensory or Motor Neuropathy

Grade ^a	Modification
1 (asymptomatic; loss of deep tendon reflexes or paresthesia) without pain or loss of function	No action
1 with pain or Grade 2 (moderate symptoms; limiting instrumental ADL ^b)	Reduce bortezomib to 1.3 mg/m ²
2 with pain or Grade 3 (severe symptoms; limiting self-care ADL ^c)	Withhold bortezomib treatment until symptoms of toxicity have resolved. When toxicity resolves, reinitiate with a reduced dose of bortezomib at 1.0 mg/m ² once per week
4 (life-threatening consequences; urgent intervention indicated)	Discontinue bortezomib

ADL = activities of daily living

^a: Grading based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.03.

^b: Instrumental ADL: refers to preparing meals, shopping for groceries or clothes, using telephone, managing money, etc

^c: Self-care ADL: refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

6.4. Cyclophosphamide

Cyclophosphamide will be given as 300 mg/m² on Days 1, 8, 15 and 22 of each cycle (continuous) by mouth (PO), for up to 8 cycles. Dose modification may be made due to myelotoxicity (excluding anemia) and cystitis during any treatment cycle.

For Grade 3 hematologic toxicity and for Grade 1 or 2 cystitis: level-1, 300 mg/m² on Days 1, 8, and 15; level-2, 300 mg/m² Days 1 and 8; level-3, 300 mg/m² Day 1. Grade 3 or 4 cystitis mandates discontinuation of cyclophosphamide.¹⁴

6.5. Corticosteroids

The corticosteroid for pre- and post-daratumumab administration is dexamethasone. The route of administration of corticosteroids prior to infusion of daratumumab during Cycle 1 must be IV.

During subsequent cycles the route of administration may be either IV or PO prior to infusion of daratumumab. Beginning in Cycle 2, post-infusion corticosteroids are optional and can be omitted at the discretion of the investigator if the subject experiences no delayed infusion reactions. Please refer to the table below for corticosteroid dosing.

Dose modification of the corticosteroids is not advised during the first cycle of treatment. However, dose modifications may be made due to Grade 2 muscle weakness, Grade 3 GI toxicity, or any other Grade 3 toxicity believed to be due to corticosteroids. For such level of toxicity the dose of corticosteroids may be reduced by 50%.

Note: All corticosteroid doses may be given PO unless specified as IV.

Table 5: Dexamethasone Dose Schedule

Cycle/Timepoint	Day 1 (pre-infusion)*	Day 1 of Week	Day of Infusion +1 Day (post-inf)	Day of Infusion +2 Days (post-inf)
Cycle 1 (Dara-CyBorD)				
Week 1 (Dara on Days 1 and 2)	20 D (IV)	--	20 D on C1D2 (IV)	Day 3: 4 D
Week 2	20 D (IV)	--	20 D	
Week 3	20 D (IV)	--	20 D	
Week 4	20 D (IV)	--	20 D	
Cycle 2 (Dara-CyBorD)				
Week 1	40 D	--	None needed ⁺	None needed ⁺
Week 2	40 D	--	None needed ⁺	None needed ⁺
Week 3	40 D	--	None needed ⁺	None needed ⁺
Week 4	40 D	--	None needed ⁺	None needed ⁺
Cycles 3-6 (Dara-CyBorD)**				
Week 1	40 D	--	None needed ⁺	None needed ⁺
Week 2	--	40 D	None needed ⁺	None needed ⁺
Week 3	40 D	--	None needed ⁺	None needed ⁺
Week 4	--	40 D	None needed ⁺	None needed ⁺
Cycles 7-8 (Dara-CyBorD)**				
Week 1	40 D		None needed ⁺	None needed ⁺
Week 2	--	40 D	None needed ⁺	None needed ⁺
Week 3	--	40 D	None needed ⁺	None needed ⁺
Week 4	--	40 D	None needed ⁺	None needed ⁺
Daratumumab Maintenance (Q28 days for 12 months; up to 12 cycles)				
Week 1 of each cycle	12 D	--	None needed ⁺	None needed ⁺

IV – intravenous, D – Dexamethasone, Q28 – every 28

* Also on Day 2 for Cycle 1 only

** Dara-CyBorD induction may be given for 4 to 8 cycles

+None needed unless subject experiences an infusion reaction

7. TREATMENT COMPLIANCE

Daratumumab will be administered as an IV infusion by qualified study-site personnel and the details of each administration will be recorded in the case report form (CRF).

Oral cyclophosphamide is self-administered by the subject. The treating team is responsible for interviewing the subject at each visit in regards to the subject compliance with oral cyclophosphamide, but cyclophosphamide intake will not be recorded in a subject's CRF.

Bortezomib is administered as an SC injection at the study-site by qualified members of the treating team. Bortezomib intake is to be recorded in a subject's CRF.

Dexamethasone will need to be administered intravenously during the first cycle of therapy and therefore compliance will be monitored by the members of the treating team. However, subsequent doses may be self-administered PO by the subject. There will be regular interviews by the study team to ensure compliance but corticosteroid intake will not be recorded in a subject's CRF.

Drug supplies for each subject will be inventoried and accounted for.

8. PRESTUDY AND CONCOMITANT THERAPY

Pre-study therapies administered up to 30 days before first dose of study drug must be recorded at screening.

Concomitant therapies must be recorded throughout the study beginning with start of the first dose of study drug until 30 days following completion of the last dose of study drug.

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens) different from the study drug must be recorded in the CRF. Recorded information will include a description of the type of the drug, treatment period, dosing regimen, route of administration, and its indication. Modification of an effective preexisting therapy should not be made for the explicit purpose of entering a subject into the study.

Subjects must not have received an investigational drug (including investigational vaccines) or used an invasive investigational medical device within 4 weeks before C1D1 (except for investigational anti-myeloma agents, which cannot be taken within 2 weeks before C1D1).

Subjects with previously untreated myeloma may receive radiation therapy to control local complications of myeloma such as fracture and nerve impingement. Subjects may also receive a short course of steroids however, no more than 160 mg of dexamethasone or equivalent.

Subjects with relapsed myeloma may have received regimens containing lenalidomide, bortezomib, corticosteroids, or high-dose melphalan prior to autologous transplant amongst other regimens including conventional alkylators.

Subjects are expected not to receive multiple myeloma therapy during the follow-up period. However, if they do receive such therapy, they are to remain in follow-up and the therapy(ies) being received are to be reported in the CRF.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

Additional Recommended Therapies

- Prophylaxis for Herpes Zoster Reactivation

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

- Prevention of steroid induced gastritis

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

- Other - Bisphosphonates

Due to the high risk of skeletal related complications in this subject population it is highly encouraged to prescribe appropriate bisphosphonates if subject agrees and the administration criteria allow.

Permitted Therapies

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

- Prevention of constipation (eg, adequate hydration, high-fiber diet, and stool softeners if needed)
- Prophylactic antiemetics, with the exception of corticosteroids
- Colony stimulating factors, erythropoietin, and transfusion of platelets and red blood cells.
- Loperamide is recommended for the treatment of diarrhea, starting at the time of the first watery stool. The loperamide dose and regimen is according to institutional guidelines. Prophylactic loperamide is not recommended.
- Adequate hydration is recommended for prevention of myeloma-related kidney disease

9. STUDY EVALUATIONS

9.1. Study Procedures

The Time and Events Schedule summarizes the frequency and timing of all measurements applicable to this study. Subject participation is to include a screening phase, an induction phase with Dara-CyBorD, optional ASCT consolidation therapy, a maintenance phase with daratumumab alone, an end-of-treatment visit and a post-treatment follow-up phase.

9.1.1. Screening Phase

Subjects who fail to meet the inclusion and exclusion criteria (ie, screen failures) may be rescreened once if their condition changes. Rescreening must be discussed with and approved by the sponsor on a case-by-case basis. Subjects who are determined to be eligible for rescreening must sign a new ICF and will then be assigned a new screening number.

9.1.1.1. Demographic Characteristics and Medical History

At the screening phase (within 28 days of C1D1/start of study drug administration), the following assessments will be done: height and weight, physical examination, ECOG performance status, vital signs, pulmonary function testing, screening serology, 12-lead electrocardiogram, blood typing (see Section 9.1.1.3), a chest x-ray, and pregnancy test (for female subjects). Laboratory tests (hematology and chemistry [including beta-2 microglobulin]) will be done for baseline values.

A medical history will be taken, including recording of prior and concomitant medications. Demographic characteristics will be recorded.

9.1.1.2. Bone Marrow Biopsy, Serum and Urine Tests

Bone marrow biopsy with Flow cytometry, serum M-protein quantitation by electrophoresis (SPEP) and serum IFE, serum FLC, serum quantitative immunoglobulins, a 24-hour urine test for M-protein quantitation by electrophoresis (UPEP), and urine IFE will be performed. All subject's samples will be tested for IgG, IgA, and IgM. Subjects with IgE or IgD myeloma will have samples tested for IgE or IgD. In addition, there will be a baseline assessment for lytic lesions and extramedullary plasmacytomas. Extramedullary plasmacytomas should be assessed for all subjects with a history of plasmacytomas or if clinically indicated, by clinical examination or radiologic imaging; a repeat assessment should be done on C1D1 if not done within 14 days prior to C1D1. The disease status tests listed here are explained further in Section 9.2.

9.1.1.3. Blood Typing/Indirect Coombs Testing

Blood Type, Rh, and Indirect Antiglobulin Test (IAT) should be done before the first dose of daratumumab; there is no need to repeat the tests if they have been performed within the 3 days prior to C1D1, and there is no need to perform these on C1D1 if there were no blood transfusions between screening and C1D1. 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 subject'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 Antiglobulin [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 subject identification wallet card for the study that includes the blood profile (ABO and Rh blood groups, 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 red blood cells with dithiothreitol.²

Possible methods for blood banks to provide safe red blood cells (RBCs) for transfusion to subjects receiving daratumumab include:

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

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

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

9.1.2. Treatment Phase

Each treatment cycle is to be 28 days.

9.1.2.1. Induction Therapy

During induction, drug administration and testing are to be performed as listed in the Time and Events Schedule. Vital signs will be monitored extensively on C1D1 and C1D2.

A physical examination, vital signs, weight, ECOG performance status, urine pregnancy test (for pre-menopausal female subjects), and laboratory tests (hematology and chemistry); SPEP, quantitative Ig, and UPEP will be done on Day 1 of each 28-day cycle.

9.1.2.2. Consolidation Stem Cell Therapy, if Eligible

Eligible subjects may undergo stem cell collection, HDT and ASCT following 4-8 cycles of induction therapy. The criteria, testing and treatment for subjects undergoing an ASCT will be as per the standard operating procedures of the transplant center.

9.1.2.3. Maintenance Therapy with Daratumumab

After the induction therapy cycles of Dara-CyBorD, and whether or not HDT/ASCT is performed, daratumumab alone will be given in 28-day cycles, for 12 cycles or a total of 16 to 20 cycles (including the cycles of induction therapy).

On Day 1 of every therapy cycle, a physical examination, vital signs, weight, ECOG performance status, and laboratory tests (central and local assessment of hematology, chemistry, and local assessment of pregnancy [with urine sample] if applicable) should be performed.

On Day 1 of every other cycle during maintenance therapy (every 56 days), SPEP, quantitative Ig, and UPEP should be performed. In addition, in case of suspected CR, suspected sCR, or progressive disease (PD), a bone marrow biopsy with Flow cytometry will be done.

9.1.2.4. End of Treatment

At the end of treatment visit, to be scheduled 30 days after the last dose, the following will be assessed:

Physical examination, ECOG performance status, and laboratory tests (hematology and chemistry).

9.1.3. Post-treatment Phase (Follow-Up)

Once the end of treatment visit has occurred, subjects will be asked to return to the study site every 12 weeks so that, if suspected CR, suspected sCR, or PD, bone marrow biopsy with Flow cytometry can be performed. Quantitative Ig will also be measured.

Lytic lesions and extramedullary plasmacytomas will be assessed if clinically indicated until PD through Month 36.

Subjects will be instructed that study drug (daratumumab) will not be made available to them after they have completed/discontinued study drug and that they should return to their primary physician to determine standard of care.

9.2. Efficacy Evaluations

Disease response and progression will be assessed based on IMWG Guidelines (see [Attachment 5](#)). Daratumumab detection on serum immunofixation has been demonstrated in subjects treated with 16 mg/kg, and may interfere with the traditional IMWG criteria of negative serum IFE for CR or sCR. To mitigate this interference, the sponsor has developed a reflex assay that utilizes anti-idiotype antibody to bind daratumumab and confirm its interference on IFE (see laboratory manual). For all subjects with VGPR and a negative M-protein by SPEP, reflex IFE testing will be performed to confirm the presence of daratumumab on IFE. In addition, for subjects who have an SPEP ≤ 0.2 g/dL and detectable IgG kappa myeloma during the study, reflex testing will also be performed to determine whether the para-protein identified on SPEP/IFE is monoclonal daratumumab or the subject's endogenous myeloma protein.

Disease evaluations must be performed on Day 1 of every cycle during the induction phase with Dara-CyBorD. Disease evaluation should be performed following ASCT for subjects who undergo ASCT, on Day 1 of their first maintenance therapy cycle. During the maintenance phase with daratumumab monotherapy, disease evaluation may be done on Day 1 of every other cycle (approximately every 56 days) or, if there are concerns for relapse, sooner. The scheduled disease assessment during any given phase may be done ± 3 days of the due date. If treatment is delayed for any reason, then the disease evaluations must be performed according to schedule, regardless of any changes to the dosing regimen.

Disease evaluations scheduled for treatment days should be collected before study treatment is administered.

Disease evaluations will be performed by a central laboratory (unless otherwise specified) according to the Time and Events Schedule until disease progression. For quantitative Ig, M-protein, and IFE measurements in serum and 24-hour urine, the investigator will use results provided by the central laboratory. Subjects with positive serum IFE and confirmed daratumumab IFE interference, that meet all other clinical criteria for CR or sCR, will be considered CR/sCR. If a bone marrow biopsy is performed for suspected CR, suspected sCR, or PD, morphology and plasma cell clonality testing will be done at the central laboratory.

9.2.1. SPEP, UPEP, and FLC Testing

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

Serum M-protein quantitation by electrophoresis (SPEP), 24-hour urine M-protein quantitation by electrophoresis (UPEP), serum immunofixation at Screening and thereafter when a CR or sCR is suspected or maintained, urine immunofixation at Screening and thereafter when a CR or sCR is suspected or maintained, and a serum free light chain assay are to be performed as outlined in the T&E Schedule. Blood and 24-hour urine samples will be collected as specified in the Time and Events Schedule until the development of confirmed disease progression.

After subjects have completed the 12 cycles of maintenance therapy with daratumumab, the timing of collection for SPEP and UPEP (and the timing of collection of FLC for subjects with light chain multiple myeloma) will change from every 4 weeks to every 12 weeks. Disease progression based on 1 of the laboratory tests alone must be confirmed by at least 1 repeat investigation performed 1 to 3 weeks later. Disease evaluations will continue beyond relapse from CR until disease progression is confirmed.

Serum and urine IFE tests and serum FLC assay will be performed at Screening and thereafter when a CR or sCR is suspected (when SPEP or UPEP are 0 or nonquantifiable) or maintained. However, for subjects with light chain multiple myeloma, serum FLC assay will be performed routinely.

9.2.2. Serum Calcium

Blood samples for calculating serum calcium corrected for albumin will be collected and analyzed centrally (as specified in the Time and Events Schedules) until the development of confirmed disease progression. Development of hypercalcemia (corrected serum calcium >11.5 mg/dL or 2.8 mM/L) can indicate disease progression or relapse if it is not attributable to any other cause (see disease response criteria). Calcium binds to albumin and only the unbound (free) calcium is biologically active; therefore, the serum calcium level must be adjusted for abnormal albumin levels ("corrected serum calcium"). The formula for adjustment is presented in [Attachment 4](#).

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

Blood samples for β 2 microglobulin and albumin are to be collected at Screening, and will be analyzed by the central laboratory.

9.2.3. Bone Marrow Examination

Bone marrow aspirate or biopsy will be performed at Screening for clinical characterization (morphology, immunohistochemistry [IHC], or immunofluorescence or flow cytometry, and cytogenetics), to perform molecular subtyping to monitor daratumumab activity in high-risk molecular subgroups. Good quality slides are required for morphological examination to determine plasma cell percentage in the bone marrow. Assessment by flow cytometry alone is not sufficient. Bone marrow examination for disease assessment will be performed centrally, and a portion of the bone marrow aspirate will be used for molecular subtyping. A reasonable attempt to obtain a fresh bone marrow aspirate is required at screening. Additional bone marrow aspirates or biopsies (or both) will be performed to confirm sCR, CR, or disease progression.

9.2.4. Assessment of Lytic Disease

A complete skeletal survey (including skull, entire vertebral column, pelvis, chest, humeri, femora, and any other bones for which the investigator suspects involvement by disease) is to be performed and evaluated by the local laboratory by roentgenography (or the local standard of care imaging, eg, low-dose CT) during the Screening Phase. Please note that the same methodology used at Screening should be used throughout the study for comparison purposes.

During the Treatment Phase and before disease progression is confirmed, imaging should be performed whenever clinically indicated based on symptoms, to document response or progression. Magnetic resonance imaging (MRI) or low-dose CT scan are acceptable methods for evaluation of bone disease, and may be included at the discretion of the investigator. If a radionuclide bone scan was used at Screening in addition to the complete skeletal survey, then both methods must be used to document disease status. These tests must be performed at the same time. However, a radionuclide bone scan does not replace a complete skeletal survey.

Sometimes subjects present with disease progression manifested by symptoms of pain due to bone changes. Therefore, disease progression may be documented, in these cases, by skeletal survey or other radiographs, depending on the symptoms that the subject experiences. If the diagnosis of disease progression is obvious by radiographic investigations, then no repeat confirmatory imaging is necessary. In instances where changes may be more subtle, repeat imaging may be performed in 1 to 3 weeks per investigator discretion.

9.2.5. Documentation of Extramedullary Plasmacytomas

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

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

Extramedullary plasmacytomas should be assessed for all subjects with a history of plasmacytomas or if clinically indicated at Screening, by clinical examination or radiologic imaging. Assessment of measurable sites of extramedullary disease will be performed and evaluated locally every 4 weeks (by physical examination) for subjects with a history of plasmacytomas or as clinically indicated during treatment for other subjects until development of confirmed CR or confirmed disease progression. If assessment can only be performed radiologically, then evaluation of extramedullary plasmacytomas may be done every 12 weeks.

For every subject, the methodology used for evaluation of each disease site should be consistent across all visits. Irradiated or excised lesions will be considered not measurable, and will be monitored only for disease progression.

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

9.3. Safety Evaluations

Safety evaluations will include adverse event monitoring, clinical laboratory parameters (hematology and serum chemistry), pregnancy testing, electrocardiogram monitoring, vital sign measurements, physical examinations, and ECOG performance status.

Since daratumumab interferes with the IAT, all subjects will receive a subject identification wallet card for the study that includes the blood profile (ABO, Rh, and IAT) determined before the first infusion of daratumumab along with information on the IAT interference for healthcare providers/blood banks.

Details regarding the Data Review Committee are provided in Section [11.6](#).

9.3.1. Adverse Events

Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the CRF. Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached.

The study will include the following evaluations of safety and tolerability according to the time points provided in the Time and Events Schedule: adverse event monitoring, clinical laboratory

parameters (hematology and serum chemistry), pregnancy testing, electrocardiogram monitoring, vital sign measurements, physical examinations, and ECOG performance status.

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) for the duration of the study. Adverse events (AEs) are to be collected on the AE forms of the CRF from time of consent through 30 days after last daratumumab infusion. During the subsequent follow-up period, serious SAEs and AEs are to be reported if the investigator considers them to be causally related to daratumumab. Adverse events will be followed by the investigator as specified in Section 12, Adverse Event Reporting.

9.3.2. Clinical Laboratory Tests

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

Tests being performed by the central laboratory include the hematology and chemistry tests listed below and serum pregnancy testing. Tests being performed by the central laboratory include, but are not limited to, the following:

- **Hematology Panel**

- hemoglobin
- hematocrit
- RBC count
- platelet count
- white blood cell (WBC) count with differential

Note: A WBC evaluation may include any abnormal cells, which will then be reported by the laboratory. A RBC evaluation may include abnormalities in the RBC count, RBC parameters, or RBC morphology, which will then be reported by the laboratory.

In addition, any other abnormal cells in a blood smear will also be reported.

- **Serum Chemistry Panel**

-sodium	-alkaline phosphatase
-potassium	-lactic acid dehydrogenase (LDH)
-chloride	-uric acid
-bicarbonate	-calcium
-blood urea nitrogen (BUN)	- phosphate
-creatinine	-albumin
-creatinine clearance	-total protein
-glucose	-magnesium
-aspartate aminotransferase (AST)	
-alanine aminotransferase (ALT)	
-gamma-glutamyltransferase (GGT)	
-total bilirubin	

Serum Pregnancy Testing [for women of childbearing potential only] at screening.

Serology (HIV antibody, hepatitis B surface antigen, and hepatitis C virus antibody) at screening.

Hepatitis C viral load testing by hepatitis C RNA PCR – for reactivation of HCV for any subjects who had prior, treated hepatitis C and no detectable circulating HCV at study entry.

Results of local hematology and chemistry tests must be evaluated before Day 1 of each cycle to guide treatment decisions, but do not need to be reported in the eCRF unless they result in a dose delay.

For women of childbearing potential, pregnancy testing (urine test) is to be done at the local laboratory within 24 hours of C1D1, and throughout the induction and maintenance phases as listed in the Time and Events Schedule.

9.3.3. *Electrocardiogram (ECG)*

During the collection of the screening ECG, subjects should be in a quiet setting without distractions (eg, television, cell phones). Subjects should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. If blood sampling or vital sign measurement is scheduled for the same time point as ECG recording, the procedures should be performed in the following order: ECG(s), vital signs, blood draw.

9.3.4. *Vital Signs*

Oral temperature, pulse/heart rate, respiratory rate, blood pressure will be taken at the times shown in the Time and Events Schedule.

Blood pressure and pulse/heart rate measurements will be assessed with the subject in a seated position with a completely automated device. Manual techniques will be used only if an automated device is not available. Blood pressure and pulse/heart rate measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

9.3.5. *Physical Examination*

A physical examination is to be done on Day 1 of each induction and maintenance therapy cycle.

9.4. *Sample Collection and Handling*

The actual dates and times of sample collection must be recorded in the CRF or laboratory requisition form. Refer to the Time and Events Schedule for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided.

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

10.1. Completion

A subject will be considered to have completed the study if he or she has completed assessments at the completion of the maintenance phase of therapy, including the end-of-treatment visit.

Subjects who prematurely discontinue study treatment for any reason before completion of the maintenance treatment phase will not be considered to have completed the study.

10.2. Discontinuation of Study Treatment/Withdrawal from the Study

Discontinuation of Study Treatment

A subject will not be automatically withdrawn from the study if they have to discontinue treatment before the end of the treatment regimen.

A subject's study treatment must be discontinued if:

- The investigator believes that for safety or tolerability reasons (eg, adverse event) it is in the best interest of the subject to discontinue study treatment
- The subject becomes pregnant
- The subject (or the subject's legally acceptable representative) withdraws consent for administration of study treatment
- The subject initiates treatment with a prohibited medication
- The subject received concurrent (non-protocol) treatment for multiple myeloma
- A subject with a history of HCV who completed treatment at least 6 months prior to screening, who does not agree to undergo regular assessment for HCV reactivation during their participation in the study
- The subject experiences unacceptable toxicity, including reactions described in Section [6.1.5](#), Management of IRRs
- The subject cannot tolerate bortezomib, cyclophosphamide or corticosteroids despite the appropriate dose reductions
- The subject's daratumumab dose is held for more than 28 days during induction cycles or if ≥ 3 consecutive planned doses are missed for reasons other than toxicity
- The subject experiences disease progression. Relapse from CR is not considered as disease progression.

If a subject discontinues study treatment for any reason before the end of the induction/consolidation phase or maintenance phase, end of treatment assessments should be obtained and post-treatment follow-up scheduled assessments should be continued through 36 months after the start of induction therapy.

The primary reason for discontinuation of study treatment is to be recorded in the CRF. If study treatment is discontinued for a reason other than disease progression, then disease evaluations will continue to be performed as specified in the Time and Events Schedule.

Withdrawal From the Study

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

- Lost to follow-up
- Withdrawal of consent
- Had a history of HCV and completed treatment at least 6 months prior to screening but test positive for HCV at any time during the regular assessments
- Death
- Sponsor terminates the study

If a subject withdraws from the study before the end of the induction or consolidation phase, end of treatment assessments should be obtained.

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

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the CRF and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw will not be replaced.

11. STATISTICAL METHODS

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

11.1. Subject Information

Analysis of primary and secondary efficacy variables will be based on the response-evaluable population, which includes all enrolled subjects who have measurable disease, receive at least 1 dose of study treatment, and have at least 1 efficacy evaluation assessment. All safety analyses will be based on the safety analysis set, which includes all enrolled subjects who receive at least 1 dose of study treatment.

Continuous variables will be summarized using descriptive statistics such as mean, standard deviation, and range. Categorical variables will be summarized using frequency tables. For time-to-event variables, the Kaplan-Meier method will be used for descriptive summaries.

11.2. Sample Size Determination

The historical CR+VGPR rate after 4 cycles of CyBorD induction therapy is 60% in previously untreated multiple myeloma subjects.¹⁷ Thirty-three (33) enrolled subjects will provide 80% power at a 5% 1-sided significance level to detect an absolute 20% increase over 60% with Dara-CyBorD.

The historical CR+VGPR rate after 4 cycles of CyBorD induction therapy is 30% in previously relapsed multiple myeloma subjects.²⁰ Thirty-five (35) enrolled subjects will provide 80% power at a 5% 1-sided significance level to detect an absolute 20% increase over 30% with Dara-CyBorD.

With the planned enrollment of 100 subjects, with a minimum of 40 newly diagnosed multiple myeloma subjects, at least 80% power will be achieved to detect an absolute 20% increase in the untreated cohort at the 5% 1-sided significance level. In Amendment 2, enrollment of subjects in the relapsed cohort is closed and expected not to exceed 15 subjects. No inferential statistics will be performed for the relapsed cohort.

11.3. Efficacy Analyses

The primary analysis will be performed after all enrolled subjects have completed 4 cycles of induction therapy disease evaluation or have been discontinued from study treatment by this time point. A final data cutoff and analysis, to update secondary endpoints and safety, will occur at the end of study when all subjects have completed follow-up at 36 months after the start of induction therapy, or until death or withdrawal of consent for study participation, whichever occurs first.

Response to study treatment and progressive disease will be evaluated by a validated computer algorithm to calculate IMWG response. The primary endpoint, rate of CR+VGPR achieved after 4 cycles of induction therapy, for newly diagnosed and relapsed subjects will be tabulated. The proportion of subjects will be analyzed using a normal approximation to the binomial distribution comparing the observed proportion to a reference of 0.60 for previously untreated subjects.

The CR+VGPR rate and its 2-sided 95% confidence interval will be provided. Other binary endpoints, including overall CR, sCR, ORR, VGPR or better rate following induction, consolidation, and maintenance will be analyzed similarly.

Time-to-event efficacy endpoints, including duration of CR, sCR, time to progression, PFS, and OS, will be descriptively summarized using the Kaplan-Meier method.

11.4. Safety Analyses

Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events are adverse events with onset during the treatment phase or that are a consequence of a pre-existing condition that has worsened since baseline. All reported adverse events will be

included in the analysis. For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group. In addition, comparisons between treatment groups will be provided if appropriate.

Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an adverse event, or who experience a severe or a serious adverse event. These will be provided using the same formats as those used for adverse events.

Clinical Laboratory Tests

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

Parameters with predefined NCI-CTCAE version 4.03 toxicity grades will be summarized. Change from baseline to the worst adverse event grade experienced by the subject during the study will be provided as shift tables.

Electrocardiogram data will be summarized by vital signs parameters (temperature, pulse/heart rate and blood pressure (systolic and diastolic). Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the abnormalities will be made.

Vital Signs

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

11.5. Interim Analysis

Three interim safety analyses are planned. The first interim safety analysis will occur after at least 20 subjects are treated for at least 1 cycle of study treatment (or discontinue before the end of Cycle 1). The second interim safety analysis will occur after at least 50 subjects complete Cycle 1 of study treatment (or discontinue before the end of Cycle 1) with a focus on infusion-related reactions during Cycle 1. The third interim safety analysis will occur after at least 50 subjects are treated for at least 4 cycles (or discontinue before the end of Cycle 4).

A Data Review Committee will be established to review the interim data and formulate recommended decisions/actions in accordance with the objectives of the interim analysis (see Section 11.6).

11.6. Data Review Committee

An internal Data Review Committee will be established to monitor data on an ongoing basis to ensure the continuing safety of the subjects enrolled in the study. The committee will meet periodically to review interim safety data and will also perform the predetermined interim safety analysis as detailed in Section 11.5, Interim Analysis. After the review, the committee will make recommendations regarding the continuation of the study. The details will be provided in a separate committee charter.

The Data Review Committee will consist of at least 2 medical experts in the relevant therapeutic area and at least 1 statistician. The committee responsibilities, authorities, and procedures will be documented in its charter.

12. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

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

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

Note: The sponsor collects adverse events starting with the signing of the ICF (refer to Section 12.3, All Adverse Events, for time of last adverse event recording).

A list of Anticipated Events for daratumumab is included as [Attachment 6](#).

Serious Adverse Event

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

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

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

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For daratumumab, the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure, and not included in the list of Anticipated Events included in this protocol (see [Attachment 6](#)).

For cyclophosphamide, bortezomib, and corticosteroids, the expectedness of an adverse event will be determined by whether or not it is listed in the respective prescribing information.

Adverse Event Associated With the Use of the Drug

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

12.1.2. Attribution Definitions

Not Related

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

Doubtful

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

Possible

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

Probable

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

Very Likely

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

12.1.3. Severity Criteria

An assessment of severity grade will be made using the following general categorical descriptors:

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

Moderate: Sufficient discomfort is present to cause interference with normal activity.

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

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

12.2. Special Reporting Situations

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

- Overdose of a sponsor study drug
- Suspected abuse/misuse of a sponsor study drug
- Accidental or occupational exposure to a sponsor study drug
- Medication error involving a sponsor product (with or without subject/patient exposure to the sponsor study drug, eg, name confusion)
- Exposure to a sponsor study drug from breastfeeding

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

12.3. Procedures

12.3.1. All Adverse Events

All adverse events and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until 30 days after the last dose of study treatment. Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study treatment, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

During the stem cell mobilization and transplantation procedures (in eligible subjects), adverse events related to stem cell mobilization and transplantation do not need to be reported in the CRF; however, any toxicity related to study treatment will continue to be reported.

All events that meet the definition of a serious adverse event will be reported as serious adverse events, regardless of whether they are protocol-specific assessments.

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

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

For all studies with an outpatient phase, including open-label studies, the subject must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

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

12.3.2. Serious Adverse Events

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

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

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

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

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

- If the subject has not experienced a significant medical event but is hospitalized overnight only for observation following infusion of daratumumab, then the hospitalization should not be reported as a serious adverse event.
- Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the CRF).

Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.

12.3.3. Pregnancy

All initial reports of pregnancy in female subjects or partners of male subjects must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study treatment. The subject should be referred to a physician experienced in teratology for evaluation and advice.

Because the effect of the study drug on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported as noted above. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

12.4. Contacting Sponsor Regarding Safety

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

13. PRODUCT QUALITY COMPLAINT HANDLING

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

13.1. Procedures

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

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

13.2. Contacting Sponsor Regarding Product Quality

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

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drug(s)

Daratumumab

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

14.2. Packaging

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

14.3. Labeling

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

14.4. Preparation, Handling, and Storage

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

Refer to the pharmacy manual/study site investigational product and procedures manual for additional guidance on study drug preparation, handling, and storage.

14.5. Drug Accountability

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

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

When the study site is an authorized destruction unit and study drug supplies are destroyed on-site, this must also be documented on the drug return form.

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

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

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Investigator's Brochure for daratumumab
- Study site investigational product and procedures manual
- Laboratory manual
- NCI-CTCAE Version 4.03
- Interactive Web Response System (IWRS) Manual
- Electronic Data Capture (eDC) Manual

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

Based on the potential infusion reactions associated with administration of daratumumab, guidelines for prevention and management of infusion reactions are provided (see Sections 6.1.4 and 6.1.5). Based on the mode of action of daratumumab, a potential risk could be infection; therefore the protocol requires the review of hematological laboratory results prior to daratumumab infusion. CD38 is distributed in erythrocytes and platelets. A significant reduction of platelets was reported in an animal study. In a human clinical study (Study GEN501), thrombocytopenia was also reported. However, safety laboratory monitoring did not show a clinically meaningful reduction of platelets. No bleeding events were observed. Anemia was also reported in Study GEN501. Free hemoglobin was mildly elevated, but other parameters did not support hemolysis.

Routine safety laboratory measurement of RBCs and platelets will be closely monitored in this study.

All subjects will be receiving standard of care (CyBorD) for multiple myeloma in this study.

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which

they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled.

The total blood volume to be collected is considered to be acceptable for subjects participating in a cancer clinical study and reasonable (eg, less than the standard blood donation [500 mL over 60 days]) over the time frame of the study.

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

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

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

16.2.2. Independent Ethics Committee or Institutional Review Board

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

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

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

this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

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

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

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

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

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

16.2.3. Informed Consent

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

the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential subjects (or their legally acceptable representatives) the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject (or legally acceptable representative) is authorizing such access, which includes permission to obtain information about his or her survival status.

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

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

16.2.4. Privacy of Personal Data

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

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

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

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

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

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

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

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

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

17.2.2. Required Prestudy Documentation

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

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.

- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

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

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

17.3. Subject Identification, Enrollment, and Screening Logs

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

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

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

17.4. Source Documentation

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

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

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

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

- Race
- History of nicotine use, eg, cigarettes (including e-cigarettes or the equivalent of e-cigarettes), cigars, chewing tobacco, patch, gum

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

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

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

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

17.5. Case Report Form Completion

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

The study data will be transcribed by study-site personnel from the source documents onto an electronic CRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the subject's source documents. Data must be entered into CRF in English. The CRF must be completed as soon as possible after a subject visit and the forms should be available for review at the next scheduled monitoring visit.

All subjective measurements (eg, pain scale information or other questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible.

If necessary, queries will be generated in the eDC tool. If corrections to a CRF are needed after the initial entry into the CRF, this can be done in either of the following ways:

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

17.6. Data Quality Assurance/Quality Control

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

Guidelines for CRF completion will be provided and reviewed with study-site personnel before the start of the study.

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

17.7. Record Retention

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

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

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

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

17.8. Monitoring

The sponsor will use a combination of monitoring techniques (central, remote, or on-site monitoring) to monitor this study.

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

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

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

Central monitoring will take place for data identified by the sponsor as requiring central review.

17.9. Study Completion/Termination

17.9.1. Study Completion/End of Study

The study is considered completed with the last scheduled study assessment shown in the Time and Events Schedule for the last subject participating in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject assessment at that study site, in the time frame specified in the Clinical Trial Agreement.

17.9.2. Study Termination

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

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

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

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

17.10. On-Site Audits

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

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

17.11. Use of Information and Publication

All information, including but not limited to information regarding daratumumab or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including exploratory research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

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

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator. Study subject identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review

at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), or the sponsor confirms there will be no multicenter study publication.

Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of Clinical Studies and Disclosure of Results

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

REFERENCES

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Attachment 1: Calculated and Measured Creatinine Clearance

Cockcroft-Gault formula:

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

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

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:

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

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

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.

Attachment 2: ECOG Performance Status Scale

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

Reference: Oken MM, Creech RH, Tormey DC, et al. Toxicity and Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-655.

Attachment 3: Asthma GuidelinesSource: https://www.nhlbi.nih.gov/files/docs/guidelines/asthma_qrg.pdf Accessed 10 May 2016.

Components of Severity		Classification of Asthma Severity																	
		Intermittent			Persistent														
					Mild			Moderate			Severe								
0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs					
Impairment	Symptoms	≤ 2 days/week			> 2 days/week but not daily			Daily			Throughout the day								
	Nighttime awakenings	0	≤ 2x/month		1-2x/month	3-4x/month		3-4x/month	> 1x/week but not nightly		> 1x/month	Often 7x/week							
	SABA use for symptom control (not prevention of EIB)	≤ 2 days/week			≤ 2 days/week but not daily		>2 days/week but not daily, and not more than 1x	Daily			Several time per day								
	Interference with normal activity	None			Minor limitation			Some limitation			Extremely limited								
	Normal FEV ₁ /FVC : 8-19 yr 85% 20-39 yr 80% 40-59 yr 75% 60-80 yr 70%	Lung function	N/A	Normal FEV ₁ between exacerbations > 80% FEV ₁ /FVC > 85%	Normal FEV ₁ between exacerbations > 80% Normal	N/A	> 80% > 80% Normal	> 80% Normal	N/A	60-80% 75-80% Reduced 5%	60-80% Reduced 5%	N/A	< 60% < 75% Reduced	< 60% Reduced					
	Exacerbations requiring oral systemic corticosteroids	0-1/year			≥ 2 exacerbations in 6 months requiring oral steroids or >4 wheezing episodes/1 year lasting >1 day and risk factors for persistent asthma	≥ 2/year Relative annual risk may be related to FEV ₁ .	≥ 2/year Relative annual risk may be related to FEV ₁ .	≥ 2 exacerbations in 6 months requiring oral steroids or >4 wheezing episodes/1 year lasting >1 day and risk factors for persistent asthma	≥ 2/year Relative annual risk may be related to FEV ₁ .	≥ 2/year Relative annual risk may be related to FEV ₁ .	≥ 2 exacerbations in 6 months requiring oral steroids or >4 wheezing episodes/1 year lasting >1 day and risk factors for persistent asthma	≥ 2/year Relative annual risk may be related to FEV ₁ .	≥ 2/year Relative annual risk may be related to FEV ₁ .						
Risk		Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category.																	
		Step 1		Step 2			Step 3 and consider short course of oral steroids	Step 3: medium dose ICS and consider short course of oral	Step 3 and consider short course of oral steroids	Step 3 and consider short course of oral steroids	Step 3: medium dose ICS OR Step 4 and consider short course of oral steroids	Step 4 or 5 and consider short course of oral steroids							
Recommended Step for Initiating Treatment		In 2-6 weeks, evaluate level of asthma control that is achieved. 0-4 years: If no clear benefit is observed in 4-6 weeks, stop treatment and consider alternate diagnosis or adjusting therapy. 5-11 and 12+ years: adjust therapy accordingly.																	

Attachment 4: Serum Calcium Corrected for Albumin

If calcium is expressed in mg/dL and albumin is expressed in g/dL:

Corrected calcium (mg/dL) =

$$\text{serum calcium (mg/dL)} + 0.8 \cdot (4 - \text{serum albumin [g/dL]})$$

If calcium is expressed in mmol/L and albumin is expressed in g/L:

Corrected calcium (mmol/L) =

$$\text{serum calcium (mmol/L)} + 0.02 \cdot (40 - \text{serum albumin [g/L]})$$

Source: <http://www.globalrph.com/calcium.htm>

Attachment 5: IMWG Guidelines
 International Myeloma Working Group (IMWG) Uniform
Response Criteria for Multiple Myeloma¹


The International Myeloma Working Group established the below criteria in order to:

- facilitate precise comparisons of efficacy between new treatment strategies in trials
- incorporate the serum free light chain (FLC) assay to include assessment of patients with oligo-secretory and non-secretory disease
- provide stricter definitions for CR (complete response)
- provide classifications that would improve detail and correct inconsistencies in prior response criteria.

The following criteria reconcile various previously used systems for assessing response and have been universally adopted.

<i>Response</i>	<i>IMWG criteria</i>
sCR	CR as defined below plus normal FLC ratio and absence of clonal cells in bone marrow ³ by immunohistochemistry or immunofluorescence ⁴
CR	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and < 5% plasma cells in bone marrow ³
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
PR	≥ 50% reduction of serum M-protein and reduction in 24 hours urinary M-protein by ≥90% or to < 200 mg/24 h If the serum and urine M-protein are unmeasurable, ⁵ 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
MR	NA

¹ BGM Durie *et al.* International uniform response criteria for multiple myeloma. *Leukemia* (2006) 1-7.

No change/Stable disease	Not meeting criteria for CR, VGPR, PR, or progressive disease
Plateau	NA
Progressive disease ⁵	<p>Increase of $\geq 25\%$ from lowest response value in any one or more of the following:</p> <p>Serum M-component and/or (the absolute increase must be ≥ 0.5 g/dL)⁶</p> <p>Urine M-component and/or (the absolute increase must be ≥ 200 mg/24 h)</p> <p>Only in patients without measurable serum and urine M-protein levels; the difference between involved and unininvolved FLC levels. The absolute increase must be > 10 mg/dL</p> <p>Bone marrow plasma cell percentage; the absolute percentage must be $\geq 10\%$⁷</p> <p>Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas</p> <p>Development of hypercalcaemia (corrected serum calcium > 11.5 mg/dL or 2.65 mmol/L) that can be attributed solely to the plasma cell proliferative disorder</p>
Relapse	<p>Clinical relapse requires one or more of:</p> <p>Direct indicators of increasing disease and/or end organ dysfunction (CRAB features).⁶ 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</p> <ol style="list-style-type: none"> 1. Development of new soft tissue plasmacytomas or bone lesions 2. Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion 3. Hypercalcemia (> 11.5 mg/dL) [2.65 mmol/L] 4. Decrease in haemoglobin of ≥ 2 g/dL [1.25 mmol/L] 5. Rise in serum creatinine by 2 mg/dL or more [177 μmol/L or more]
Relapse from CR ⁵ (To be used only if the end point studied is DFS) ⁸	<p>Any one or more of the following:</p> <p>Reappearance of serum or urine M-protein by immunofixation or electrophoresis</p> <p>Development of $\geq 5\%$ plasma cells in the bone marrow⁷</p> <p>Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcaemia)</p>

Adapted from Durie BGM, et al. Leukemia 2006; 20: 1467-1473; and Kyle RA, Rajkumar SV. Leukemia 2008;23:3-9.

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 unininvolved free light chain (FLC) levels.

³ Confirmation with repeat bone marrow biopsy not needed.

⁴ 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.

⁵ All relapse categories require two consecutive assessments made at anytime 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 progressive disease shown here to be classified as progressive disease for the purposes of calculating time to progression and progression-free survival. The definitions of relapse, clinical relapse and relapse from CR are not to be used in calculation of time to progression or progression-free survival.

⁶ For progressive disease, serum M-component increases of ≥ 1 gm/dL are sufficient to define relapse if starting M-component is ≥ 5 g/dL.

⁷ Relapse from CR has the 5% cut-off versus 10% for other categories of relapse.

⁸ For purposes of calculating time to progression and progression-free survival, CR patients should also be evaluated using criteria listed above for progressive disease.

Attachment 6: Anticipated Events**Anticipated Event**

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

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

- Amyloidosis
- Anaemia
- Bleeding
- Bone diseases (ie, spinal cord compression, osteolytic lesions, fracture)
- Hypercalcaemia
- Hyperuricemia
- Hyperviscosity syndrome
- Infection (ie, pneumonia, herpes zoster, meningitis, septicaemia, endocarditis, osteomyelitis, cellulitis, pyelonephritis, urinary tract infection, haemophilus infections)
- Neutropenia
- Plasma cell myeloma recurrent
- Renal failure or insufficiency
- Thrombocytopenia

Reporting of Anticipated Events

These events will be captured on the CRF and in the database, and will be reported to the sponsor as described in Section 12.3, All Adverse Events. Any event that meets serious adverse event criteria will be reported to the sponsor within the appropriate timeline as described in Section 12.3.2, Serious Adverse Events. These anticipated events are exempt from expedited reporting as individual single cases to Health Authorities. However if based on an aggregate review, it is determined that an anticipated event is possibly related to study drug, the sponsor will report these events in an expedited manner.

Statistical Analysis

Details of statistical analysis of anticipated events, including the frequency of review and threshold to trigger an aggregate analysis of anticipated events will be provided in a separate Anticipated Events Safety Monitoring Plan.

INVESTIGATOR AGREEMENT

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

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

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Thomas Lin, MD, PhD

Institution: Janssen Scientific Affairs, LLC

Signature: _____ Date: 10 MAY 2017
(Day Month Year)

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