Official Title of Study:

Study of Daratumumab (JNJ-54767414 (HuMax® CD38) in Combination with Bortezomib (VELCADE), Thalidomide, and Dexamethasone (VTD) in the First Line Treatment of Transplant Eligible Subjects with Newly Diagnosed Multiple Myeloma.

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Intergroupe Francophone du Myelome (IFM)
in Collaboration with
Dutch-Belgian Cooperative Trial Group for Hematology Oncology (HOVON)
And Janssen Research & Development

Clinical Protocol

Study of Daratumumab (JNJ-54767414 (HuMax® CD38) in Combination with Bortezomib (VELCADE), Thalidomide, and Dexamethasone (VTD) in the First Line Treatment of Transplant Eligible Subjects with Newly Diagnosed Multiple Myeloma.

Protocol IFM 2015-01 /HO131/54767414MMY3006; Phase 3
Initial Version dated 14 January 2015
AMENDMENT 1 dated 24 August 2015
AMENDMENT 2 dated 21 March 2016
AMENDMENT 3 dated 05 July 2019
AMENDMENT 4 dated 14JAN2021

JNJ-54767414 (daratumumab)

Status: Approved for Dossier Use
Date: 14 January 2021

Summary of protocol versions

version	date	modifications
initial version	14/01/2015	
Amendment 1	24/08/2015	Main protocol changes: Inclusion criteria N°2 and exclusion N° 13 and 18 modified, precision on MRD evaluation, new CRAB criteria added, allowance of premedication 3 hours before Dara and montelukast added, collect of AE during graft, details on sCR assessment.
Amendment 2	21/03/2016	Main protocol changes: precision about MRD and response assessment during maintenance phase, inclusion criteria 2 and 5, exclusion criteria 2/7/8. Precisions about vital signs and immunogenicity data, precision about montelukast for patient receiving daratumumab on part II only, precision of the delay between consolidation and maintenance phases.
Amendment 3	05/07/2019	Main protocol changes: Precisions and clarifications added regarding EOT visit and FU visits (Pre-PD/PD/Survival) procedures. Addition of IRR definition. Update of safety information in line with IB update (IB 15 and its addendum 1) Addition of recommendations already communicated to sites for Part I for harmonization purposes. Clarification regarding procedure in case of suspected daratumumab interference on SPEP and IFE. Clarification for recording the response to treatment. Clarification for recording any new malignancy event as an SAE. Clarifications regarding SAE declaration circuit. Changes in formulation/structure for accuracy and better understanding of protocol procedures. New MRD assessments during Pre-Progression Follow-up Changes in bisphosphonate therapy recommendations Change of IFM Director
Amendment 4	14/01/2021	Modification of Pre-PD follow-up visit frequency IDMC meetings not needed after the unblinding of the data The interim analysis for PFS met the predefined boundary and turned into the final analysis of part 2 for PFS. Change in monitoring strategy: risk-based approach with remote quality control of data/Risk-based monitoring Addition of analyses of screening aliquots using NGS methodology

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SYNOPSIS

Study of Daratumumab (JNJ-54767414 (HuMax® CD38) in Combination with Bortezomib (VELCADE), Thalidomide, and Dexamethasone (VTD) in the First Line Treatment of Transplant Eligible Subjects with Newly Diagnosed Multiple Myeloma

EudraCT Number: 2014-004781-15

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

OBJECTIVES AND HYPOTHESIS

Primary Objectives:

- The primary objective in Part 1 is to determine if the addition of daratumumab to VTD will increase the proportion of subjects achieving stringent complete response (sCR) post completion of consolidation therapy compared with VTD alone.
- The primary objective in Part 2 is to determine if the use of daratumumab as single agent in maintenance compared to observation only will increase progression-free survival (PFS) when used after autologous stem cell transplant and consolidation therapy.

Secondary Objectives:

In Part 1, major secondary efficacy objectives are to determine if the addition of daratumumab to VTD will improve:

- Progression-free survival (PFS) from first randomization
- Time to progression (TTP) from first randomization
- Complete response (CR) rate by the end of ASCT/consolidation
- Minimal residual disease (MRD) negative rate by the end of ASCT/consolidation
- Post-induction stringent complete response (sCR) rate
- Progression-free survival after next line of therapy (PFS2)
- Post-induction overall response rate (ORR) and rate of very good partial response (VGPR) or better
- Overall survival (OS)
- Duration of CR and sCR

In Part 2, major secondary efficacy objectives are to determine if the addition of daratumumab to VTD will improve the assessment during maintenance of:

- Time to progression
- CR rate
- MRD negative rate
- PFS2
- Rate of improved response

- Rate of MRD negative conversion
- ORR
- OS

Other secondary objectives throughout the study are:

- To evaluate quality of life and health economic/resource utilization
- To assess immunogenicity of daratumumab
- To assess safety and tolerability of daratumumab in combination with VTD
- Rate of MRD conversion during Pre-PD Follow-Up.

Exploratory Objectives:

- To evaluate daratumumab's impact on response and resistance to treatment

Hypothesis

As this study integrates induction therapy as well as post-transplant consolidation and maintenance therapy into a single, 2-stage randomization design to address 2 distinct questions about the effectiveness of daratumumab treatment during induction/consolidation and maintenance, there are two primary hypotheses for this study:

Hypothesis for Induction/Consolidation: first randomization

Addition of daratumumab to VTD improves post-consolidation sCR rate compared with VTD alone.

Hypothesis for Maintenance: second randomization

Daratumumab maintenance after ASCT prolongs PFS compared with observation**.**

OVERVIEW OF STUDY DESIGN

This is a randomized, open-label, active control, parallel group, multicenter, Phase 3 study in subjects with previously untreated multiple myeloma. The planned number of subjects to be treated in this study is as follows:

1080 subjects (540/arm) for first randomization (induction)

Approximately 800 subjects (400/arm) of the initial 1080 subjects will be randomized to maintenance. The actual accrual into the Maintenance Phase may be greater than 800 if a higher-than-expected proportion of subjects in the induction/consolidation stage achieve response and are randomized in the Maintenance Phase.

The study will consist of 3 phases. The Screening Phase will extend up to 28 days prior to Cycle 1, Day 1. The Treatment Phase will be conducted in 2 parts, as described below, and will extend from Cycle 1 Day 1 until treatment discontinuation due to progressive disease, unacceptable toxicity, ineligibility for second randomization, or 2 years of maintenance therapy/observation. The Follow-up (FU) Phase will extend from treatment discontinuation until death, lost to follow-up, withdrawal of consent, or study end, whichever occurs first.

The 2 parts in the Treatment Phase are described below.

Part 1: Induction/ASCT/Consolidation Phase (1:1 Randomization)

Arm A: VTD induction therapy (4 cycles), followed by ASCT, followed by 2 cycles of VTD consolidation

Arm B: VTD plus daratumumab induction therapy (4 cycles), followed by ASCT, followed by 2 cycles of VTD plus daratumumab consolidation

The consolidation phase of treatment will begin approximately 30 days after ASCT, when the subject has recovered sufficiently and engraftment is complete. Response will be evaluated at Day 100 post ASCT.

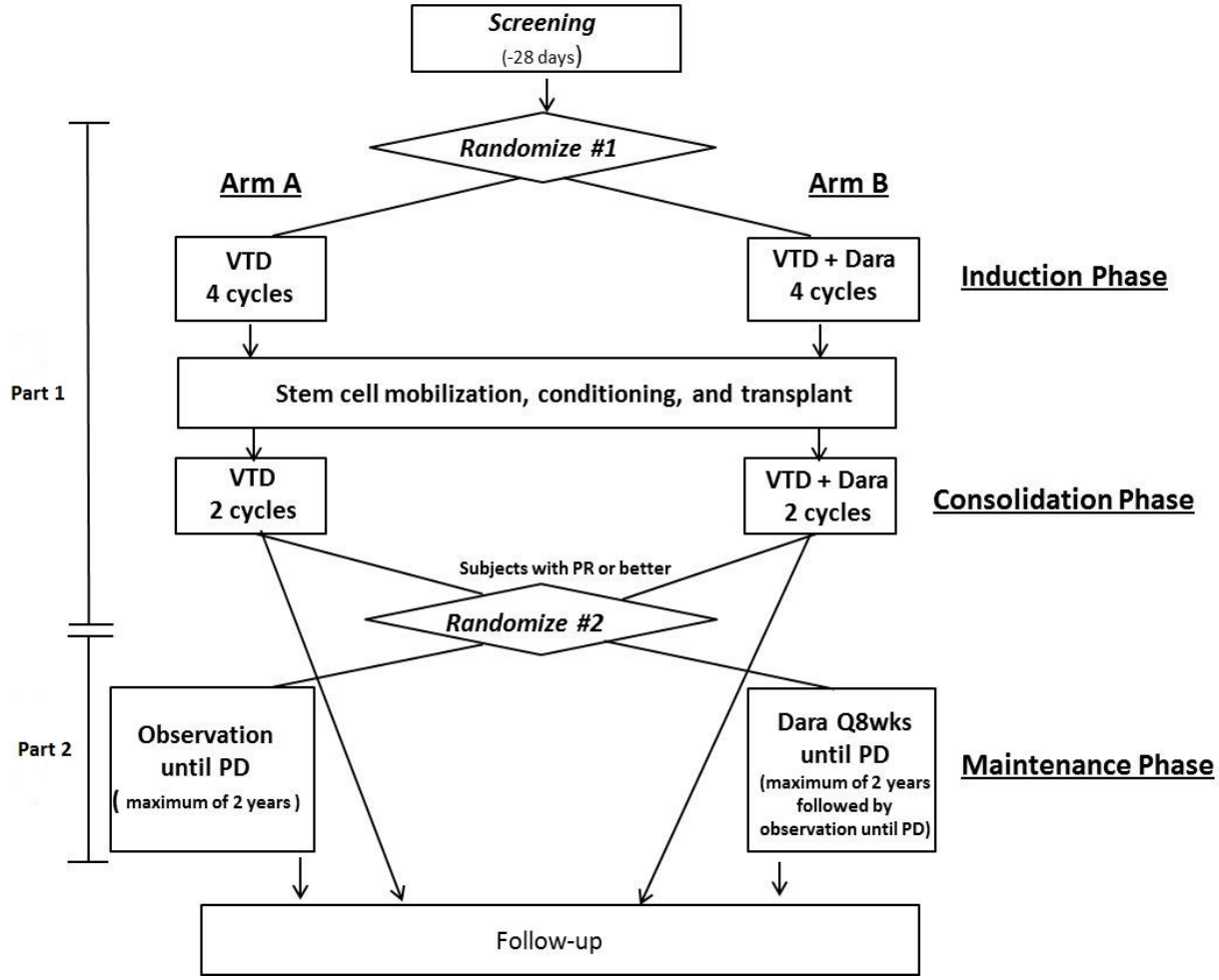
Part 2: Maintenance Phase (1:1 Re-randomization of subjects achieving at least a PR after consolidation)

Subjects with at least a PR will be randomized after determination of response at approximately Day 100 after ASCT, and will enter the Maintenance Phase upon completion of consolidation therapy.

Arm A: Observation only until documented disease progression (limited to 2 years maximum duration)

Arm B: Daratumumab monotherapy until documented disease progression (limited to 2 years maximum duration)

Subjects who are not randomized in Part 2 will enter in the Follow-up Phase and will be followed until disease progression, death or lost to follow up, withdrawal of consent or study end even if they receive subsequent anticancer treatments.



In Arm B, daratumumab (16 mg/kg) will be administered by intravenous (IV) infusion once every week for 8 weeks (VTD Induction Cycle 1-2), then once every 2 weeks for 8 weeks (VTD Induction Cycle 3-4), and following ASCT once every 2 weeks for 8 weeks (VTD consolidation Cycle 5-6). Following subsequent re randomization, subjects assigned to the maintenance Arm B will receive daratumumab (16 mg/kg) once every 8 weeks until documented disease progression (limited to a maximum duration of 2 years).

Permuted block randomization will be implemented in this study. Subjects will be stratified at first randomization by site affiliation (IFM or HOVON), International Staging System stage I, II, or III (β-2 microglobulin and albumin) and by cytogenetics (standard risk or high risk as defined by presence of del17p or t(4;14), as centrally confirmed during screening).

Response will be assessed 100 days after ASCT and eligibility for the second randomization will be determined. Subjects will be stratified at the second randomization by type of induction treatment (VTD +/- daratumumab) and by depth of response to induction/consolidation therapy (as determined by MRD status and post-consolidation response).

Assessment of tumor response and disease progression will be conducted in accordance with the International Myeloma Working Group (IMWG) response criteria. An assessment of MRD will be conducted using flow cytometry and NGS on bone marrow aspirates for all patients in induction/consolidation phases and for patients who achieve at least VGPR in maintenance phase. Safety evaluations will include adverse event monitoring, physical examinations, electrocardiogram monitoring (ECGs), clinical laboratory parameters (hematology and chemistry), vital sign measurements, and Eastern Cooperative Oncology Group (ECOG) performance status.

Two primary analyses are planned. The first primary analysis, with a purpose to evaluate response by measuring the stringent complete response (sCR) rate, will be performed after all subjects have completed the Day 100 post-ASCT response evaluation or have been discontinued from study treatment by this timepoint. The second primary analysis, for PFS, will be performed when approximately 390 PFS events have been observed. An interim analysis is planned for the maintenance stage after 273 (70%) PFS events are observed in the population of subjects who are re-randomized. In case the Interim analysis for PFS meets the pre-defined boundary, this Interim analysis reflects the primary analysis for PFS. No PFS analysis at 390 PFS events will be done. The next pre-planned analysis in that case will be the final data cutoff at the end of study, when approximately 350 subjects have died, or approximately 5 years after the last subject is randomized in the second randomization, whichever comes first.

SUBJECT POPULATION

Inclusion Criteria

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

1. Subject must be between 18 and 65 years of age.

2. Subject must have documented multiple myeloma satisfying the CRAB or biomarkers of malignancy criteria (see Attachment 1) and measurable disease as defined by:

    - Monoclonal plasma cells in the bone marrow ≥10% or presence of a biopsy proven plasmacytoma AND any one or more of the following myeloma defining events:
        - Hypercalcemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than ULN or >2.75 mmol/L (>11 mg/dL)
        - Renal insufficiency: creatinine clearance <40mL/min or serum creatinine >177 μmol/L (>2 mg/dL)
        - Anemia: hemoglobin >2 g/dL below the lower limit of normal or hemoglobin <10 g/dL
        - Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT
        - Clonal bone marrow plasma cell percentage ≥60%
        - Involved: uninvolved serum free light chain ratio ≥100
        - >1 focal lesion on MRI studies
    - Measurable disease as defined by any of the following:
        - IgG multiple myeloma: Serum monoclonal paraprotein (M-protein) level ≥1.0 g/dL or urine M-protein level ≥200 mg/24 hours; or
        - IgA, IgE, IgD, or IgM multiple myeloma: serum M-protein level ≥0.5 g/dL or urine M-protein level ≥200 mg/24 hours; or
        - IgD multiple myeloma: serum M-protein level <0.5 g/dL and Serum immunoglobulin free light chain ≥10 mg/dL and abnormal serum immunoglobulin kappa lambda free light chain ratio; or
        - Light chain multiple myeloma without measurable disease in the serum or the urine: Serum immunoglobulin free light chain ≥10 mg/dL and abnormal serum immunoglobulin kappa lambda free light chain ratio

3. Newly diagnosed subjects eligible for high dose therapy and autologous stem cell transplantation.

4. Subject must have an ECOG performance status score of 0, 1, or 2 (see Attachment 2).

5. Subject must have pretreatment clinical laboratory values meeting the following criteria during the Screening Phase (Lab tests should be repeated if done more than 15 days before C1D1):

    a) hemoglobin ≥7.5 g/dL (≥5 mmol/L; prior red blood cell [RBC] transfusion or recombinant human erythropoietin use is permitted);

    b) absolute neutrophil count (ANC) ≥1.0 x 10^9/L (GCSF use is permitted);

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

    d) ALT ≤2.5 x ULN;

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

    f) calculated creatinine clearance ≥40 mL/min/1.73 m^2 (see Attachment 3);

    g) corrected serum calcium ≤14 mg/dL (<3.5 mmol/L); or free ionized calcium ≤6.5 mg/dL (≤1.6 mmol/L) (see Attachment 4);

    h) platelet count ≥70 x 10^9/L for subjects in whom <50% of bone marrow nucleated cells are plasma cells; otherwise platelet count >50x10^9/L (transfusions are not permitted to achieve this minimum platelet count).

6. Women who are partners of men and of childbearing potential must be practicing one of the following methods of birth control: subcutaneous hormonal implant, levonorgestrel-releasing intra-uterine system, medroxyprogesterone acetate depot, tubal sterilization, ovulation inhibitory progesterone only pills, or sexual intercourse with a vasectomized male partner (vasectomy must be confirmed by 2 negative semen analyses). Or women will commit to absolute and continuous abstinence confirmed to her physician on a monthly basis. Childbearing potential is defined in Section 9.1.2. Contraception will start 4 weeks before the start of therapy, during therapy including dose interruptions, for 4 weeks after discontinuation of thalidomide and for 4 months after discontinuation of daratumumab.

7. A woman of childbearing potential must have 2 negative serum or urine pregnancy tests at Screening, first within 10 to 14 days prior to dosing and the second within 24 hours prior to dosing.

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

Exclusion Criteria

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

1. Subject has received daratumumab or other anti-CD38 therapies previously.

2. Subject has a diagnosis of primary amyloidosis, monoclonal gammopathy of undetermined significance, smoldering multiple myeloma, or solitary plasmacytoma. Monoclonal gammopathy of undetermined significance is defined by presence of serum M-protein <3 g/dL; absence of lytic bone lesions, anemia, hypercalcemia, and renal insufficiency related to the M-protein; and (if determined) proportion of plasma cells in the bone marrow of 10% or less (Kyle 2003[25]). Smoldering multiple myeloma is defined as asymptomatic multiple myeloma with absence of related organ or tissue impairment (ROTI) end organ damage (Kyle 2003[25], Kyle 2007[26]).

3. Subject has a diagnosis of Waldenström's macroglobulinemia, or other conditions in which IgM M-protein is present in the absence of a clonal plasma cell infiltration with lytic bone lesions.

4. Subject has prior or current systemic therapy or SCT for any plasma cell dyscrasia, with the exception of an emergency use of a short course (equivalent of dexamethasone 40 mg/day for a maximum 4 days) of corticosteroids before treatment.

5. Subject has peripheral neuropathy or neuropathic pain Grade 2 or higher, as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.

6. Subject has had any prior or concurrent invasive malignancy (other than multiple myeloma) within 10 years of study start except adequately treated basal cell or squamous cell carcinoma of the skin, carcinoma in situ of the cervix, localized prostate adenocarcinoma diagnosed ≥3 years and without evidence of biochemical failure, or other cancer for which the subject has undergone potentially curative therapy and has no evidence of that disease for ≥10 years.

7. Subject has had radiation therapy within 14 days of C1D1.

8. Subject has had plasmapheresis within 28 days of C1D1.

9. Subject is exhibiting clinical signs of meningeal involvement of multiple myeloma.

10. a) Subject has known chronic obstructive pulmonary disease (COPD) with a Forced Expiratory Volume in 1 second (FEV_1) < 50% of predicted normal. Note that FEV_1testing is required for patients suspected of having COPD and subjects must be excluded if FEV_1 <50% of predicted normal.

    b) Subject has known moderate or severe persistent asthma within the past 2 years (see Attachment 5), 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).

11. Subject is known to be seropositive for history of human immunodeficiency virus (HIV) or known to have active hepatitis B or hepatitis C.

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

13. Subject has clinically significant cardiac disease, including:

    - myocardial infarction within 1 year before randomization, or an 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 Grade ≥2) or clinically significant ECG abnormalities
    - screening 12-lead ECG showing a baseline QT interval as corrected by Fridericia's formula (QTcF) >470 msec

14. Subject has known allergies, hypersensitivity, or intolerance to boron or mannitol, corticosteroids, monoclonal antibodies or human proteins, or their excipients (refer to the Investigator's Brochure), or known sensitivity to mammalian-derived products.

    Or subject has known hypersensitivity to thalidomide.

15. Subject has plasma cell leukemia (according to WHO criterion: ≥20% of cells in the peripheral blood with an absolute plasma cell count of more than 2×10^9/L) or POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes).

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

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

18. Subject has had major surgery within 2 weeks before randomization or will not have fully recovered from surgery, or has surgery planned during the time the subject is expected to participate in the study. Kyphoplasty or Vertebroplasty is not considered major surgery.

19. Subject has received an investigational drug (including investigational vaccines) or used an invasive investigational medical device within 4 weeks before randomization or is currently enrolled in an interventional investigational study.

20. Subject has contraindications to the use of any components of the backbone treatment regimens, per local prescribing information.

21. Incidence of gastrointestinal disease that may significantly alter the absorption of oral drugs.

22. Subjects unable or unwilling to undergo antithrombotic prophylactic treatment.

DOSAGE AND ADMINISTRATION

Daratumumab (16mg/kg) will be administered by intravenous (IV) infusion once every week for 8 weeks (VTD induction Cycle 1-2), then every 2 weeks for the remaining induction cycles and consolidation cycles based on treatment assignment. Following subsequent re randomization, subjects assigned to the daratumumab maintenance arm will receive daratumumab (16mg/kg) once every 8 weeks until documented disease progression (limited to a maximum duration of 2 years).

Subjects will receive 1.3 mg/m2 bortezomib as a SC injection twice a week (Days 1, 4, 8, and 11) for four 28-day induction cycles (Cycles 1 to 4), and two consolidation cycles (Cycles 5 and 6), with an option to change the schedule from twice a week to once a week, should toxicity be encountered. Cycles will remain 28 days in length regardless of injection interval.

Thalidomide will be administered PO at 100 mg daily for 4 x28 day induction cycles and 2 x 28 day consolidation cycles. Thalidomide should be taken as a single dose at bedtime, to reduce the impact of somnolence. Thalidomide can be taken with or without food.

Dexamethasone will be administered on scheduled days as indicated in the Time and Events Schedule at 40 mg during Cycles 1 and 2. In Cycles 3 and 4, dexamethasone will be administered at 40 mg on Days 1-2 and 20 mg on subsequent dosing days. Dexamethasone 20 mg will be administered in Cycles 5 and 6. On daratumumab infusion days, in the induction/consolidation phase, dexamethasone may be administered intravenously 1 hour before the daratumumab infusion. On days when daratumumab is not administered, dexamethasone is administered PO. Dexamethasone tablets are to be taken with or immediately after a meal or snack, preferably in the morning.

In the maintenance phase, dexamethasone 20 mg will be administered as pre-medication on daratumumab infusion days.

SAFETY EVALUATIONS

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

BIOMARKER EVALUATIONS

Biomarkers for MMY3006 will focus on the evaluation of MRD in bone marrow aspirates and on the assessment of clinical efficacy in high-risk molecular subgroups.

IMMUNOGENICITY EVALUATIONS

Samples to assess the generation of antibodies to daratumumab (immunogenicity) and associated serum daratumumab concentration levels will be obtained from all subjects according to the Time and Events Schedule.

EFFICACY EVALUATIONS

Assessment of tumor response and disease progression will be conducted in accordance with the IMWG response criteria. Efficacy evaluations will include measurements of tumor burden/residual disease, myeloma proteins, bone marrow examinations, skeletal surveys, extramedullary plasmacytomas, and serum calcium corrected for albumin.

STATISTICAL METHODS

Sample Size

The sample size of this study takes into consideration the statistical power for the primary comparisons in both stages of the study. For Part 2 (maintenance phase), it is assumed that median PFS from the second randomization is 45 months for observation, and daratumumab maintenance will decrease the risk of progression or death by 25% (HR=0.75; estimated median PFS of 60 months for daratumumab maintenance). To achieve 80% power with a significance level of 0.05, 390 PFS events are needed. Assuming a 36 months accrual and 45 months of additional follow-up, approximately 800 subjects (400/arm) will be randomized in the second randomization (daratumumab maintenance vs. observation).

Assuming that 75% of subjects in the induction/ASCT/consolidation stage are eligible to be randomized for maintenance, which takes into account the expected response rate as well as potential dropouts, 1080 subjects (540/arm) will be randomized in the first randomization (daratumumab in combination with VTD induction/ASCT/VTD consolidation vs. VTD induction/ASCT/VTD consolidation). This sample size would provide at least over 85% power to detect an improvement in sCR rate from 25% to 35% at a 2-sided α of 0.05.

Analysis Population

Analysis of primary and secondary efficacy variables will be based on the intent-to-treat (ITT) population, which includes all subjects randomized in the first randomization. In addition, maintenance-specific analyses will use the maintenance-specific intent-to-treat population (ITT-m), which will include all subjects who are randomized in the second randomization.

All safety analyses will be based on the safety analysis set. The safety population will be defined separately for the induction/ASCT/consolidation and maintenance stages. These populations will include all subjects randomized at each stage who received at least 1 dose of study drugs at the respective stage.

Efficacy Analyses

The primary comparison of the 2 randomized induction/consolidation treatments will be made with respect to sCR rate using the Cochran-Mantel-Haenszel chi square test in the ITT population. A Mantel-Haenszel odds ratio, along with its 2-sided 95% confidence interval, will be calculated. All binary secondary endpoints for the induction/ASCT/consolidation stage will be analyzed similarly as the primary endpoint (sCR rate).

The statistical comparison between the 2 induction regimens with respect to PFS from the first randomization will need to take into consideration subsequent maintenance assignment (daratumumab maintenance or observation). A usual “as-randomized”-type of intent-to-treat analysis that compares the 2 induction treatments with respect to PFS without considering maintenance treatment has been shown to produce potentially biased estimates of treatment effects. As such, 2 appropriate intent-to-treat (ITT)-type of induction comparisons of particular interest, 1 specific to each maintenance treatment (daratumumab maintenance or observation), will be conducted:

- daratumumab+VTD (D-VTD) induction/consolidation followed by daratumumab maintenance vs. VTD induction/consolidation followed by daratumumab maintenance, and
- daratumumab+VTD (D-VTD) induction/consolidation followed by observation vs. VTD induction/consolidation followed by observation

For each of the 2 comparisons, the analysis will include any subjects who are randomized in the first randomization and are then subsequently randomized to the specific maintenance treatment as well as those subjects who are randomized in the first randomization but are not randomized in the second randomization. A stratified Cox regression analysis with inverse probability weighting will be performed (Lokhnygina 200730), which yields unbiased estimates of treatment effects and maintains Type I error rate. The overall

comparison of induction treatments will be made treating these 2 comparisons as 2 strata with the variance estimated using the robust variance estimator (the sandwich estimate). These 3 comparisons will all be tested with the significance level of 0.05 (2-sided) following the closed testing procedure. Essentially, the statistical significance is established for each of the 2 maintenance-specific comparisons if both itself and the overall induction comparison are significant at the 2-sided level of 0.05. Other time-to-event endpoints, except for duration of response, will be analyzed similarly. Duration of response will be presented descriptively using the weighted Kaplan-Meier estimates by Miyahara and Wahed 2010[36].

The primary comparison of the 2 randomized maintenance treatments (daratumumab maintenance and observation) will be made with respect to PFS from the second randomization using a stratified log-rank test in the ITT-m population. The Kaplan-Meier method will be used to estimate the distribution of PFS from the second randomization for each treatment. The treatment effect (hazard ratio) and its 2-sided 95% confidence intervals are to be estimated using a stratified Cox regression model with maintenance treatment as the sole explanatory variable. In addition, the interaction between induction/consolidation and maintenance will be tested at a 2-sided significance level of 0.05 by a stratified Cox regression model that includes the interaction term between maintenance treatment and induction/consolidation treatment. All secondary time-to-event endpoints in the maintenance stage will be analyzed similarly as for the primary endpoint (PFS from the second randomization).

The comparison of the 2 randomized maintenance arms on binary secondary endpoints will be made using the Cochran-Mantel-Haenszel chi square test in the population of all subjects that are randomized in the second randomization. The observed rate of the binary outcome will be provided along its 2-sided 95% CIs. A Mantel-Haenszel odds ratio, along with its 2-sided 95% confidence interval, will be calculated.

Safety Analyses

In general, adverse events that occurred during the induction/consolidation and maintenance stages will be summarized separately. Treatment-emergent adverse events for each stage will be defined as events that occur or worsen after administration of the first dose of during that stage and through 30 days after the last dose of study drug in that stage and before the next phase of treatment begins. Adverse events will be summarized by system organ class and preferred terms, NCI toxicity grade, and by action taken with study treatment.

Summaries, listings, datasets, or subject narratives will 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.

Table 1. TIME AND EVENTS SCHEDULE: INDUCTION AND CONSOLIDATION PHASES

	Notes	Screening Phase	Induction Treatment (Cycles 1-4)		ASCT	Consolidation Treatment (Cycles 5-6)	Day 100 post ASCT
		within 28 days before randomization	D1	D28	(refer to Section 9.1.3)	D1	proceed to Table 3
Study treatment should be initiated within 3 days after randomization. Induction and consolidation cycles are approximately 28 days in duration. Treatment will be for a maximum of 4 induction cycles and 2 consolidation cycles. The start of each cycle may occur ±3 days of the scheduled day in order to accommodate the schedule of the site or subject. Details of ASCT will be collected as per Section 9.1.3.							
Procedures							
Informed consent	ICF must be signed before any study-related procedures are performed.	X					
Eligibility criteria		X					X
Demography/ Medical History		X					
Height		X					
Chest X-ray	May be performed within 42 days before randomization	X					
FEV_1test	Subjects with COPD or asthma, FEV_1 should be measured	X					
ECOG		X		C4			X
12-lead ECG	Acceptable for screening if performed as part of SOC within 42 days before randomization	X		C4			X
Physical exam	Including neurological exam	X	Symptom and disease directed exam as clinically indicated				
Vital signs, weight		X	Please see Table 2 for details.				
Blood type and IAT results	Includes ABO, Rh, and IAT results. Provide results on wallet card.		C1D1 predose				
Laboratory Assessments							
Pregnancy test	For women of childbearing potential only. During screening, within 10-14 days prior to first dose and again within 24 hrs prior to first dose. During study, weekly during Cycle 1 and then monthly in women with regular menstrual cycles or every 2 weeks in women with irregular menstrual cycles. Please refer to Section 9.2 for details.						
Hematology	Local lab. Testing have to be performed within the 2 weeks before C1D1	X	Please see Table 2 for details.				
Serum chemistry	Local lab. Testing have to be performed within the 2 weeks before C1D1	X	Please see Table 2 for details.				
Daratumumab immunogenicity and serum concentration	For all subjects: Sample to be taken prior to treatment on C1D1. Following daratumumab administration If an infusion reaction occurs, obtain unscheduled blood sample as soon as possible. Samples to be sent to central laboratory.		C1D1 predose				

	Notes	Screening Phase	Induction Treatment (Cycles 1-4)		ASCT	Consolidation Treatment (Cycles 5-6)	Day 100 post ASCT
		within 28 days before randomization	D1	D28	(refer to Section 9.1.3)	D1	proceed to Table 3
Disease Evaluations: Every effort should be made to conduct disease evaluations as per schedule (window ±3 days). Refer to Section 9.6 for details on efficacy evaluations. Response assessment for primary efficacy endpoints should occur as close to Day 100 post-ASCT as possible (window up to Day 114 post ASCT).							
Cytogenetics/FISH (stratification)	For screening (up to 42 days before randomization) A core biopsy and aspirate is strongly preferred for screening and to confirm response (sCR). If not available, morphologic review of the aspirate smear is acceptable. Flow cytometry should be systematically performed at Day 100 to evaluate sCR.	X					
Bone Marrow Exam Myeloma disease evaluation		X		C4			X
Serum disease evaluations (SPEP)	Blood sample to be sent to central laboratory. IFE and FLC when CR is suspected or maintained. FLC every cycle for subjects with light chain myeloma. Not required C1D1.	X	X	C4		X	X
Quantitative Ig	Blood. Central lab	X		C4			X
Urine disease evaluations (UPEP)	24H Urine. Sample to be sent to central laboratory. IFE when CR is suspected or maintained. Not required C1D1.	X	X	C4		X	X
β2-microglobulin	Central lab.	X					
Calcium	Local lab.	X	X	C4		X	X
Albumin	Local.and central lab	X	X	C4		X	X
Assessment of lytic disease	Acceptable for screening if performed as part of SOC within 42 days before randomization	X	As clinically indicated				
Extramedullary plasmacytomas	Subjects with history of plasmacytoma; acceptable for screening if performed as part of SOC within 42 days before randomization	X	If applicable, by physical exam every 4 wks, by radiologic exam (if required) every 12 wks				
Patient Reported Outcome	EORTC-QLQ-30 and EQ-5D-5L at each specified visit. To be completed before any other study procedures are performed.	X		C4			X
Ongoing Subject Review							
Adverse Events	See Section 12 for detailed instructions.	continuous from the time of signing of ICF until 30 days after last dose of last study drug					
Concomitant Medications	See Section 8 for detailed instructions.	continuous from the time of signing of ICF until 30 days after last dose of last study drug					

Table 2. TIME AND EVENTS SCHEDULE: STUDY DRUG DOSING, INDUCTION AND CONSOLIDATION PHASES

Study Day	Notes	Week 1			Week 2			Week 3		Week 4		
		D1	D2	D4	D8	D9	D11	D15	D16	D22	D23	D28
Cycles are 4 weeks (28 days) in duration and are based on the administration of VELCADE. Treatment will be for 4 x 28 days induction cycles and following ASCT 2x consolidation cycles.The start of each cycle may occur ±3 days of the scheduled day in order to accommodate the schedule of the site or subject. On dosing days where the chemotherapy combination products are given with daratumumab, study treatment should be administered in the following order (when more than 1 component is scheduled): dexamethasone, daratumumab, bortezomib and thalidomide (at bed time).												
Hematology	Local lab. Testing may be performed up to 2 days before infusion. Results of hematology tests must be evaluated before treatment. Perform at additional timepoints, as clinically indicated.	X			C1-C2			X		C1-C2		
Clinical Chemistry		X										
Weight	If weight changes by more than 10% from baseline, the dose of all study treatments will be re-calculated	X										
Vital Signs	For Arm A: to be measured at the beginning of the visit. For Arm B: Vital signs (blood pressure, temperature, pulse) measured in sitting position. On Cycle 1 Day 1: immediately before the start of dara infusion; at 0.5, 1, 1.5, 2, 3.5 hrs after the start of the infusion; at end of infusion; and 0.5, 1hr after end of infusion. For all other infusions, vital signs will be measured immediately before infusion start and at end of dara infusion.	X			C1-C2			X		C1-C2		
Diary review	Accountability/exposure check	X										
Pre-infusion Medications, Arm B only												
Antihistamine	Administer not more than 3 hours before dara infusion. Paracetamol or acetaminophen 650-1000 mg. H1 receptor antagonist (dosing according to institutional standard) ; 10mg of montelukast is required prior to cycle 1 day 1 of Daratumumab and is optional before all other doses	X			C1-C2			X		C1-C2		
Paracetamol		X			C1-C2			X		C1-C2		
Montelukast		X										
Study Drug Administration, Arm A and Arm B												
Dexamethasone	Administer 1 hr before dara infusion. Dexamethasone 40mg in C1 and C2. In C3 and C4, dexamethasone 40mg on D1 and D2, dexamethasone 20mg on subsequent dosing days. Dexamethasone 20mg in C5 and C6. Also serves as pre-infusion medication for daratumumab.	X	X		X	X		X	X	C1-C2	C1-C2	
Bortezomib	Administer by SC injection. Dose may be delayed up to 48 hrs, however subsequent doses must be adjusted as all VELCADE doses must be at least 72 hrs apart. Doses that need to be withheld are skipped and will not be made up later in the cycle.	X		X	X		X					
Thalidomide	Dispense on Day 1 for self-administration.	100 mg every day at bedtime.										
Study Drug Administration, Arm B Only												

Daratumumab	Refer to IP manual for recommendations on daratumumab infusion rate. Skip if infusion cannot be given within 1 wk.	X			C1-C2			X		C1-C2		

Table 3. TIME AND EVENTS SCHEDULE: MAINTENANCE PHASE

		Maintenance Treatment Phase (Weeks)															EOT	Pre-PD FU	PD	Survival FU
	Notes	1	9	17	25	33	41	49	52	57	65	73	81	89	97	105				
	Repeat Day 100 post -ASCT assessments if they were not done within 14 days of Week 1 of the Maintenance Phase. Study treatment should be initiated within 10 days after randomization. Week 1 corresponds to date of first daratumumab maintenance infusion for subjects in Arm B and randomization date for subjects in Arm A. The start of each cycle/visit may occur ±3 weeks of the scheduled day																	This visit may occur ±3 weeks of the scheduled day		This visit may occur ±3 weeks of the scheduled day
	Procedures																			
2nd randomization	within 10 days of Wk1D1 of Maintenance																			
ECOG					X				X			X				X				8wks and 16wks post PD Then every 4 months
12-lead ECG		As clinically indicated																		
Physical exam		Symptom and disease directed exam as clinically indicated																		
Weight	If a subject's weight changes >10% from baseline, the dose of all study drug will be re-calculated	X	X	X	X	X	X	X		X	X	X	X	X	X	X				
Vital signs	For Arm A: to be measured at the beginning of the visit. For Arm B: Vital signs (blood pressure, temperature, pulse) measured in sitting position. For 1st infusion: immediately before the start of dara infusion; at 0.5, 1, 1.5, 2, 3.5 hrs after the start of the infusion; at end of infusion; and 0.5, 1hr after end of infusion. For all other infusions, vital signs will be	X	X	X	X	X	X	X		X	X	X	X	X	X	X				

	Notes	Maintenance Treatment Phase (Weeks)															EOT	Pre-PD FU	PD	Survival FU
		1	9	17	25	33	41	49	52	57	65	73	81	89	97	105				
	measured immediately before infusion start and at end of dara infusion.																			
Assessment of lytic disease, and extramedullary plasmacytomas	Same type of imaging as done for screening procedures for lytic disease. Same method of assessment done at screening for extramedullary plasmacytomas (if applicable)																X		X	
Study Drug Administration (Arm B only, following second randomization)																				
Daratumumab	Administer premedications as per Section 6.1.3 10mg of montelukast is required prior to 1st infusion of dara if patient was in VTD Arm during Part 1 and is optional before all other doses.	X	X	X	X	X	X	X		X	X	X	X	X	X	X				
Laboratory Assessments																				
Pregnancy test	Women of childbearing potential in Arm B only	X	X	X	X	X	X	X		X	X	X	X	X	X	X	x			
Hematology	For Arm A: at the time of the visit. For Arm B: Testing may be performed up to 2 days before infusion days. Results of hematology tests must be evaluated before each study drug administration. Perform at additional timepoints, as clinically indicated. To be done by local lab.	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X			
Serum chemistry		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X			

	Notes	Maintenance Treatment Phase (Weeks)															EOT	Pre-PD FU	PD	Survival FU
		1	9	17	25	33	41	49	52	57	65	73	81	89	97	105				
Daratumumab immunogenicity and serum concentration	To be taken from all pts For Arm B: to be taken predose if it falls on a dara dosing day. .Samples to be sent to central laboratory. In addition, following administration of daratumumab if an infusion reaction occurs, obtain unscheduled blood sample as soon as possible.	X							X									Randomization #1 or #2 Arm B patients only: 8wks post last dose of dara		
	Disease Evaluations: Every effort should be made to conduct disease evaluations as per schedule (window ±3 days). Refer to Section 9.2 for details on efficacy evaluations.																			
Serum disease evaluations (SPEP)	IFE and FLC when CR is suspected or maintained. FLC every cycle for subjects with light chain myeloma. Central lab.		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Q12wk until PD	X	
Quantitative Ig	Central lab.				X				X			X				X	X		X	
Urine disease evaluations (UPEP)	IFE when CR is suspected or maintained. Central lab.		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Q12wk until PD	X	
Calcium,	Local lab.		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Q12wk until PD		
Albumin	Local & Central Lab		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Q12wk until PD		
Bone Marrow aspirate/biopsy for myeloma disease evaluation	A core biopsy and aspirate is strongly preferred to confirm response (sCR). If not available, morphologic review of the aspirate smear is acceptable. This is done by the local laboratory. An aspirate for Flow Cytometry/MRD should be systematically performed				X				X							X	X	X (please refer to table 3C)		

	Notes	Maintenance Treatment Phase (Weeks)															EOT	Pre-PD FU	PD	Survival FU
		1	9	17	25	33	41	49	52	57	65	73	81	89	97	105				
	and sent to the central lab whenever it will be necessary to evaluate sCR.																			
Assessment of lytic disease	See Section 9.6.6 for detailed instructions.	As clinically indicated																		
Extramedullary plasmacytomas	Subjects with history of plasmacytoma (cf. § 9.6.7)	If applicable, by physical exam every 4 wks, by radiologic exam (if required) every 12 wks															X	X		
PRO	EORTC-QLQ-30 and EQ-5D-5L at each specified visit. To be completed before any other study procedures are performed.				X				X			X				X				8wks and 16wks post PD
Follow-up Assessments (after PD), every 4 months																				
Second primary malignancies		<----------X---------->																		
PFS2																		X		X
Anticancer Therapy																		X		X
Survival		<----------X---------->																X		X
Ongoing Subject Review																				
Adverse Events	See Section 12 for detailed instructions.	<----------X- until 30 days post last protocol regimen dose or last visit for OBS arm---------->																		
Concomitant Medications	See Section 8 for detailed instructions.	<----------X- until 30 days post last protocol regimen dose or last visit for OBS arm ---------->																		

Abbreviations: AE=adverse event; C=cycle; COPD=chronic obstructive pulmonary disease; CR=complete response; ECOG=Eastern Cooperative Oncology Group; D=day; Dara=daratumumab; ECG=electrocardiogram; EOT= End-of-Treatment visit to be performed for all arms; FEV_1= Forced Expiratory Volume (in 1 second); FFPE=formalin-fixed paraffin embedded; FLC=free light chain; FU: follow-up; ICF=informed consent form; IP=investigational product; MRD=minimal residual disease; MRI=magnetic resonance imaging; PBMC= peripheral blood mononuclear cell ; PK=pharmacokinetics; PD= disease progression; PRO=patient reported outcome; SAE=serious adverse event; SOC=standard of care; SPEP=serum M-protein quantitation by electrophoresis; UPEP=urine M-protein quantitation by electrophoresis; Wk=week

Table 3 A. TIME AND EVENTS SCHEDULE (BIOMARKER SAMPLES): INDUCTION AND CONSOLIDATION PHASES

Sample	Notes	Test	Screening Phase	Induction Treatment (Cycles 1-4)		ASCT	Consolidation Treatment (Cycles 5-6)	Day 100 post ASCT
			within 28 days before randomization	D1	D28		D1	
Biomarker laboratory assessments								
Bone marrow aspirate/biopsy	For screening (up to 42 days before randomization) For response/MRD analysis fresh bone marrow aspirate is required. Flow Cytometry should be systematically performed at Day 100 to evaluate sCR. All samples for analysis to be sent to central laboratory	MRD (Next Gen Seq)	X		C4			X
		Response/MRD (Centralised flow)			C4			X
		Immuno phenotyping/Flow (HOVON pts only)	X					X
		Sequencing (DNA/RNA)	X					
Whole blood	Central lab.HOVON pts Only	Immunophenotyping (HOVON pts only	X		C1			X
Whole blood	Central lab, processed to plasma/PBMC's	Biomarkers	X					X

Table 3 B. TIME AND EVENTS SCHEDULE (BIOMARKER SAMPLES): MAINTENANCE PHASE

		Maintenance Treatment Phase (Weeks)															FU	PD
	Notes	1	9	17	25	33	41	49	52	57	65	73	81	89	97	105		
Week 1 corresponds to date of first daratumumab maintenance infusion for subjects in Arm B and randomization date for subjects in Arm A. The start of each cycle/visit may occur ±3 weeks of the scheduled day																		
Biomarker laboratory assessments																		
Bone marrow aspirate for MRD (NGS & Flow cytometry in selected pts)	For Response/MRD (Centralised flow) fresh bone marrow aspirate is required. Flow Cytometry should be systematically performed for patients who achieve at least VGPR or whenever it will be necessary to evaluate sCR. All samples for analysis to be sent to central laboratory				X(at least VGPR)				X(at least VGPR)							X(at least VGPR)	X (please refer to table 3 C)	
Immunophenotyping/bio-markers	Bone marrow aspirate,Central lab. (HOVON pts only)				X				X							X		X
Cytogenetics (FISH/DNA/RNA Analysis)	Bone marrow aspirate/biopsy (Central Lab)																	X
Blood samples immunophenotyping/ biomarkers	Central lab.(HOVON pts only)				X				X							X		X

Table 3 C. TIME AND EVENTS SCHEDULE (BIOMARKER SAMPLES): Pre-PD FU phase

	Notes	Pre-PD FU Phase (at some timepoint after the end of maintenance phase*)		
		At 1 year*	At 2 years*	At 3 years*
Biomarker laboratory assessments				
Bone marrow aspirate for MRD (NGS & Flow cytometry in MRD negative patients after week 105 or last MRD assessment since D100)	An aspirate for Flow Cytometry/MRD should be systematically performed and sent to the central lab	X	X	X

*The Pre-PD follow up visit closest to this sampling timepoint can be used for MRD sampling.

ABBREVIATIONS

ANC	Absolute Neutrophil Count
ADCC	antibody-dependent cell-mediated cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
AE	adverse event
ALT	ALanine aminotransferase
ANC	absolute neutrophil count
ASA	AcetylSalicylic Acid
ASCO	American Society of Clinical Oncology
ASCT	Autologous Stem Cell Transplantation
AST	alanine aspartate transferase
AUC(0-t)	area under the serum concentration versus time curve between time zero and a defined time point t
BFU-E	Blast Forming Unit – Erythrocyte
BM-MNC	bone marrow mononuclear cell
BSA	body surface area
BUCY	Busulfan n –cyclophosphamide
BUMEL	busulfan + melphalan
BUN	Blood urea nitrogen
CDC	complement-dependent cytotoxicity
CFU GM	Colony Forming Unitt-Granulocyte Macrofage
CI	confidence Interval
CIP	complement inhibitory proteins
CL	Total systemic clearance of drug after IV administration
CL/F	Apparent systemic clearance of drug after extravascular administration
Cmax	Maximum observed Concentration
Cmin	Minimum observed Concentration
CNV	Copy number variation
COPD	chronic obstructive pulmonary disease
CR	Complete Response
CRAB	hyperCalcemia Renal Insufficiency Anemia Bone lesions
CT	Computed Tomography
Dara	Daratumumab
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
D-VTD	daratumumab+VTD
DVD	doxorubicin+VELCADE+dexamethasone
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
eDC	electronic Data Capture
EOT	end-of-Treatment
FEV_1	Forced Expiratory Volume (in 1 second)
FFPE	formalin-fixed paraffin embedded
FLC	Free Light Chain
FU	Follow-up
G-CSF	granulocyte colony stimulating factor
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HDT-ASCT	high dose therapy and autologous stem cell transplant
HOVON	Haemato Oncology Foundation for Adults in the Netherlands
HIV	Human Immunodeficiency Virus
HR	hazard ratio
IAT	Indirect Antiglobulin Test (also known as indirect Coombs test)
ICA	Isotype Control Antibody
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee

IEC	Independent Ethics Committee
IFE	Immunofixation
IFM	Intergroupe Francophone du Myelome
IHC	ImmunoHistoChemistry
IL	InterLeukin
IMiD	immunomodulatory agent
IMWG	International Myeloma Working Group
IP	Investigational Product
IRB	Institutional Review Board
ITT	intention to treat
ITT-m	maintenance specific intention to treat
ISS	International Staging System
IV	Intravenous
IWRS	interactive web-based randomization system
LDH	lactic acid dehydrogenase
LMWH	Low Molecular Weight Heparin
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MEL 140	Melphalan 140 mg/m²
MGUS	Monoclonal Gammopathy of Undetermined Significance
MM	Multiple Myeloma
MoA	mechanism of action
M protein	monoclonal paraprotein
MP	Melphalan+Prednisone
MR	Minimal Response
MRD	Minimal Residual Disease
MRI	Magnetic Resonance Imaging
MTD	maximum-tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
nCR	near CR
NK	Natural Killer cell
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PBSC	peripheral blood stem cells
PCA	Progenitor Cell Assay
PCP	pneumocystis carinii pneumonia
PD	progressive disease
PET	Positron emission tomography
PFS	progression-free survival
Pre-PD FU	Pre-Progression Follow-Up
PK	Pharmacokinetics
PI	proteasome inhibitor
PO	Per Os
POEMS	polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes
Pom-dex	Pomalidomide-dexamethasone
PQC	product quality complaint
PR	Partial Response
PRO	patient reported outcome
QD	every day
QIgs	quantitative immunoglobulins
QTcF	QT interval corrected by Fridericia's formula
RBC	red blood cell
Rd / RVD	lenalidomide (Revlimid) + dexamethasone / Revlimid + VELCADE + dexamethasone
ROTI	related organ or tissue impairment
SAE	serious adverse event
SC	Subcutaneous
sCR	stringent Complete Response

SCT	Stem Cell Transplantation
SD	Stable Disease
SNP	Single Nucleotide Polymorphisms
SOC	standard of care
SPEP	Serum M-protein ElectroPhoresis
t1/2	half-life
TBI	Total Boby Irradiation
TD	Thalidomide + dexamethasone
TTP	time to progression
ULN	upper limit of normal
UPEP	24-hour urine M-protein quantitation by electrophoresis
V	volume of distribution
VAD	vincristine+doxorubicin+dexamethasone
VCD	VELCADE + cyclophosphamide + dexamethasone
VD	VELCADE (bortezomib) + dexamethasone
VGPR	very good partial response
VMP	VELCADE + melphalan + prednisone
Vss/F	Apparent volume of distribution at steady-state
VTD	VELCADE (bortezomib) +thalidomide+dexamethasone
WHO	World Health Organization
Wk	Week

1. INTRODUCTION

1.1. Background

1.1.1. Multiple Myeloma

Multiple myeloma is a malignant disorder of the plasma cells, characterized by uncontrolled and progressive proliferation of a plasma cell clone. The proliferating multiple myeloma cells displace the normal bone marrow, leading to dysfunction in normal hematopoietic tissue and destruction of the normal bone marrow architecture, which is reflected by clinical findings such as anemia, paraprotein in serum or urine, and bone resorption seen as diffuse osteoporosis or lytic lesions shown in radiographs (Kyle 2003[25]).

Treatment choices for multiple myeloma vary with the aggressiveness of the disease and related prognostic factors (Palumbo 2011[45]). Newly diagnosed patients in good physical health with active disease will generally receive high-dose chemotherapy with autologous stem cell transplantation (ASCT) (Attal 19961, Child 2003[10]). Eligibility for ASCT is established primarily by age and comorbidities (Harousseau 2009[21]). For patients in whom transplantation is not an option, treatment traditionally consists of systemic chemotherapy, with adjunctive use of radiation or surgery in selected cases associated with extramedullary disease (Engelhardt 2014[14], NCCN 2013[40], Palumbo 2009[46], Smith 2005[53]).

The therapeutic landscape of multiple myeloma has changed markedly in the past decade with the introduction of the novel immunomodulatory agents, thalidomide, lenalidomide, and pomalidomide, as well as proteasome inhibitors, bortezomib (VELCADE®) and carfilzomib. New approaches to therapy that incorporate these agents have produced significantly higher response rates and improved duration of both progression-free survival (PFS) and overall survival (OS) in the context of randomized, controlled studies. Collectively, novel therapies for multiple myeloma have been associated with substantial improvements in patient outcome (Kumar 2012b[24]).

1.1.2. Daratumumab

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

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, complement-dependent cytotoxicity (CDC) occurs rapidly and demonstrates maximal myeloma cell killing by daratumumab within 1 hour of antibody-mediated activation of the complement proteins (de Weers 2011[11]). Daratumumab-induced antibody-dependent cell-mediated cytotoxicity (ADCC) is slower in its action, with maximal ADCC by daratumumab observed at 4 hours in vitro (de Weers 2011[11]). Daratumumab has also been shown to induce antibody-dependent cellular phagocytosis (ADCP)

in the presence of macrophages within 4 hours in vitro (Overdijk 2013[42]). The precise role of some or all of these effector functions in reducing tumor burden in patients is unknown.

1.1.3. Nonclinical Studies

Two ex vivo studies evaluated the effects of combining daratumumab with chemotherapeutic agents and immunomodulator agents that are currently used for the treatment of multiple myeloma. In the first study (GMB3003-069), a combination of lenalidomide and daratumumab against multiple myeloma was evaluated (data on file). Daratumumab-dependent cell-mediated cytotoxicity of purified primary multiple myeloma cells and the patient-derived multiple myeloma cell line UM-9 killing was significantly augmented by lenalidomide pretreatment of peripheral blood mononuclear cells (PBMC) from healthy donors (effector cells). Synergy was demonstrated between lenalidomide and daratumumab-induced ADCC in bone marrow mononuclear cells of subjects with multiple myeloma. Daratumumab-induced ADCC of UM-9 cells was significantly up-regulated in PBMCs that were derived from 3 subjects with multiple myeloma during lenalidomide treatment. From this study, it is concluded that lenalidomide and daratumumab enhance killing of multiple myeloma cells ex vivo via ADCC.

In a second study (GMB3003-070), the potential benefit of combining daratumumab with multi-drug chemotherapy regimens was evaluated in fresh tumor cells from subjects with multiple myeloma (data on file). Lysis of primary tumor cells was measured directly in bone marrow mononuclear cell (BM-MNC) 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 that were refractory to lenalidomide and bortezomib treatment. Treatment of BM-MNC with lenalidomide or bortezomib resulted in 10% and 18% lysis, respectively. A combination of lenalidomide and bortezomib resulted in 25% lysis of BM-MNC. When daratumumab was added to either lenalidomide or bortezomib, a 2-fold increase in lysis was observed compared with lenalidomide or bortezomib alone. When daratumumab was added to combinations of dexamethasone, lenalidomide and bortezomib or to bortezomib, prednisone, and dexamethasone, the cell lysis was significantly increased ($p<0.001$) compared with the triple combination alone (no daratumumab) (van der Veer 2011b[57]). Refer to Figure 1 and Figure 2.

Figure 1: Daratumumab-Enhanced Multiple Myeloma Cell Killing by Key Multiple Myeloma Chemotherapeutic Agents

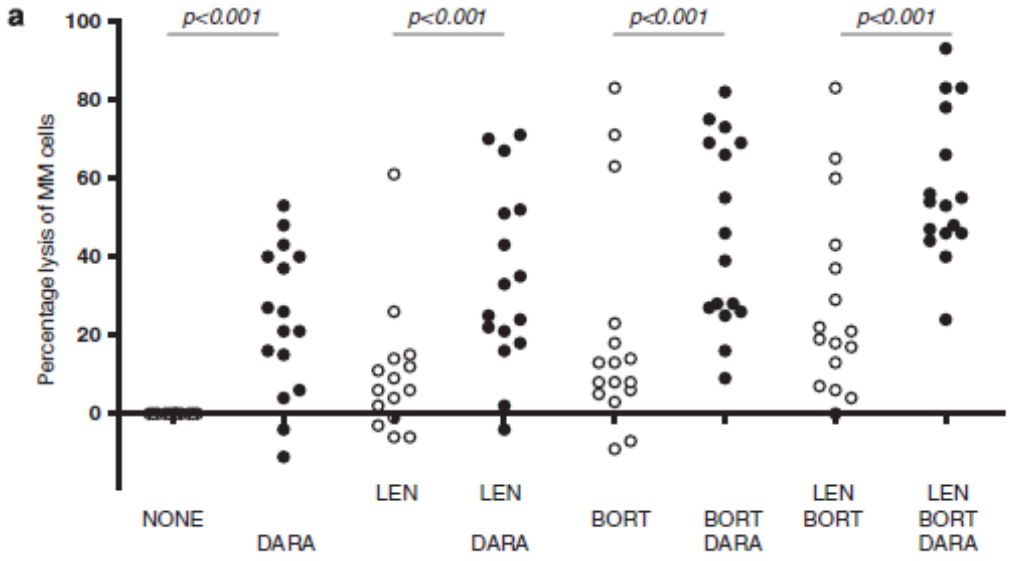
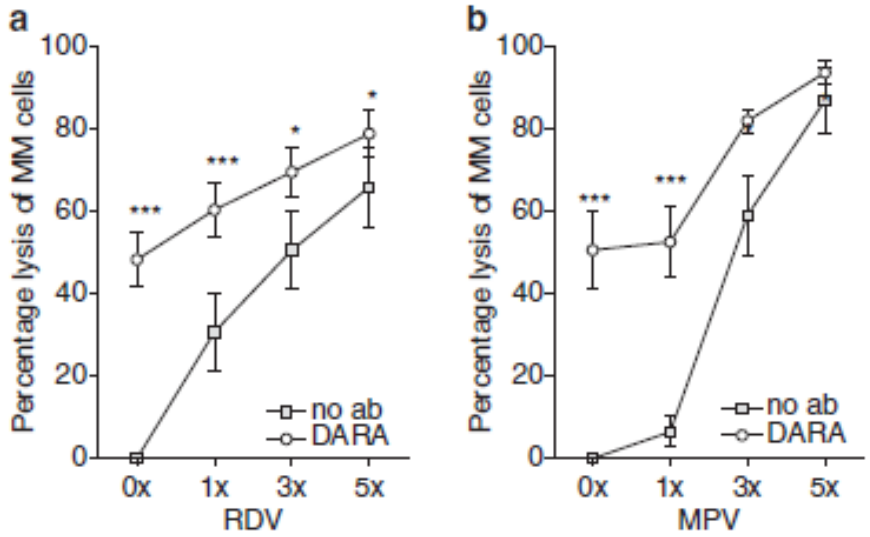


Figure 2: Dose-dependent Lysis of Multiple Myeloma cells in Triple Chemotherapy Treatments



In toxicology studies in cynomolgus monkeys and chimpanzees, the major observed toxicities were cytokine release syndrome and thrombocytopenia. A minor decrease in red blood parameters was also observed. Cytokine release was seen only following the first dose and was markedly reduced following implementation of a 10 mg predose of daratumumab. The effect on platelets and red cells was reversible.

To assess the effect of daratumumab on hematopoietic progenitor cells, colony forming units – granulocyte-macrophage (CFU-GM) and blast forming units – erythrocyte (BFU-E) were counted in a progenitor cell assay (PCA). Using fresh or thawed unselected mobilized blood progenitor cells, CFU-GM and BFU-E in plates including DARA or isotype-control antibody (ICA) at

500ng/ml were not significantly different from control plates. At 3 weeks post-SCT, NK cells were a median of 30% of mononuclear cells and actively lysed a median of 75% of target cells with DARA compared to ICA ($P < 0.05$). (personal communication, Raymond Comenzo).

1.1.4. Clinical Studies

1.1.4.1. Single-Agent Daratumumab Studies (GEN501 and MMY2002)

Two single-agent studies with daratumumab are ongoing (Studies GEN501 and MMY2002; Table 4). Seventy-seven (77) subjects have been treated in Parts 1 and 2 of Study GEN501 with doses ranging from ≤1 mg/kg to 24 mg/kg, and 124 subjects have been treated in Study MMY2002.

Table 4: Daratumumab Single-Agent Studies GEN501 and MMY2002

<table>
<tr><th>Study Number</th><th>Study Design</th><th colspan="2">Number of subjects Treated/
Treatment Regimen</th></tr>
<tr><td rowspan="4">GEN501</td><td rowspan="4">Open-label, Phase 1/2, first-in-human, single-agent study in subjects with multiple myeloma whose disease is relapsed or refractory to at least 2 prior lines of therapies

Population was heavily treated with prior treatment, including ASCT, chemotherapy based regimens, IMiDs, and PIs</td><td colspan="2"><u>Part 1</u>
n=32 total treated with daratumumab weekly

0.005-1 mg/kg (n=17)
2 mg/kg (n=3)
4 mg/kg (n=3)
8 mg/kg (n=3)
16 mg/kg (n=3)
24 mg/kg (n=3)</td></tr>
<tr><td colspan="2"><u>Part 2</u>
n=51 total treated</td></tr>
<tr><td>8 mg/kg (n=30)

First dose, followed by a 3-week resting period, followed by weekly doses for 7 weeks, then q2w for an additional 14 weeks, and monthly, until the subject experiences disease progression or unmanageable toxicity</td><td>16 mg/kg (n=21)

Weekly for 8 weeks, followed by q2w for an additional 16 weeks, and monthly, for up to 96 weeks, or until the subject experiences disease progression or unmanageable toxicity</td></tr>
<tr><td>MMY2002</td><td>Open-label, multicenter, 2-stage, Phase 2 study of daratumumab for the treatment of subjects with multiple myeloma who have received at least 3 prior lines of therapy including a PI and an IMiD or whose disease is double refractory to both a PI and an IMiD</td><td colspan="2">Part 1, Stage 1 (18 subjects randomized to 8mg/kg and 16 subjects randomized to 16mg/kg): total of 34 subjects

Part 1, Stage 2 (16mg/kg): total of 25 subjects

Stage 2 (16mg/kg): total of 65 subjects</td></tr>
<tr><td colspan="4">ASCT=autologous stem cell transplant; IMiD= immunomodulatory agent; PI=proteasome inhibitor</td></tr>
</table>

Among the 32 subjects treated in Part 1 of Study GEN501, the maximum tolerated dose (MTD) was not reached following intravenous (IV) infusions up to 24 mg/kg. Two subjects experienced dose-limiting toxicities (DLTs) in the lower dose cohorts (a subject in the 0.1-mg/kg group had Grade 3 anemia and Grade 4 thrombocytopenia, and a subject in the 1.0-mg/kg group had Grade 3 aspartate aminotransferase increased).

Among the 51 subjects treated in Part 2 of Study GEN501, serious adverse events (SAEs) were reported in 37% of subjects (43% of subjects in the 8-mg/kg group and 29% of subjects in the 16 mg/kg-group). The most frequently reported SAEs were pneumonia (6% subjects), and pyrexia (4% of subjects).

Among the 34 subjects treated in Stage 1 of Study MMY2002, SAEs were reported in 27% of subjects (33% of subjects in the 8 mg/kg group, and 19% of subjects in the 16 mg/kg group). The most frequently reported SAE was renal failure acute (6% of subjects).

1.1.4.2. Combination Daratumumab Studies

One study of daratumumab in combination with lenalidomide and dexamethasone (Study GEN503), and 1 study of daratumumab in combination with various backbone treatment regimens (Study MMY1001) are ongoing.

Table 5: Daratumumab Combination Studies GEN503 and MMY1001

Study Number	Study Design	Treatment Regimen	Status/Estimated Start Date Number of subjects Treated/Planned
GEN503	Open-label, Phase 1/2 multicenter, dose-escalating study investigating the safety of daratumumab in combination with lenalidomide and dexamethasone in subjects with relapsed or refractory multiple myeloma	Phase 1: 2-16 mg/kg daratumumab, in combination with lenalidomide (25 mg daily Days 1-21 of 28 days) and dexamethasone (40 mg weekly)	Phase 1: Ongoing (n=13 subjects treated) 2 mg/kg (n=3) 4 mg/kg (n=3) 8 mg/kg (n=4) 16 mg/kg (n=3)
		Phase 2: 16 mg/kg daratumumab, in combination with lenalidomide (25 mg daily Days 1-21 of 28 days) and dexamethasone (40 mg weekly)	Part 2: n=18 subjects treated approximately 30 subjects planned
MMY1001	Open-label, non-randomized, multicenter, Phase 1b study to evaluate the safety, tolerability, and dose regimen of daratumumab when administered in combination with various backbone treatment regimens for multiple myeloma in either the newly diagnosed or those who have received at least 2 prior therapies, depending on the backbone treatment regimen	Daratumumab 16 mg/kg (initially, with possibility to de-escalate, if necessary) The backbone regimens to be combined with daratumumab include bortezomib-dexamethasone (VD), VMP, VTD, and pomalidomide-dexamethasone	n=19 subjects treated[1] VTD (n=6) VMP (n=6) Vd (n=1) Pom-dex (n=6) approximately 80 subjects planned

1. As of 18July2014

Pom-dex=pomalidomide-dexamethasone; VMP-bortezomib-melphalan-prednisone; VTD=bortezomib-thalidomide-dexamethasone

Based on preliminary efficacy data, 15 of 20 efficacy evaluable subjects in Study GEN503 have achieved a PR or better following treatment with daratumumab in combination with lenalidomide and dexamethasone.

The safety profile observed in Study GEN503 is consistent with historical safety data for lenalidomide and dexamethasone. Doses ranged from 2 mg/kg to 16 mg/kg daratumumab, in combination with the approved doses of lenalidomide (25 mg daily Days 1-21 of 28 days) and dexamethasone (40 mg weekly). No dose-limiting toxicity (DLT) drug-related safety signals have been observed in this heavily pre-treated population of subjects with advanced multiple myeloma. The Part 2 daratumumab dose was determined to be 16 mg/kg. Across all dose cohorts in Part 1 and in the 16 mg/kg expansion cohort for Part 2, the most frequently reported Grade 3 or higher AE was neutropenia (6 subjects), which is a known toxicity of lenalidomide. Eight serious adverse events (SAEs) have been reported. All SAEs were assessed by the investigator as not related to daratumumab. Four subjects experienced infusion related reactions during the first infusion of daratumumab. These events were determined by the investigator to be related to daratumumab. In all instances, daratumumab was interrupted temporarily and restarted without complication or further incident.

In study MMY1001, preliminary safety is available from 6 subjects treated in the VTD + daratumumab cohort and 6 subjects treated in the VMP + daratumumab cohort. No serious AEs or dose-limiting toxicities have been reported in either cohort. Adverse events have been those expected for VTD or VMP alone; with the exception of infusion related reactions (Grade 1 or Grade 2) attributable to daratumumab.

Planned Phase 3 combination studies include a Phase 3 study (MMY3003) comparing daratumumab, lenalidomide, and dexamethasone with Rd and a Phase 3 study (MMY3004) comparing daratumumab, bortezomib, and dexamethasone with Vd. Both studies are in patients with relapsed or refractory multiple myeloma and are planned to start in the second half of 2014. 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.

1.2. Overall Rationale for the Study

Treatment choices for multiple myeloma vary with age, performance status, comorbidity, the aggressiveness of the disease, and related prognostic factors (Palumbo 2011[45]). Newly diagnosed patients with multiple myeloma are typically categorized into 2 subpopulations usually defined by their age and suitability for the subsequent approach to treatment. Younger patients will typically receive an induction regimen followed by consolidation treatment with high-dose chemotherapy and ASCT. For those not considered suitable for high-dose chemotherapy and ASCT, longer-term treatment with multi-agent combinations including alkylators, high-dose steroids, and novel agents are currently considered as standards of care.

Recent studies have indicated that multiple-drug combinations are superior over single- or double-agent combinations in treating multiple myeloma (Cavo 20126, van der Veer 2011b[57]). In

particular, bortezomib-based treatment regimens have demonstrated significant improvements in response, PFS, and OS compared with non-bortezomib-based therapy, both in newly diagnosed transplant ineligible patients and those suitable for induction and transplant (Sonneveld 2013[54], Dimopoulos 2009[12]). The addition of new drugs to available regimens, or combinations of new drugs, can improve clinical benefit because of the induction of a higher rate of initial complete responses (CRs), which then improves relapse-free survival and OS. Contingent on the premise that the combined agents have non-overlapping and synergistic mechanisms of actions (MoAs), the immediate and effective targeting of the tumors with multiple agents appears to be a successful strategy in improving the clinical outcome of multiple myeloma therapy. Such a strategy is in agreement with the emerging concept that the genetic signature of multiple myeloma, and consequently the patient's susceptibility to a specific agent, will be highly heterogeneous, which may benefit from multi-drug combination therapies. Nevertheless, the CR rate of the best chemotherapeutic combinations is currently <50%, indicating that even multi-drug combinations cannot cure multiple myeloma, and all current combination therapies eventually induce drug resistance (Rosiñol 2012[51], Reeder 2009[50]).

In an ex vivo flow cytometry-based assay platform, addition of daratumumab to both bortezomib-melphalan-prednisone (VMP) and lenalidomide-bortezomib-dexamethasone significantly increased the treatment effect by almost doubling the bone marrow mononuclear cells lysis levels (van der Veer 2011b[57]). Daratumumab's immediate and effective cell mediated cytotoxic effects against multiple myeloma cells, combined with the observed remarkable synergy with lenalidomide-bortezomib (even among patients who are refractory to lenalidomide-bortezomib), may potentially improve the clinical outcome for patients with multiple myeloma when combined with these agents in combination regimens (van der Veer 2011b[57]).

Induction Therapy in Transplant-eligible Patients

Induction regimens for transplant-eligible patients are given with the intention of reducing the plasma cell disease burden and improving the depth of response.

Response rates to induction therapy have been significantly increased by the use of novel agent-based combinations. VD, which is superior to the classical vincristine, Adriamycin and high-dose dexamethasone (VAD) regimen, has become the backbone of induction therapy before ASCT (Harousseau 2010c[19]). The addition of another agent to the VD backbone to form a triple combination such as thalidomide (VTD), doxorubicin (DVD or PAD), lenalidomide (RVD), or cyclophosphamide (VCD), has yielded yet higher response rates in Phase II trials. Three prospective studies have already shown that VTD is superior to thalidomide and dexamethasone (TD) or VD. (Harousseau 2010b[20], Cavo 20107, Rosiñol 2012[51], Moreau 2011b[37]). Overall, Bortezomib-based induction regimens have demonstrated significant improvements in response and PFS/OS in this induction setting compared with non-bortezomib-based induction and are generally well-tolerated, with a higher rate of peripheral neuropathy but no apparent increase in risk of death during induction (Sonneveld 2013[54]). In newly diagnosed patients, bortezomib-dexamethasone (VD) and bortezomib-thalidomide-dexamethasone (VTD) are now considered standard induction regimens for patients eligible for ASCT (Engelhardt 2014[14], Moreau 2013[38], NCCN 2013[40]).

High Dose Chemotherapy and Stem Cell Rescue

High dose chemotherapy for myeloma was introduced in the early 1980's, after it was demonstrated that complete remissions could be induced in a substantial percentage of patients (McElwain 1983[34]). The risks (morbidity and mortality) associated with such an approach were high, but were subsequently reduced by the application of autologous stem cell rescue.

Bone marrow was the source of stem cells in the early studies, however peripheral blood stem cells (PBSC) are now used routinely as autologous rescue (Child 2003[10]). Autologous SCT has now become the standard approach to improve or deepen response and can be considered a form of consolidation. However consolidation more routinely refers to a period of intensification therapy after ASCT. After attaining an optimal response from induction therapy, blood stem cells are mobilized in peripheral blood with the use of G-CSF with either cyclophosphamide or in some cases plerixafor (Mozobil) (Giralt 2009[16]). They are then harvested by apheresis/ leukapheresis.

Conditioning Therapy

Patients are then given high dose therapy with melphalan, typically 100-200 mg/m^2 over a period of 1 to 2 days followed by rescue using the previously collected stem cells. Melphalan together with total body irradiation (MEL140 + TBI), busulphan plus melphalan (BUMEL) and busulphan followed by cyclophosphamide (BUCY) are also potential options for conditioning therapy.

Consolidation Therapy in Transplant-eligible Patients

Post-transplant, patients are given a further short intense period of treatment in order to deepen the quality of the response obtained with induction therapy. This treatment is most commonly referred to as consolidation therapy.

Upgraded rates of CR and CR-nCR, in the range between 10% and 30%, have been reported with post-ASCT use of bortezomib or lenalidomide as single agents (Mellqvist 2009[35], Attal 20092). VTD consolidation (2 cycles) following tandem ASCT was able to reduce the relapse rate and prolong PFS in the prospective trial conducted by the GIMEMA with VTD (Cavo 20126). In several of these studies, consolidation therapy with VTD yielded molecular remissions in up to 60% of patients (Ladetto 2010[27], Terragna 2010[55]).

Moreover, in a recent retrospective analysis comparing VTD induction followed by single ASCT versus VTD induction, single ASCT and VTD consolidation (2 cycles), the IFM showed that the use of consolidation was associated with an improvement in response rates and PFS. (Leleu 2013[29])

The current IFM recommendations for the treatment of frontline MM in symptomatic patients eligible for high-dose therapy outside clinical trials comprise VTD induction (4 cycles), ASCT prepared by melphalan 200 mg/m^2, followed by VTD consolidation (2 cycles).

Maintenance Therapy

Maintaining response after successful induction, high dose chemotherapy with transplant and consolidation is an important goal in treating multiple myeloma. It is now accepted that patients who are on treatment for longer periods do better than those on short course treatments.

To date, several groups in different countries have adopted a maintenance strategy in their protocols. In Germany patients are maintained with single agent thalidomide. Admittedly, there is no accepted standard for maintenance but an agreed need to do so. The major limitation is the toxicity of the commonly available drugs which are suitable for use long term. Thalidomide, as maintenance therapy after ASCT, has been investigated and has been shown to improve response quality and increased PFS (Ludwig 2012[31]). However it has been associated with increased peripheral neuropathy and thromboembolisms (Palumbo 2008c[44], Morgan 2012[39]). Similarly, lenalidomide, given as maintenance therapy after ASCT, has also been investigated in 2 randomized, prospective trials (McCarthy 2012[32], Attal 20123). In a study of lenalidomide maintenance therapy, initiated at Day 100 after hematopoietic stem cell transplantation, lenalidomide treatment significantly improved time to disease progression and OS among patients with multiple myeloma; however, it was associated with more toxicity and second cancers.

Summary

Induction prior to and consolidation and maintenance following ACST is now emerging as a widely accepted treatment approach in newly diagnosed multiple myeloma patients who are deemed to be eligible for high dose therapy with autologous stem cell transplant.

The clinical utility of improving the depth of response using consolidation therapy and preserving response in the long term using maintenance therapy has been demonstrated in a number of studies. However, multiple myeloma still remains incurable, and the agents currently available for long term therapy have a number of shortcomings in terms of safety and tolerability.

Strategies directed at improving and maintaining response for longer periods of time and new treatment options directed at alternative mechanisms are urgently needed for patients with multiple myeloma.

Daratumumab with its novel mechanism of action together and good profile of tolerability is ideally suited to being investigated as an adjunct to induction, consolidation and subsequent long term maintenance therapy

The target population for this study is newly diagnosed subjects with a confirmed diagnosis of symptomatic multiple myeloma and measurable disease who are suitable for high dose treatment with ASCT.

The safety profile of daratumumab to date, which does not appear to overlap with those known for approved agents, combined with its distinct MoA, suggest that the therapeutic profile of daratumumab combined with various backbone regimens may improve the treatment effect of these regimens. Additionally, daratumumab as a single agent may prolong the progression free

interval for these patients. The detailed rationale for the study design elements are provided in Section 3.2.

2. OBJECTIVES AND HYPOTHESIS

2.1. Objectives

Primary Objective

- The primary objective in Part 1 is to determine if the addition of daratumumab to VTD will increase the proportion of subjects achieving stringent complete response (sCR) post completion of consolidation therapy compared with VTD alone.
- The primary objective in Part 2 is to determine if the use of daratumumab as single agent in maintenance compared to observation only will increase progression-free survival (PFS) when used after autologous stem cell transplant and consolidation therapy.

Secondary Objectives

In Part 1, major secondary efficacy objectives are to determine if the addition of daratumumab to VTD will improve:

- Progression-free survival (PFS) from first randomization
- Time to progression (TTP) from first randomization
- Complete response (CR) rate by the end of ASCT/consolidation
- Minimal residual disease (MRD) negative rate by the end of ASCT/consolidation
- Post-induction stringent complete response (sCR) rate
- Progression-free survival after next line of therapy (PFS2)
- Post-induction overall response rate (ORR) and rate of very good partial response (VGPR) or better
- Overall survival (OS)
- Duration of CR and sCR

In Part 2, major secondary efficacy objectives are to determine if the addition of daratumumab to VTD will improve the assessment during maintenance of:

- Time to progression
- CR rate
- MRD negative rate
- PFS2
- Rate of improved response
- Rate of MRD negative conversion
- ORR

- OS

Other secondary objectives throughout the study are:

- To evaluate quality of life and health economic/resource utilization
- To assess immunogenicity of daratumumab
- To assess safety and tolerability of daratumumab in combination with VTD
- Rate of MRD conversion during Pre-PD Follow-Up.

Exploratory Objectives

The exploratory objective is:

- To evaluate daratumumab's impact on response and resistance to treatment

2.2. Hypothesis

As this study integrates induction therapy as well as post-transplant consolidation and maintenance therapy into a single, 2-stage randomization design to address 2 distinct questions about the effectiveness of daratumumab treatment during induction/consolidation and maintenance, there are two primary hypotheses for this study:

Hypothesis for Induction/Consolidation: first randomization

- Addition of daratumumab to VTD improves post-consolidation sCR rate compared with VTD alone.

Hypothesis for Maintenance: second randomization

- Daratumumab maintenance after ASCT prolongs PFS compared with observation**.**

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a randomized, open-label, active control, parallel group, multicenter, Phase 3 study in subjects with previously untreated multiple myeloma. The planned number of subjects to be treated in this study is as follows:

- 1080 subjects (540/arm) for first randomization (induction)
- Approximately 800 subjects (400/arm) of the initial 1080 subjects will be randomized to maintenance. The actual accrual into the Maintenance Phase may be greater than 800 if a higher-than-expected proportion of subjects in the induction/consolidation stage achieve response and are randomized in the Maintenance Phase.

The study will consist of 3 phases. The Screening Phase will extend up to 28 days prior to Cycle 1, Day 1. The Treatment Phase will be conducted in 2 parts, as described below, and will extend from

Cycle 1 Day 1 until treatment discontinuation due to progressive disease, unacceptable toxicity, ineligibility for second randomization, or 2 years of maintenance therapy/observation. The Follow-up Phase will extend from treatment discontinuation until death, lost to follow-up, withdrawal of consent, or study end, whichever occurs first.

The 2 parts in the Treatment Phase are described below.

Part 1: Induction/ASCT/Consolidation Phase (1:1 Randomization)

Arm A: VTD induction therapy (4 cycles), followed by ASCT, followed by 2 cycles of VTD consolidation

Arm B: VTD plus daratumumab induction therapy (4 cycles), followed by ASCT, followed by 2 cycles of VTD plus daratumumab consolidation

The consolidation phase of treatment will begin approximately 30 days after ASCT, when the subject has recovered sufficiently and engraftment is complete. Response will be evaluated at Day 100 post ASCT.

Part 2: Maintenance Phase (1:1 Re-randomization of subjects achieving at least a PR after consolidation)

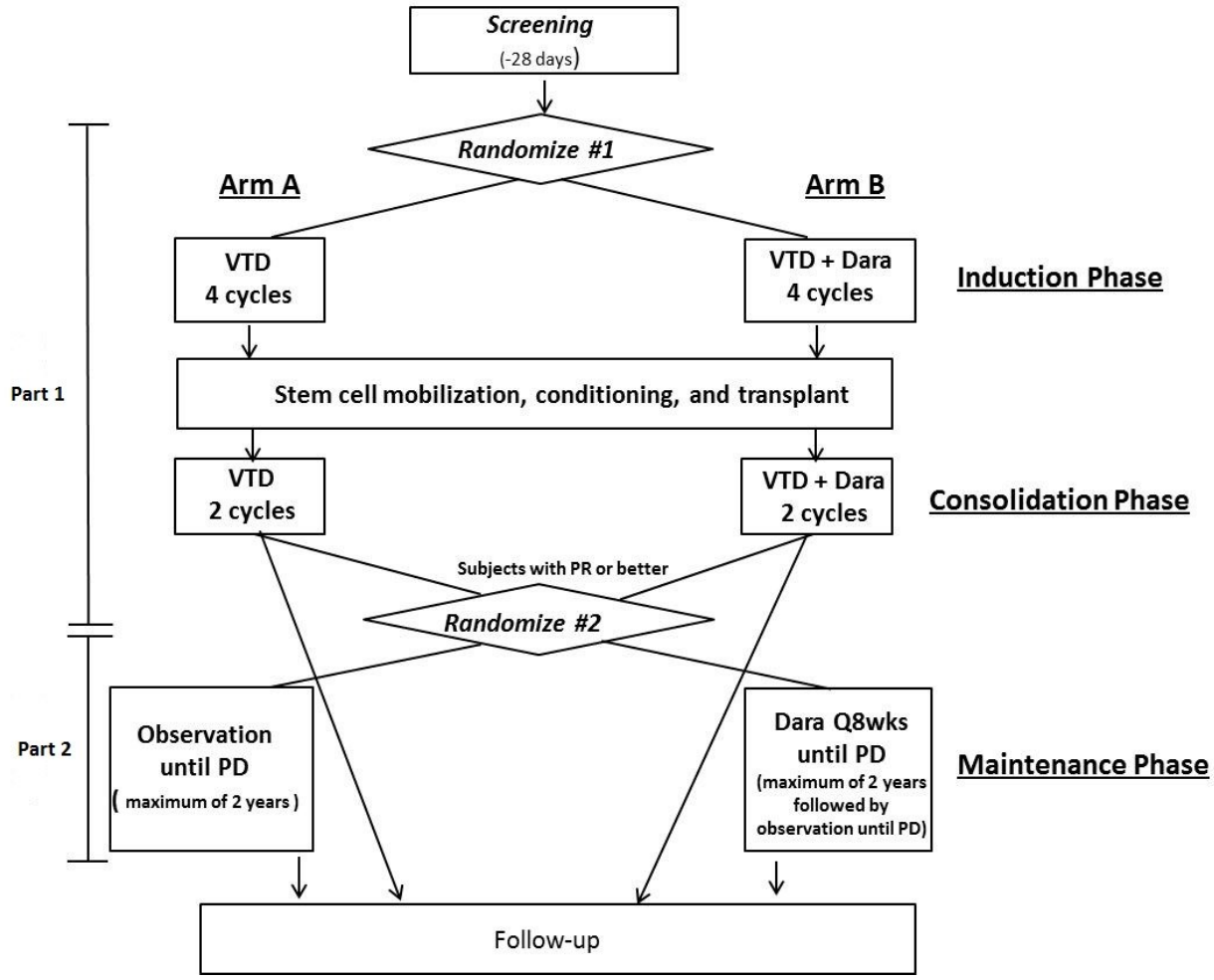
Subjects with at least a PR will be randomized after determination of response at approximately Day 100 after ASCT, and will enter the Maintenance Phase upon completion of consolidation therapy.

Arm A: Observation only until documented disease progression (limited to 2 years maximum duration)

Arm B: Daratumumab monotherapy until documented disease progression (limited to 2 years maximum duration)

Subjects who are not randomized in Part 2 will enter in the Follow-up Phase and will be followed until disease progression, death or lost to follow up, withdrawal of consent or study end even if they receive subsequent anticancer treatments A schematic overview of the study is provided in Figure 3.

Figure 3: Study MMY3006 Study Scheme



In Arm B, daratumumab (16 mg/kg) will be administered by intravenous (IV) infusion once every week for 8 weeks (VTD Induction Cycle 1-2), then once every 2 weeks for 8 weeks (VTD Induction Cycle 3-4), and following ASCT once every 2 weeks for 8 weeks (VTD consolidation Cycle 5-6). Following subsequent re randomization, subjects assigned to the maintenance Arm B will receive daratumumab (16 mg/kg) once every 8 weeks until documented disease progression (limited to a maximum duration of 2 years).

Permuted block randomization will be implemented in this study. Subjects will be stratified at first randomization by site affiliation (IFM or HOVON), International Staging System stage I, II, or III (β-2 microglobulin and albumin) and by cytogenetics (standard risk or high risk as defined by presence of del17p or t(4;14), as centrally confirmed during screening) .

Response will be assessed 100 days after ASCT and eligibility for the second randomization will be determined. Subjects will be stratified at the second randomization by type of induction treatment (VTD +/- daratumumab) and by depth of response to induction/consolidation therapy (as determined by MRD status and post-consolidation response). The stratification factors for the second randomization are presented in Table 6.

Assessment of tumor response and disease progression will be conducted in accordance with the International Myeloma Working Group (IMWG) response criteria. An assessment of MRD will be conducted using flow cytometry and next-generation sequencing on bone marrow aspirate for all patients in induction/consolidation phases and for patients who achieve at least VGPR in maintenance phase. MRD assessment will be performed also every year during Pre-PD FU if the MRD remains negative (after W105 of maintenance). Safety evaluations will include adverse event monitoring, physical examinations, electrocardiogram monitoring (ECGs), clinical laboratory parameters (hematology and chemistry), vital sign measurements, and Eastern Cooperative Oncology Group (ECOG) performance status.

Two primary analyses are planned. The first primary analysis, with a purpose to evaluate response by measuring the stringent complete response (sCR) rate, will be performed after all subjects have completed the Day 100 post-ASCT response evaluation or have been discontinued from study treatment by this timepoint. The second primary analysis, for PFS, will be performed when approximately 390 PFS events have been observed. An interim analysis is planned for the maintenance stage after 273 (70%) PFS events are observed in the population of subjects who are re-randomized. In case the Interim analysis for PFS meets the pre-defined boundary, this Interim analysis reflects the primary analysis for PFS. No PFS analysis at 390 PFS events will be done. The next pre-planned analysis in that case will be the final data cutoff

at the end of study, when approximately 350 subjects have died, or approximately 5 years after the last subject is randomized in the second randomization, whichever comes first. Investigators will be informed when the cutoffs are to occur. All available data prior to the time of a clinical cutoff will be included in each of the respective analyses.

3.2. An Independent Data Monitoring Committee (IDMC) will be formed to review data including those from interim analyses of overall safety (please see Section 11.9). At the part 2 interim analysis, the primary endpoint was met, and the study data was unblinded. No new safety signals were observed. No further IDMC meetings will be scheduled. Safety data will be reviewed by regular Pharmacovigilance aggregate data review. Study Design Rationale

Rationale for Study Design and Endpoints:

The aim of the study is to demonstrate the clinical activity of daratumumab in the first instance by assessment of the level of response post consolidation therapy. Subsequent confirmation of the longer-term benefit of daratumumab treatment will be by long-term follow-up to assess PFS. Furthermore, the contribution of maintaining subjects on daratumumab monotherapy post consolidation as a maintenance therapy will also be explored.

In order to facilitate this, a 2-stage randomization design will be used to evaluate the efficacy of daratumumab, both as part of the induction/consolidation regimen and as maintenance therapy after consolidation. In order to isolate the net contribution of the benefit of maintaining daratumumab post consolidation, those achieving a PR or better subjects will be re-randomized in a second stage to daratumumab monotherapy as maintenance treatment (for up to 2 years) or

observation. This will enable the net contribution of maintenance treatment to be isolated, while at the same time investigating continuous daratumumab therapy.

This design is capable of evaluating various sequences of induction/ASCT/consolidation regimens (eg, daratumumab + SOC vs SOC) and maintenance therapies (eg, daratumumab maintenance vs observation) simultaneously in 1 study, and has been established as being more efficient than conventional development means of utilizing multiple studies or a factorial design.

The post ASCT/consolidation assessment of sCR has the advantage that it is not influenced by maintenance treatment, and thus is an immediate measure of efficacy for the induction/consolidation regimens being compared in Part 1. It has also been well-established as being strongly correlated with long-term clinical outcomes including PFS and OS. A group of internationally renowned experts in the field of myeloma recommended that CR should be used as an appropriate surrogate endpoint for regulatory purposes in the newly diagnosed multiple myeloma setting (Rajkumar 2011[47]).

Rationale for Stringent Complete Response (sCR)

Traditionally long- term outcomes have served as the principle means of measuring efficacy in multiple myeloma trials. However, as response rates, length of disease-free interval and corresponding OS rates improve, it becomes more and more difficult to demonstrate incremental benefit in a reasonable time frame. In the front line treatment of multiple myeloma the level of tumor burden reduction particularly the achievement of complete and very good partial responses, has emerged as a powerful predictive factor associated with a prolonged PFS and OS (van de Velde 2007[56], Lahuerta 2008[28], Blade 20004, Harousseau 2009b[18], Harousseau 2009a[17],Chanan-Khan 20108, Gay 2011[15]).

Furthermore, given that a VGPR or CR is now achievable in a vast majority of patients in the first-line when the latest generation of therapies are used together with high dose therapy and autologous transplant, more stringent definitions of response are required in order to account for deeper levels of response up to and including the possibility of complete eradication of the plasma cell clone.

A majority of the response definitions are based on serologic and cytologic results, in order to more carefully identify high-quality responses occurring beyond the CR level, the IMWG in 2006 introduced the category of stringent complete response (sCR), as defined by a negative immunofixation plus normal free-light chain ratio and the absence of clonal bone marrow plasma cells by immunohistochemistry or immunofluorescence (Durie 2006[13]).

The predictive value of sCR was highlighted in a study by Kapoor et al that determined the maximal response rates achieved in 445 consecutive patients who underwent ASCT within 12 months of diagnosis. The study identified patients who achieved varying degrees of CR; 109 of whom (25%) achieved a sCR after ASCT. In terms of outcome, the median OS rate from the time of transplantation for the patients who attained an sCR was not reached, this was in contrast to those patients achieving conventional CR, where the median OS was 81 months and for near CR (nCR) 60 months. Five-year OS rates for the 3 response categories were 80%, 53%, and 47% for

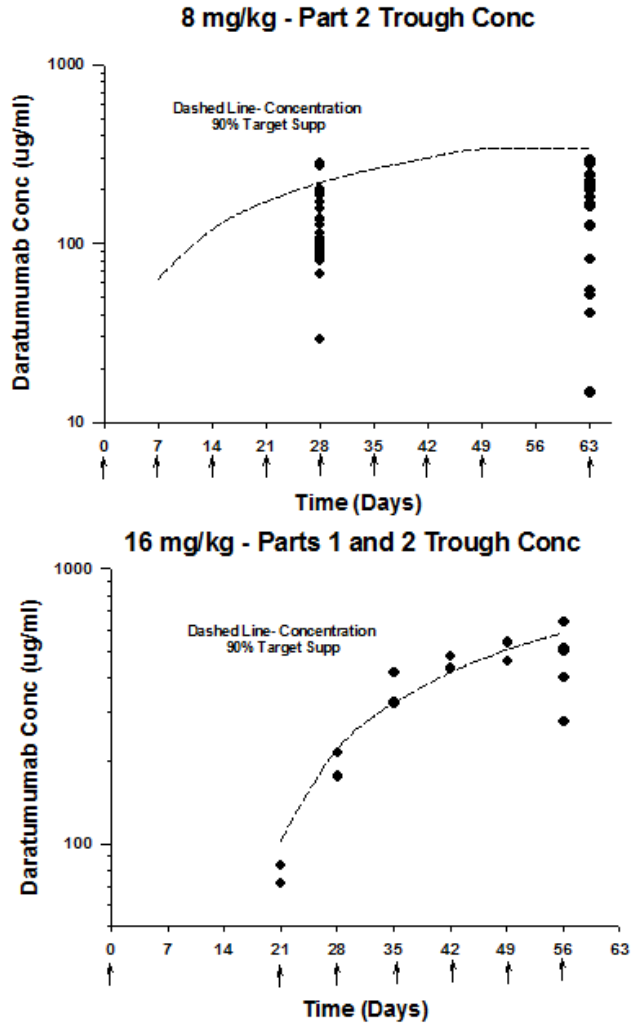
sCR, CR, and nCR, respectively. In terms of impact on time to progression, the TTP from ASCT of patients achieving an sCR was significantly longer (50 months) compared to the patients achieving CR or nCR (20 months and 19 months, respectively). On multivariable analysis, post ASCT response of sCR was found to be an independent prognostic factor for survival versus CR (HR=0.44; 95% CI, 0.25 to 0.80; p=0.008), in addition to proliferation rate, pre-ASCT cytogenetics, and performance status. In a landmark analysis, OS of subjects surviving at least 2 years post-transplantation and achieving sCR was superior (median OS not reached) compared to the conventional CR group (median OS of 70 months) (p=0.007). (Kapoor 2013[23]).

Rationale for Daratumumab Dose Selection

Based on pharmacokinetic (PK), clinical activity, and clinical safety data, the 16 mg/kg daratumumab dose was selected for this study.

Target Saturation: Clinical PK data are available from Parts 1 and 2 of the ongoing Study GEN501. For the 8 and 16 mg/kg dose levels, the relationship between observed trough concentration and concentration associated with 90% target suppression is presented in Figure 4. The concentration associated with 90% target suppression was calculated using the principles of target mediated disposition. Specifically, the dashed lines represent the expected concentration when 90% of clearance related to target binding is inhibited

Figure 4: Study GEN501 8 and 16 mg/kg Dose Levels - Observed Trough Concentration vs. 90% Target Suppression Concentration



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

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

Following repeated doses of 8 mg/kg, observed trough concentrations are below those predicted for 90% suppression. However, following repeated doses of 16 mg/kg, the observed trough concentrations are similar to those predicted for 90% suppression. Therefore, the 16 mg/kg dose is the lowest dose that results in 90% target suppression at all timepoints. Following the initial weekly dosing period, the impact of target-mediated clearance will be decreased due to target suppression. Therefore, the frequency of dosing is decreased following long-term treatment.

Clinical Activity Data: The rate and depth of clinical response is higher for the 16-mg/kg dose compared with the 8-mg/kg dose, based on data from Part 2 of Study GEN501 and from Study MMY2002 (both ongoing studies). Across the 2 studies, VGPRs were observed in 6 of 36 subjects treated at the 16-mg/kg dose, while no VGPR was observed in 48 subjects treated at the 8-mg/kg dose. In addition, in Part 1 of GEN501, 16 mg/kg was the lowest dose resulting in complete bone marrow clearance.

In Part 2 of Study GEN501, the ORRs (i.e., PR or greater) were reported in 3/30 (10%) subjects in the 8 mg/kg dose regimen and 7/20 (35%) subjects in 16 mg/kg dose regimen. For Study MMY2002, the unconfirmed ORRs for the 8 mg/kg and 16 mg/kg dose regimens were similar to those observed in GEN501. These data are still maturing. The preliminary data support that full target saturation at the 16 mg/kg dose is needed to achieve higher and deeper response rates. As these studies are ongoing, data are still emerging, and subject response may change as the data mature.

Clinical Safety Data: In addition, the 16 mg/kg dose and schedule was shown to have an acceptable and manageable safety profile among the subjects for whom preliminary data were available in Studies GEN501 and MMY2002.

Rationale for Immunogenicity Evaluations

Immunogenicity to daratumumab is possible. Therefore, samples to determine the presence of antibodies to daratumumab (immunogenicity) will be collected from all subjects. All of the serum concentration assessments collected during the study will be used to interpret the immunogenicity data. The information from these samples and data from other studies will be used to determine the immunogenicity of daratumumab.

Rationale for Biomarker Evaluations

Biomarkers collected in this study will provide information about daratumumab in multiple myeloma and will focus on two key objectives: the evaluation of minimal residual disease (MRD) and the efficacy of daratumumab + VTD (compared to VTD) in high-risk molecular subgroups. In addition, exploratory studies may examine the effects of daratumumab + VTD on immune cell subpopulations following transplant.

4. SUBJECT POPULATION

Screening for eligible subjects will be performed within 28 days before administration of the study drug. 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's representative before enrolling a subject in the study. For a discussion of the statistical considerations of subject selection, refer to Section 11.2.

4.1. Inclusion Criteria

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

1. Subject must be between 18 and 65 years of age.

2. Subject must have documented multiple myeloma satisfying the CRAB or biomarkers of malignancy criteria (see Attachment 1) and measurable disease as defined by:

    - Monoclonal plasma cells in the bone marrow ≥10% or presence of a biopsy proven plasmacytoma AND any one or more of the following myeloma defining events:
        - Hypercalcemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than ULN or >2.75 mmol/L (>11 mg/dL)
        - Renal insufficiency: creatinine clearance <40mL/min or serum creatinine >177 µmol/L (>2 mg/dL)
        - Anemia: hemoglobin >2 g/dL below the lower limit of normal or hemoglobin <10 g/dL
        - Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT
        - Clonal bone marrow plasma cell percentage ≥60%
        - Involved: uninvolved serum free light chain ratio ≥100
        - >1 focal lesion on MRI studies
    - Measurable disease as defined by any of the following:
        - IgG multiple myeloma: Serum monoclonal paraprotein (M-protein) level ≥1.0 g/dL or urine M-protein level ≥200 mg/24 hours; or
        - IgA, IgE, IgD, or IgM multiple myeloma: serum M-protein level ≥0.5 g/dL or urine M-protein level ≥200 mg/24 hours; or
        - IgD multiple myeloma : serum M-protein level <0.5 g/dL and Serum immunoglobulin free light chain ≥10 mg/dL and abnormal serum immunoglobulin kappa lambda free light chain ratio; or
        - Light chain multiple myeloma without measurable disease in the serum or the urine: Serum immunoglobulin free light chain ≥10 mg/dL and abnormal serum immunoglobulin kappa lambda free light chain ratio

3. Newly diagnosed subjects eligible for high dose therapy and autologous stem cell transplantation.

4. Subject must have an ECOG performance status score of 0, 1, or 2 (see Attachment 2).

5. Subject must have pretreatment clinical laboratory values meeting the following criteria during the Screening Phase (Lab tests should be repeated if done more than 15 days before C1D1):

    a) hemoglobin ≥7.5 g/dL (≥5 mmol/L; prior red blood cell [RBC] transfusion or recombinant human erythropoietin use is permitted);

    b) absolute neutrophil count (ANC) ≥1.0 x 10^9/L (GCSF use is permitted);

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

    d) ALT ≤2.5 x ULN;

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

    f) calculated creatinine clearance ≥40 mL/min/1.73 m^2 (see Attachment 3);

    g) corrected serum calcium ≤14 mg/dL (<3.5 mmol/L); or free ionized calcium ≤6.5 mg/dL (≤1.6 mmol/L) (see Attachment 4);

    h) platelet count ≥70 x 10^9/L for subjects in whom <50% of bone marrow nucleated cells are plasma cells; otherwise platelet count >50x10^9/L (transfusions are not permitted to achieve this minimum platelet count).

6. Women who are partners of men and of childbearing potential must be practicing one of the following methods of birth control: subcutaneous hormonal implant, levonorgestrel-releasing intra-uterine system, medroxyprogesterone acetate depot, tubal sterilization, ovulation inhibitory progesterone only pills, or sexual intercourse with a vasectomized male partner (vasectomy must be confirmed by 2 negative semen analyses). Or women will commit to absolute and continuous abstinence confirmed to her physician on a monthly basis. Childbearing potential is defined in Section 9.1.2. Contraception will start 4 weeks before the start of therapy, during therapy including dose interruptions, for 4 weeks after discontinuation of thalidomide and for 4 months after discontinuation of daratumumab.

7. A woman of childbearing potential must have 2 negative serum or urine pregnancy tests at Screening, first within 10 to 14 days prior to dosing and the second within 24 hours prior to dosing.

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

4.2. Exclusion Criteria

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

1. Subject has received daratumumab or other anti-CD38 therapies previously.

2. Subject has a diagnosis of primary amyloidosis, monoclonal gammopathy of undetermined significance, smoldering multiple myeloma, or solitary plasmacytoma. Monoclonal gammopathy of undetermined significance is defined by presence of serum M-protein <3 g/dL; absence of lytic bone lesions, anemia, hypercalcemia, and renal insufficiency related to the M-protein; and (if determined) proportion of plasma cells in the bone marrow of 10% or less (Kyle 2003[25]). Smoldering multiple myeloma is defined as asymptomatic multiple myeloma with absence of related organ or tissue impairment (ROTI) end organ damage (Kyle 2003[25], Kyle 2007[26]).

3. Subject has a diagnosis of Waldenström's macroglobulinemia, or other conditions in which IgM M-protein is present in the absence of a clonal plasma cell infiltration with lytic bone lesions.

4. Subject has prior or current systemic therapy or SCT for any plasma cell dyscrasia, with the exception of an emergency use of a short course (equivalent of dexamethasone 40 mg/day for a maximum 4 days) of corticosteroids before treatment.

5. Subject has peripheral neuropathy or neuropathic pain Grade 2 or higher, as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.

6. Subject has had any prior or concurrent invasive malignancy (other than multiple myeloma) within 10 years of study start except adequately treated basal cell or squamous cell carcinoma of the skin, carcinoma in situ of the cervix, localized prostate adenocarcinoma diagnosed ≥3 years and without evidence of biochemical failure, or other cancer for which the subject has undergone potentially curative therapy and has no evidence of that disease for ≥10 years.

7. Subject has had radiation therapy within 14 days of C1D1.

8. Subject has had plasmapheresis within 28 days of C1D1.

9. Subject is exhibiting clinical signs of meningeal involvement of multiple myeloma.

10. a) Subject has known chronic obstructive pulmonary disease (COPD) with an Forced Expiratory Volume in 1 second (FEV_1) < 50% of predicted normal. Note that FEV_1 testing is required for patients suspected of having COPD and subjects must be excluded if FEV_1 <50% of predicted normal.

    b) Subject has known moderate or severe persistent asthma within the past 2 years (see Attachment 5), 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).

11. Subject is known to be seropositive for history of human immunodeficiency virus (HIV) or known to have active hepatitis B or hepatitis C.

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

13. Subject has clinically significant cardiac disease, including:

    - myocardial infarction within 1 year before randomization, or an 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 Grade ≥2) or clinically significant ECG abnormalities
    - screening 12-lead ECG showing a baseline QT interval as corrected by Fridericia's formula (QTcF) >470 msec

14. Subject has known allergies, hypersensitivity, or intolerance to boron or mannitol, corticosteroids, monoclonal antibodies or human proteins, or their excipients (refer to the Investigator's Brochure), or known sensitivity to mammalian-derived products.

    Or subject has known hypersensitivity to thalidomide.

15. Subject has plasma cell leukemia (according to WHO criterion: ≥20% of cells in the peripheral blood with an absolute plasma cell count of more than 2×10^9/L) or POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes).

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

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

18. Subject has had major surgery within 2 weeks before randomization or will not have fully recovered from surgery, or has surgery planned during the time the subject is expected to participate in the study. Kyphoplasty or Vertebroplasty are not considered major surgery.

19. Subject has received an investigational drug (including investigational vaccines) or used an invasive investigational medical device within 4 weeks before randomization or is currently enrolled in an interventional investigational study.

20. Subject has contraindications to the use of any components of the backbone treatment regimens, per local prescribing information.

21. Incidence of gastrointestinal disease that may significantly alter the absorption of oral drugs.

22. Subjects unable or unwilling to undergo antithrombotic prophylactic treatment.

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

4.3. Prohibitions and Restrictions

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

1. A woman of childbearing potential must remain on a highly effective method of birth control (see inclusion criteria). Guidelines presented in the Celgene thalidomide pregnancy prevention program must be followed. Contraception must begin 4 weeks before initiating treatment with thalidomide or daratumumab, during therapy, during dose interruptions and continuing for 4 weeks after discontinuation of thalidomide and for 4 months following discontinuation of daratumumab. Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy.

2. Serum (urine in the case where serum is not possible in a timely manner) pregnancy test to be performed for all women of childbearing potential regularly during the study, at 4 weeks following the last dose of thalidomide, at the End-of-Treatment Visit, and at 4 months after the last dose of daratumumab. In addition, a pregnancy test may be done at any time during the study at the discretion of the investigator if a subject misses a period or has unusual menstrual bleeding.

3. A man who has not had a vasectomy and who is sexually active with a woman of childbearing potential must agree to use a barrier method of birth control eg, condom with spermicidal foam/gel/film/cream/suppository, and all men must also not donate sperm during the study, for 1 week after discontinuation of thalidomide and for 4 months following discontinuation of daratumumab. The exception to this restriction is that if the subject's female partner is surgically sterile, a second method of birth control is not required.

4. **Daratumumab Interference with Indirect Antiglobulin Test (IAT) results**

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

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

a) Providing ABO/RhD compatible, phenotypically (standard or extended phenotyping prior to daratumumab administration) 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.

5. TREATMENT ALLOCATION AND BLINDING

Subjects will be assigned in a randomized manner to receive either 16 mg/kg daratumumab in combination with VTD or VTD alone as induction and consolidation therapy. Subjects who successfully completed consolidation with a response of PR or better according to the IMWG criteria will be assigned a second time in a randomized manner to receive daratumumab alone or observation until documented progression of disease (limited to a maximum duration of 2 years). Permuted block randomization will be implemented in this study.

Subjects will be stratified at first randomization by site affiliation (IFM or HOVON), International Staging System stage I, II, or III (β-2 microglobulin and albumin) and by cytogenetics (standard risk or high risk as defined by presence of del17p or t(4;14), as centrally confirmed during

screening). Subjects will be stratified at the second randomization by type of induction treatment and by depth of response to induction/consolidation therapy (as determined by MRD status and post-consolidation response). For stratification purposes, if cytogenetic results are not available (i.e., due to technical reasons), the subject will be assumed to have normal cytogenetics and if MRD status is not available the subject will be assumed to be MRD positive. The stratification factors for the second randomization are presented in Table 6.

Table 6: Part 2 (Maintenance Phase) Stratification Factors

Randomized to VTD arm the induction/ASCT/consolidation phase				
MRD Status	**IMWG Response**			
	sCR	CR	VGPR	PR
Negative	Stratum 1	Stratum 1	Stratum 1	NA
Positive	Stratum 2	Stratum 3	Stratum 3	Stratum 4
Randomized to VTD+dara arm the induction/ASCT/consolidation phase				
MRD Status	**IMWG Response**			
	sCR	CR	VGPR	PR
Negative	Stratum 5	Stratum 5	Stratum 5	NA
Positive	Stratum 6	Stratum 7	Stratum 7	Stratum 8
CR=complete response; IMWG=International Myeloma Working Group; MRD=minimum residual disease; PR=partial response; sCR=stringent complete response; VGPR=very good partial response				

The investigator will screen and if eligible randomize each subject using an interactive web-based randomization system (IWRS). Each subject will be assigned a unique subject number.

This is an open-label study. Subjects and sites will not be blinded to treatment assignment.

6. DOSAGE AND ADMINISTRATION

In this protocol, daratumumab is the investigational product. Daratumumab is to be administered as described in the Time and Events Schedule. On dosing days where the chemotherapy combination products are given with daratumumab, dexamethasone should be administered 1 hour before the daratumumab infusion, bortezomib should be administered after the end of the daratumumab infusion and thalidomide should be taken as a single dose at bedtime.

Detailed information on the composition of daratumumab can be found in the Investigational Product (IP) Manual. All drugs to be used in this study should only be handled by staff specially trained in the safe handling of them. The cytotoxic drugs should be handled and prepared with caution, and the use of gloves and other appropriate protective clothing is recommended. The pharmacist or person authorized to dispense bortezomib and daratumumab will prepare these drugs under aseptic conditions.

The cycle of VTD is approximately 28 days (4 weeks) in duration, and treatment will be for a maximum of 4 induction cycles and 2 consolidation cycles. The cycles during the maintenance period are approximately 8 weeks in duration, and treatment will continue until disease progression with a limit of up to 2 years.

The start of each cycle may occur ±3 days (induction/consolidation phases) and ± 3 weeks (maintenance phase) of the scheduled day in order to accommodate the schedule of the site or subject. Subjects will be treated for the allowed maximal treatment period or until disease progression, unacceptable toxicity, or other reasons as listed in Section 10.2.

6.1. Daratumumab

6.1.1. Daratumumab Preparation

The infusion solution will be prepared on the day of the planned infusion. Detailed instructions for preparation and administration of daratumumab will be supplied in the IP Manual or equivalent document.

6.1.2. Daratumumab Administration and Infusion Rate

Daratumumab (16mg/kg) will be administered by intravenous (IV) infusion once every week for 8 weeks (VTD induction Cycle 1-2), then every 2 weeks for the remaining induction cycles and consolidation cycles based on treatment assignment. Following second randomization, subjects assigned to the daratumumab maintenance arm will receive daratumumab (16mg/kg) once every 8 weeks until documented disease progression (limited to a maximum duration of 2 years).

Each subject's dose will be calculated based on the subject's weight and rounded to the nearest kilogram. There is no cap on the absolute dose allowed, as long as the dose does not exceed 16 mg/kg. If a subject's weight changes by more than 10% from baseline, the dose of daratumumab will be re-calculated. For recommendations on daratumumab infusion rate, please refer to the IP Manual. All infusions will be performed as outpatient visits. Subjects will receive preinfusion medications and postinfusion medications as outlined in Section 6.1.3.

As noted Table 2, vital signs should be monitored extensively on Cycle 1 Day 1 before, during, and after the first infusion of daratumumab immediately before the start of dara infusion; at 0.5, 1, 1.5, 2, 3.5 hours after the start of the infusion; at end of infusion; and 0.5, 1 hour after end of infusion. For all other infusions, vital signs should be measured immediately 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.

As noted Table 3, vital signs should be monitored extensively on week 1 for the 1st administration of daratumumab in Part 2 for patients who were randomized in VTD Arm in Part 1; immediately before the start of dara infusion; at 0.5, 1, 1.5, 2, 3.5 hours after the start of the infusion; at end of infusion; and 0.5, 1 hour after end of infusion.

6.1.3. Guidelines for Prevention and Management of Infusion Reactions

6.1.3.1. Preinfusion Medication

Preinfusion medications for subjects receiving daratumumab in either part 1 or part 2 of the study and will be administered as described in the Time and Events Schedules.

On daratumumab infusion days, subjects will receive the following medications prior to infusion:

- Paracetamol (acetaminophen) 650-1000 mg IV or orally (PO) up to 3 hours prior to daratumumab infusion
- An antihistamine (H_1 receptor antagonist according to institutional standard) up to 3 hours prior to infusion
- Montelukast should be given up to 3 hours prior to daratumumab administration.

  For Part 1, 10mg is required on Cycle 1 Day 1 and optional for all other doses of daratumumab.

  For Part 2, for first administration, 10mg is required on Week 1 infusion and optional for all other doses of daratumumab.

- Dexamethasone 40 mg IV or PO on Cycles 1 and 2 on infusion days. In Cycles 3 and 4, Dexamethasone 40 mg IV or PO on Day 1 and 20 mg IV or PO for subsequent dosing days.

  For Part 1, Dexamethasone, as study treatment, should be administered 1 hour before daratumumab infusion.

  For Part 2, Dexamethasone, as premedication, should be administered up to 3 hours prior to daratumumab infusion.

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

6.1.3.2. Postinfusion Medication

For subjects with higher risk of respiratory complications (eg, subjects who have a FEV_1 <80%), patients with mild asthma or mild COPD, the following postinfusion medications should be considered:

- Antihistamine
- Short-acting β2 adrenergic receptor agonist such as salbutamol
- Control medications for lung disease (eg, inhaled corticosteroids ± long-acting β2 adrenergic receptor agonists for subjects with asthma; long-acting bronchodilators such as tiotropium or salmeterol ± inhaled corticosteroids for subjects with COPD)

In addition, these at-risk subjects may be hospitalized for monitoring for up to 2 nights after an infusion. If subjects are hospitalized, then their FEV_1 should be measured before discharge. If these subjects are not hospitalized, then a follow up telephone call should be made to monitor their condition within 48 hours after all infusions. If the subject has not experienced a significant medical event but is hospitalized overnight only for observation, then the hospitalization should

not be reported as a serious adverse event. Investigators may prescribe bronchodilators, antihistamines, and corticosteroids that are deemed necessary to provide adequate supportive care in the event a bronchospasm occurs after subjects are released from the hospital/clinic. If, after 4 full doses, an at-risk subject experiences no major infusion-related reactions, then these postinfusion medications may be stopped at the investigator's discretion.

6.1.4. Management of Infusion-Related Reactions

Subjects should be carefully observed during daratumumab infusions. Particular caution should be taken for the first infusion of daratumumab which may occur at the start of either part 1 or part 2 of the study depending on the treatment assignment.

Trained study staff at the clinic should be prepared to intervene in case of any infusion reactions occurring, and resources necessary for resuscitation (eg, agents such as epinephrine and aerosolized bronchodilator, also medical equipment such as oxygen tanks, , and a defibrillator) must be available. Attention to staffing should be considered when multiple subjects will be dosed at the same time.

If an infusion-related reaction develops, then the infusion should be paused. Subjects who experience adverse events during the infusion must be treated according to the investigator's judgment and best clinical practice. The following guidelines may apply:

- Subjects should be treated with acetaminophen, antihistamine, or corticosteroids. Intravenous saline may be indicated. For bronchospasm, urticaria, or dyspnea, subjects may require antihistamines, oxygen, corticosteroids, or bronchodilators. For hypotension, subjects may require vasopressors.
- In the event of a life-threatening infusion-related reaction (which may include pulmonary or cardiac events), or anaphylactic reaction, daratumumab should be discontinued and no additional daratumumab should be administered to the subject. Aggressive symptomatic treatment should be applied.

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

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

If the investigator assesses an adverse event to be related to the daratumumab infusion, then the infusion should be paused. When the subject's condition is stable, the infusion may be restarted at the investigator's discretion. Upon restart, the infusion rate should be half of that used before the interruption. Subsequently, the infusion rate may be increased at the investigator's discretion.

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

6.1.4.2. Infusion-Related Reactions (IRR) of Grade 3 or Higher

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

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

If the intensity of the adverse event returns to Grade 3 after restart of the infusion, then the procedure described in this section may be repeated at the investigator's discretion. Should the intensity of the adverse event increase to Grade 3 for a third time, then treatment with daratumumab will be discontinued for that subject. An IRR is defined as any adverse event (AE) occurring during or within the 24 hours after the Daratumumab infusion and assessed as related to Daratumumab infusion.

6.2. Bortezomib, Thalidomide, and Dexamethasone (VTD)

Sites will use commercially available chemotherapy treatments for administration in this study unless otherwise communicated. Before administering, refer to the currently approved package inserts for complete prescribing information.

6.2.1. Dose Calculation of Bortezomib

The amount (in mg) of bortezomib to be administered will be determined by BSA, which will be calculated according to a standard nomogram (Attachment 7). 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). On treatment days when both bortezomib and daratumumab are administered, bortezomib must be administered after the end of the daratumumab infusion.

6.2.2. Bortezomib Administration

Subjects will receive 1.3 mg/m^2 bortezomib as a SC injection twice a week (Days 1, 4, 8, and 11) for four 28-day induction cycles (Cycles 1 to 4), and two consolidation cycles (Cycles 5 and 6), with an option to change the schedule from twice a week to once a week, should toxicity be encountered. Cycles will remain 28 days in length regardless of injection interval.

Bortezomib will be supplied in sterile, single-use vials containing 3.5 mg of bortezomib. For SC administration, each vial of bortezomib for Injection should be reconstituted within 8 hours before dosing with 1.4 mL of normal (0.9%) saline (sodium chloride for injection) so that the reconstituted solution contains bortezomib at a concentration of 2.5 mg/mL. If a subject's weight changes by more than 10% from baseline, the dose of bortezomib will be re-calculated.

Bortezomib may be administered IV if injection site reactions are encountered. Please refer to local prescribing information for further details on either SC or IV administration.

6.2.3. Thalidomide Administration

Thalidomide will be administered PO at 100 mg daily for 4 x28 days induction cycles and 2 x 28 days consolidation cycles. Thalidomide should be taken as a single dose at bedtime, to reduce the impact of somnolence. Thalidomide can be taken with or without food. Breaking or dividing thalidomide is strongly discouraged.

Thalidomide dose may be reduced, or the treatment schedule may be modified for the management of the study drug-related toxicities.

6.2.4. Dexamethasone Administration

Dexamethasone will be administered on scheduled days as indicated in the Time and Events Schedule at 40 mg during Cycles 1 and 2. In Cycles 3 and 4, dexamethasone will be administered at 40 mg on Days 1-2 and 20 mg on subsequent dosing days. Dexamethasone 20 mg will be administered in Cycles 5 and 6. On daratumumab infusion days, in the induction/consolidation phase, dexamethasone may be administered intravenously 1 hour before the daratumumab infusion. On days when daratumumab is not administered, dexamethasone is administered PO. Dexamethasone tablets are to be taken with or immediately after a meal or snack, preferably in the morning.

In the maintenance phase, dexamethasone 20 mg will be administered as pre-medication on daratumumab infusion days up to 3 hours prior to infusion.

Dexamethasone dose may be reduced, or the treatment schedule may be modified for the management of the study drug-related toxicities.

6.3. Dose Delays and Dose Modifications (General Principles)

6.3.1. Cycle Delay

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 NCI CTCAE, Version 4. Dose modifications or delays will be made based on the toxicity experienced during the previous cycle of therapy or newly encountered on Day 1 of a cycle. For any neurological deficits that develop, it is strongly recommended that these be evaluated by the same physician who performed the neurological assessment at baseline. The parameters in Table 7 must be met on the first day of a new cycle (i.e., the following represent baseline inclusion criteria levels):

Table 7: Re-treatment criteria before the start of each cycle[a]

Laboratory parameter	Requirements before each study agent administration
ANC	≥1.0 x 10^9/L with or without neutrophil growth factors
Platelet count	≥70 x 10^9/L with or without platelet transfusions, thrombopoietic cytokines, or both
Hemoglobin	≥7.5 g/dL (≥4.96 mmol/L) with or without transfusion, erythropoietin, or both
Other clinically significant toxicity[a]	Recovery to Grade ≤ 1 or baseline, unless described otherwise in the dose modification guidelines
[a] Refer to Section 0 for management of neurotoxicity.	

If the above parameters are not met during the induction/consolidation phase, the start of the next cycle will be held for a minimum of 1 week and a maximum of 28 days until recovery to the specified levels. During the cycle delay, daratumumab, bortezomib, dexamethasone and thalidomide, (all applicable) must be held. If there is a delay in the start of a new cycle (i.e., none of the study medications are given during this period) for more than 28 days due to insufficient recovery from toxicity, subjects will discontinue taking the study drugs permanently (unless Sponsor approves continuation) and have procedures performed as outlined in Section 10.2.

If the above parameters are not met during the maintenance phase, the start of the next cycle will be held for a minimum of 3 weeks and a maximum of 28 days until recovery to the specified levels.

6.3.2. Dose Modification Guidelines

Toxicities should be attributed, whenever possible, to a specific study drug so that dose modifications can be made rationally. Reduction of a single agent and not others is appropriate if toxicity is considered to be related primarily to 1 of the agents. If multiple toxicities are attributed to an individual study drug, dose adjustment should be made according to the guidelines for the most severe toxicity. Please refer to the tables below for dose reduction steps and dose modification guidelines.

Once dose reduction for a medication has been implemented, unless otherwise stated specifically in the table below, dose re-escalation should not occur, unless in the judgment of the investigator there is clinical benefit and a reasonable and acceptable risk profile.

6.3.3. Daratumumab Dose Modification

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

6.3.3.1. Daratumumab-Related Toxicity Management

Refer to Section 6.1.3 for details on management of infusion-related reactions. If any of the following criteria are met and the event cannot be ascribed to bortezomib or thalidomide, the daratumumab infusion must be held to allow for recovery from toxicity. The criteria for a dose delay are:

- Grade 4 hematologic toxicity
- Grade 3 thrombocytopenia with bleeding
- Febrile neutropenia
- 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

If daratumumab administration does not commence within the prespecified window (Table 8) of the scheduled administration date, then the dose will be considered a missed dose. Administration may resume at the next planned dosing date.

Table 8: Daratumumab-Related Toxicity Management

Frequency	Dose Missed	Dosing Resumption
Weekly	>3 days	next planned weekly dosing date
Every 2 weeks	>7 days	next planned every-2-weeks dosing date
Every 4 weeks	>21 days	next planned every-four-weeks dosing date
Every 8 weeks	>28 days	next planned every-8-weeks dosing date

A missed dose will not be made up. If a dose is delayed, then the dates of all subsequent doses must be adjusted during the study Part 1. Any adverse event deemed to be related to daratumumab that requires a dose hold of more than 28 days will result in permanent discontinuation of daratumumab (unless Sponsor approves continuation).

6.3.3.2. Daratumumab Interruption or Missed Doses

A daratumumab dose that is held for more than the permitted time (Table 8) 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's study team at the earliest possible time. Subjects whose dose was delayed for more than 28 days should be withdrawn from study treatment, unless, upon consultation with the sponsor and the review of safety and efficacy, continuation is agreed upon.

6.3.4. Dose Reductions (Bortezomib, Thalidomide, and Dexamethasone)

Bortezomib will be modified or discontinued according to the guidelines presented in Table 9.

Table 9: Dose Modification for Bortezomib

Starting Dose	First Dose Reduction	Second Dose Reduction	Third Dose Reduction
Bortezomib 1.3 mg/m^2 on Days 1, 4, 8, 11	Bortezomib 1.3 mg/m^2 on Days 1, 8	Bortezomib 1.0 mg/m^2 on Days 1, 8	Discontinue bortezomib

Thalidomide will be reduced or discontinued according to the guidelines presented in Table 10.

Table 10: Dose Reduction for Thalidomide

Starting Dose	First Dose Reduction	Second Dose Reduction	Third Dose Reduction
100 mg QD	50 mg QD	50 mg *every second day*	Discontinue thalidomide
QD=every day			

Dexamethasone will be reduced or discontinued according to the guidelines presented in Table 11.

Table 11: Dose Reductions for Dexamethasone

First Dose Reduction	Second Dose Reduction	Third Dose Reduction
Reduce dexamethasone by 50% from previous dose	Skip dexamethasone on days when daratumumab is not given.	Discontinue dexamethasone

If reduction of dexamethasone dose occurs prior to Week 2 of Cycle 3, dose of dexamethasone from Week 2 of Cycle 3 onwards should also be reduced by 50% (ie. 10mg instead of 20mg). Dose Modification Guidelines for Bortezomib, Thalidomide and Dexamethasone.

Dose modification guidelines for bortezomib, thalidomide and, dexamethasone are provided in Table 12.

Table 12: Dose Modification Guidelines for Bortezomib, Dexamethasone and Thalidomide

Body System	NCI-CTC Adverse Event and or Symptom and Category	Bortezomib	Thalidomide	Dexamethasone
Allergic reactions	Allergic reaction or hypersensitivity Grade 2 OR 3	Hold all therapy. If the toxicity resolves to ≤ Grade 1, restart study drug(s). Modify/reduce by 1 dose level the suspected medication(s) AND implement appropriate anti-allergic prophylaxis therapy. If the reaction was anaphylactic in nature, do not resume any of the suspected study drug(s). NOTE: If the reaction was cutaneous in nature, refer to the cutaneous category below.		
	Allergic reaction or hypersensitivity Grade 4	Discontinue study drug(s).		
Constitutional	Fluid Retention (i.e., edema) >Grade 3 (limiting function and unresponsive to therapy or anasarca)			Administer diuretics as needed and decrease dexamethasone or prednisone dose by 1 dose level; if edema persists despite above measures, decrease dose another dose-level. Discontinue dexamethasone or prednisone and do not resume if symptoms persist despite second reduction.
	Fatigue[a] ≥ Grade 3 (i.e., severe fatigue interfering with activities of daily living)		Reduce dose of Thalidomide by 1 dose level. If symptoms persist, modify bortezomib also by 1 dose level.	
Cutaneous	Non-blistering rash Grade 2	Hold thalidomide and bortezomib therapies. Begin treatment with antihistamines and/or low-dose steroids as per institutional practice. If the toxicity resolves to ≤ Grade 1, restart thalidomide and bortezomib modified/reduced by 1 dose level		
	Non-blistering rash ≥ Grade 3 or 4	Hold thalidomide and bortezomib therapies. Begin treatment with antihistamines and/or low-dose steroids as per institutional practice. If the toxicity resolves to ≤ Grade 1, restart bortezomib (only) modified/ reduced by 1 dose level and continue antihistamines and/or low-dose steroids as per institutional practice. If no further symptoms are seen, then restart thalidomide at 1 dose reduction level. If toxicity recurs despite above measure, discontinue bortezomib and/or thalidomide permanently, as appropriate.		
	Desquamating (blistering) rash- any grade or erythema multiform ≥ Grade 3	Discontinue thalidomide AND bortezomib permanently. Hold other therapies. Begin treatment with antihistamines and/or low-dose steroids as per institutional practice. If the toxicity resolves to ≤ Grade 1, restart other medications.		

[a] Determine if fatigue is possibly not medication-related but due to an underlying cause (eg, infection, progression of disease, diarrhea, anemia, depression) and treat these symptoms/causes as appropriate.

Body System	NCI-CTC Adverse Event and or Symptom and Category	Bortezomib	Thalidomide	Dexamethasone
Gastrointestinal	Constipation[b] Requiring manual extraction. ≥ Grade 3	Hold bortezomib and thalidomide. Upon recovery to ≤ Grade 1, restart bortezomib and thalidomide modified/ reduced by 1 dose level.		
	Diarrhea[c] ≥ Grade 3	Hold bortezomib and consider loperamide therapy. Upon recovery to ≤ Grade 1, restart bortezomib modified/reduced by 1 dose level.		
	Dyspepsia, gastric or duodenal ulcer, gastritis Grade 1-2 (requiring medical management)			Treat with histamine-2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, decrease dexamethasone or prednisone dose by 1 dose level.
	Dyspepsia, gastric or duodenal ulcer, gastritis ≥ Grade 3 (requiring hospitalization or surgery)			Hold dexamethasone and consider treatment with histamine-2 blockers, sucralfate, or omeprazole. Restart dexamethasone or prednisone reduced by 1 dose level if symptoms are adequately controlled. If symptoms persist despite above measures, discontinue dexamethasone or prednisone and do not resume.

[b] Prior to dose reduction of medications, consider/eliminate other possible causes of constipation.

[c] Prior to dose reduction of medications, consider/eliminate other possible causes (i.e., bacterial or viral infections) of diarrhea.

Hematological[d]	Neutropenia Grade 3 (without complications)	No dose reduction required of either bortezomib or thalidomide. Consider treatment with G-CSF.	
	Neutropenia associated with fever (≥38.5ºC): Grade 3 or neutropenia Grade 4	Hold therapy with all drugs until recovery to baseline OR ≤ Grade 2. Upon recovery, restart thalidomide reduced by 1 dose level. Maintain bortezomib at current dose and consider G-CSF support. If recurrence is seen, modify/reduce bortezomib by 1 dose level.	
	Thrombocytopenia Grade 3 (without complications)	No dose reduction required for either bortezomib or thalidomide.	
	Platelet count <25,000/µL (i.e., Grade 4) or Grade 3 thrombocytopenia with bleeding	Hold therapy with all drugs until recovery to baseline OR ≤ Grade 2. Upon recovery, restart thalidomide at current dose and bortezomib modified/reduced by 1 dose level. If recurrence is seen, reduce thalidomide by 1 dose-level and bortezomib by 1 *further* dose-level.	
Infection	Herpes Zoster[e] activation or reactivation ANY grade	Hold ALL therapies until lesions are dry. If not already underway, begin antiviral treatment Once the infection is resolved all medications can be restarted without a dose reduction; however, continued antiviral prophylaxis is required.	

Body System	NCI-CTC Adverse Event and or Symptom and Category		Bortezomib	Thalidomide	Dexamethasone
Musculoskeletal	Muscle weakness >Grade 2 (symptomatic and interfering with function +/- interfering with activities of daily living)				Decrease dexamethasone dose by 1 dose level. If weakness persists despite above measures, decrease dose by 1 *further* dose level. If symptoms *still* persist, discontinue and do not resume if symptoms persist.

[d] In the event of concurrent neutropenia and thrombocytopenia, please refer to the recommendation provided for thrombocytopenia in which it is recommended to first dose reduce bortezomib and then thalidomide.

[e] In the event that a subject is already receiving antiviral treatment at the time of the Herpes Zoster activation, consider switching to or adding another antiviral agent.

Metabolic	Hyperglycemia ≥ Grade 3				Treatment with insulin or oral hypoglycemics. If uncontrolled despite above measures, decrease dose by 1 dose level until levels are satisfactory.
Neurological[f]	Somnolence ≥ Grade 3			Reduce thalidomide by 1 dose level. If symptoms persist, reduce by a further dose level. If then unresolved, discontinue thalidomide.	
	Peripheral Neuropathy (Sensory or Motor) and/or Neuropathic Pain	Grade 1 (paresthesias and/or loss of reflexes) without pain or loss of function	No action required.		
		Grade 1 with pain or Grade 2 (interfering with function but not with activities of daily living)	Modify/reduce bortezomib and thalidomide by 1 dose level.		
		Grade 2 with pain or Grade 3 (interfering with activities of daily living)	Hold bortezomib until toxicity resolves to <Grade 2. When toxicity resolves, reinitiate with a reduction in dose level and schedule (i.e. modify by 2 dose levels Discontinue thalidomide permanently.		
		Grade 4 (permanent sensory loss that interferes with function)	Discontinue bortezomib and thalidomide permanently.		

[f] The neurotoxicity-directed questionnaire is a useful tool for determining the presence and intensity of neuropathic pain and/or peripheral neuropathy from the subject's perspective. Neuropathic symptoms are more prominent than abnormalities on the clinical examination. After the subject completes the neurotoxicity directed questionnaire, the questionnaire should be reviewed to assist with the evaluation of the onset and intensity of peripheral neuropathy and other neurotoxicities that may require intervention or dose modification.

Body System	NCI-CTC Adverse Event and or Symptom and Category	Bortezomib	Thalidomide	Dexamethasone
Neuro-psychological	Confusion or mood alteration >Grade 2 (interfering with function +/- interfering with activities of daily living)			Hold dexamethasone until symptoms resolve. Restart with 1 dose level reduction. If symptoms persist despite above measures, discontinue dexamethasone and do not resume.
Thromboembolic	Venous and /or pulmonary thrombo-embolism ≥ Grade 3 [Deep vein thrombosis or cardiac thrombosis intervention indicate; eg: anticoagulation, lysis, filter, invasive procedure.]		Stop thalidomide until toxicity resolves and, if not already given, start anticoagulation therapy. Restart thalidomide at 1 dose level lower after adequate anticoagulation,	Stop until toxicity resolves and, if not already given, start anticoagulation therapy. Restart dexamethasone or prednisone at full dose after adequate anticoagulation,
Renal Impairment				
Other toxicities	Any reported ≥ Grade 3	Determine attribution of the toxicity and hold the therapy (ies) as appropriate. If toxicity resolves to ≤ Grade 1, resume therapy with 1 level of dose modification/reduction.		

7. TREATMENT COMPLIANCE

Daratumumab and the components of the backbone regimens will be administered by qualified site staff, and the details of each administration will be recorded in the electronic case report form (eCRF). Subjects will be provided with a diary to record intake of thalidomide and dexamethasone. Additional details are provided in the IP Manual.

8. PRESTUDY AND CONCOMITANT THERAPY

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 8.3. The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

Routine systemic use of the following concomitant medications will be collected in the eCRF and recorded in the source documents beginning with signing of the ICF to 30 days after the last dose of the last study treatment or until the start of subsequent anticancer treatment, if earlier: growth factors, transfusions, anti-infectives (antibacterials, antivirals, and antimycotics), steroids, anti-arrhythmics and other cardiac supportive therapy, anti-epileptics, centrally acting psychiatric medication, anti-histamines and other medications targeting postinfusion systemic reactions, bisphosphonates, and any anticancer therapy (including radiation). During the transplant period (that is to say the period from the first day of hospitalization to the day before C5D1) only the concomitant treatments used to treat AE specified in Section 9.1.3. will have to be recorded. Concomitant medications to manage AEs and SAEs will be recorded as per Section 12.3.1.

8.1. Recommended Therapies

8.1.1. Prevention of Deep Venous Thrombosis

All subjects who receive thalidomide are required to receive prophylactic anti-thrombotic treatment, including low-molecular-weight heparin and aspirin (acetylsalicylic acid). It is mandatory that every subject receives 1 of these 2 prophylactic measures (either aspirin at a minimum of 100 mg PO per day or daily subcutaneous low molecular weight heparin injections, per investigator preference).

8.1.2. Therapy for Tumor Lysis Syndrome

Subjects should be monitored for symptoms of tumor lysis syndrome. Management of tumor lysis syndrome, including dehydration and abnormal laboratory test results such as hyperkalemia, hyperuricemia, and hypocalcemia, is highly recommended. It is also recommended that high-risk subjects, i.e., those with a high tumor burden, be treated prophylactically in accordance with local standards (eg, rehydration; diuretics; allopurinol 300 mg daily and medication to increase urate excretion). Subjects are to be provided prophylactic therapy to manage infusion reactions during the Treatment Phase, as described in Section 6.1.3.1.

8.1.3. Prophylaxis Against Pneumocystis carinii Pneumonia

Pneumocystis carinii pneumonia (PCP) prophylaxis should be considered, as per institutional guidelines.

8.1.4. Prophylaxis for Herpes Zoster Reactivation

Prophylaxis for herpes zoster reactivation is recommended during the Treatment Phase. Acceptable antiviral therapy includes acyclovir (eg, 400 mg given orally 3 times a day, or 800 mg given orally 2 times a day or per institutional standards), famcyclovir (eg, 125 mg given 3 days orally, twice a day or per institutional standards), or valacyclovir (eg, 500 mg given orally, twice a day or per institutional standards), initiated within 1 week of the first dose and continue for 3 months following treatment.

8.1.5. Bisphosphonate Therapy

Bisphosphonate therapy is recommended to be continued per treatment guidelines (NCCN 2013). Commercially available IV bisphosphonates (pamidronate and zoledronic acid) are preferred when available, and should be used according to the manufacturer's recommendations, as described in the prescribing information, for subjects with osteolytic or osteopenic myelomatous bone disease. Oral bisphosphonates may be used as alternatives if IV bisphosphonates are not available at the study site.

Subjects who are currently using bisphosphonate therapy when they enter the study should continue the same treatment. If clinically indicated, subjects may initiate bisphosphonate therapy as soon as possible during Screening and no later than the end of Cycle 1. After Cycle 1, investigators could prescribe bisphosphonates to subjects who have not received it before, as per investigator judgment but only after checking if there is no disease progression.

Management of Hepatitis B Virus Reactivation

For patients with positive HBV serology, clinical and laboratory monitoring of signs of inactivation should be performed during treatment and for at least six (6) months after stopping treatment with daratumumab. A consultation with a doctor specializing in the treatment of HBV infections should be considered, if necessary.

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

8.2. Permitted Therapies

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

- Colony stimulating factors, erythropoietin, and transfusion of platelets and red cells. Erythropoietic agents may increase thromboembolic risk; if administered, subjects should be instructed to seek medical care if they develop symptoms of thromboembolism such as shortness of breath, chest pain, arm or leg swelling. Particularly, a hemoglobin concentration above 12g/dl should lead to discontinuation of erythropoietic agents.

- 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
- It is important to prevent constipation (eg, adequate hydration, high-fiber diet, and stool softeners if needed)
- Adequate hydration is recommended for prevention of myeloma-related kidney disease
- Prophylactic antiemetics, with the exception of corticosteroids
- An emergency short course of corticosteroid (equivalent of dexamethasone 40 mg/day for a maximum 4 days) is permitted before treatment.

8.3. Prohibited Therapies

Concomitant administration of any other antineoplastic therapy for the intention of treating multiple myeloma not defined in the study protocol is prohibited, including medications that target CD38. Continuation of daratumumab and components of the VTD regimen during or after emergency orthopedic surgery or radiotherapy because of the subject's benefit may occur only in the absence of disease progression and after consultation with and approval by the sponsor. Such emergency radiotherapy may consist of localized radiotherapy for pain control or for stabilization of an extensive bone lesion at high risk of pathologic fracture or damage to surrounding tissues in a subject in whom delay of systemic therapy is not appropriate. Such radiotherapy is to occur within the first 2 cycles of treatment and the absence of evidence of disease progression is to be reviewed and approved by the sponsor.

Concomitant administration of investigational agents is prohibited. Administration of commercially available agents with activity against or under investigation for multiple myeloma, including systemic corticosteroids (>10 mg prednisone per day or equivalent) (other than those given for infusion-related reactions as described in Section 6.1.3.2) should be avoided. Nonsteroidal anti-inflammatory agents should be avoided to prevent myeloma-related kidney disease.

Typically, IV contrast is NOT used in computed tomography (CT) scanning of the subjects with secretory multiple myeloma because of the risk to the kidney. If administration of IV contrast is necessary, then adequate precautions including hydration are indicated. The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedules summarize the frequency and timing of assessments applicable to this study. Study assessments will be performed only after written informed consent is obtained. Every effort should be made to keep subjects on the study schedule as planned from Cycle 1 Day 1. At each visit, study assessments should be completed before the administration of any treatment.

Any missed visits, tests not performed, or examinations that are not conducted must be reported as such in the eCRF.

All visit-specific PRO assessments should preferably be conducted/completed before any tests, procedures, or other consultations for that visit to prevent influencing subject perceptions. Refer to Section 9.7 for details.

Urine and blood collections should be kept as close to the specified time as possible. Other measurements may be done earlier than specified, if needed. Additional pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.

The total blood volume for the study is estimated at approximately 50 mL during screening, 400 mL in Part 1 (Induction/ASCT/Consolidation Phase), and approximately 500 mL in Part 2 (2-year Maintenance Phase). This includes laboratory assessments associated with safety, efficacy, and pharmacokinetic evaluations, as well as scientific research samples. Repeat or unscheduled samples may be taken for safety reasons upon investigator judgment, in case of disease progression, or for technical issues with the samples.

9.1.2. Screening Phase

The signed ICF must be obtained before any study-specific procedures are performed. The Screening Phase begins when the first screening assessment is conducted. During the Screening Phase, eligibility criteria will be reviewed, and a complete clinical evaluation will be performed as specified in the Time and Events Schedule. Screening procedures will be performed within 28 days before Cycle 1 Day 1; however, results of tests such as skeletal survey, radiologic tests (eg, magnetic resonance imaging [MRI]) to document baseline size of known or suspected extramedullary plasmacytomas; ECG; chest x rays; or bone marrow aspirate/biopsy) performed up to 6 weeks (42 days) before randomization as routine standard of care for the subject’s disease can be used.

A negative pregnancy test for women of childbearing potential must be documented within 10 to 14 days and again within 24 hours before the first dose of any component of the treatment regimen.

If approved by the sponsor, subjects who are screen failures may be rescreened if their condition changes (see Section 4.2 for details).

9.1.3. Treatment Phase

Details of the procedures performed during the Treatment Phase are outlined in the Time and Events Schedules.

The study treatment should be initiated within 3 days after the first randomization.

The Treatment Phase begins on Cycle 1 Day 1 and continues until disease progression, completion of the planned maintenance treatment duration for a maximum of 2 years, or for the other reasons outlined in Section 10.2. Subjects will be closely monitored for adverse events, laboratory

abnormalities, and clinical response. Clinical evaluations and laboratory studies may be repeated more frequently, if clinically indicated. If disease progression is diagnosed, then the subject will discontinue the study drugs, complete the End-of-Treatment Visit, and enter the Follow-up Phase.

Study Part 1

Induction Treatment

Subjects will receive up to 4 x 28 days cycles of VTD induction therapy as described in Section 6.2. Subjects in Arm B will receive daratumumab in addition to VTD as described in Section 6.1.

Efficacy will be assessed at the start of each cycle.

Post Induction Efficacy Assessment (end of Cycle 4)

A bone marrow biopsy/aspirate (preferably both but morphologic review of the aspirate smear may be done if a core biopsy is not available) will be performed at the end of Cycle 4 to determine the plasma cell burden. The time window for this assessment is +/-3 days. As long as disease progression is not observed, subjects may proceed to stem cell mobilization. Subjects who cannot proceed to stem cell mobilization at this timepoint, based on investigator discretion or institutional practice, will be withdrawn from treatment. Subjects with disease progression will also be withdrawn from treatment. These subjects will enter in the follow-up phase.

Mobilization and Harvesting Stem Cells

Stem cell mobilization will be performed using cyclophosphamide (recommended dose of 3 g/m^2) and G-CSF (recommended dose of 10 microg/kg/day until the last day of the collection for a maximum of 10 days) after Cycle 4 and stem cells will be harvested based on response to mobilization.

The use of Plerixafor is permitted per institutional practice in case of failure.

It is recommended not to exceed a maximum of 4 weeks after the end of Cycle 4 to start the mobilization.

In case of subsequent of failure with Plerixafor bone marrow harvest may be performed.

Sufficient stem cells should be harvested to enable multiple transplants in accordance with institutional standards.

An assessment of the efficiency of mobilization/harvesting will be recorded in the eCRF (please see Section 9.2). During the transplant period (that is to say the period from the first day of hospitalization to the day before C5D1), neutropenia and thrombocytopenia resulting from bone marrow aplasia will not be recorded as AEs in the eCRF. Only the following have to be recorded in the eCRF:
- any evolution of ongoing AE
- any new AE related, or that appears to be related, to Daratumumab

- any new infection from at least grade 3
- any new oral mucositis from at least grade 3.

It is recommended not to exceed a maximum of 4-8 weeks between the mobilization and the start of melphalan.

Conditioning (melphalan)

Subjects will receive melphalan 200mg/m^2 as conditioning therapy over a period of 24 to 48 hours.

Transplant

Subjects will have a single re-infusion of stem cells 24-48 hours after high dose melphalan (+ permitted tolerance)

Engraftment/Recovery (Day 1-60 post ASCT)

Subjects will be monitored for successful engraftment; support therapy will be administered according to institutional/study group standards.

Consolidation (30-60 days)

Consolidation therapy may commence when engraftment (ANC > $0.5x10^9$/L and platelets >$20x10^9$/L without transfusion) is complete and when in the opinion of the investigator the subject is fit enough to tolerate subsequent systemic therapy (30-60 days post ASCT).

Subjects will receive a further 2 x 28-day cycles of VTD as described in Section 6.2. Subjects randomly assigned to Arm B will receive daratumumab as described in Section 6.1.

Efficacy will be assessed at the start of each cycle.

Post consolidation efficacy assessment (Day 100 post ASCT)

Subjects will be assessed for efficacy for the primary endpoint at Day 100 post ASCT. If subjects are still receiving consolidation therapy at Day 100, the assessment of efficacy should be performed immediately upon completion of consolidation therapy. The time window for this assessment is +/- 3 days from Day 100 or from end of consolidation therapy, as applicable.

Study Part 2

Randomization to Maintenance/Observation Phase (continuing from end of last consolidation cycle, 50 days)

Subjects who complete consolidation and attain a minimum of a partial response or better according to the IMWG criteria will be eligible for re-randomization to either daratumumab

maintenance or observation. Subjects who are not eligible for re-randomization will enter the Follow-up Phase.

The maximum time period between the end of the last consolidation cycle and second randomization should be no more than 50 days. Any assigned treatment should be initiated no later than 10 days after the second randomization in to part 2 of the study.

Maintenance phase

Subjects are randomly assigned to Arm A (observation) or Arm B (they will receive daratumumab as described in Section 6.1).

All subjects will be assessed for efficacy every 8 weeks after re-randomization, additional assessments of MRD status will also be performed for patients who achieve at least VGPR (weeks 25, 52, 105 or whenever it will be necessary).

End-of-Treatment Visit (EOT)

Subjects will be treated for the maximal allowed treatment duration (or until disease progression, unacceptable toxicity, or for the other reasons outlined in Section 10.2). Unless a subject withdraws consent for study participation, is lost to follow-up, or dies, an End-of-Treatment Visit is to be scheduled within 30 days after the last dose of all components of the treatment regimen have been discontinued, or within 30 days after the last observation visit (for subject in Arm A) or as soon as possible before the start of subsequent therapy.

Every effort should be made to conduct the End-of-Treatment Visit before the subject starts subsequent therapy.

Adverse events and concomitant therapies that occur within 30 days after the last visit (last dose of any component of the treatment regimen or the last observation visit) must be collected. Additional information on reporting of adverse events can be found in Section 12.

During the EOT visit, a complete evaluation should be performed:

- Hematology/Serum chemistry (local laboratory),
- Disease evaluation (central laboratory),
- Bone marrow examination (myelogram and MRD assessment (if applicable))
- Assessment of lytic disease (same type of imaging as performed for screening procedures), if applicable.
- Extramedullary plasmacytoma assessment (same type of evaluation as performed for screening visit and/or during study treatment) if applicable
- Adverse event

- Concomitant medication

9.1.4. Follow-Up Phase

The Follow-up Phase will begin once a subject permanently discontinues treatment with study medications, except for subjects randomized to Arm A (observation) in the Maintenance Phase. These subjects will enter the Follow-up Phase 2 years after the second randomization or upon disease progression, withdrawal of consent, or start of new anticancer therapy, whichever is earliest.

For all subjects who complete or discontinue study drug without disease progression (Pre-PD), disease evaluations should continue to be performed every 12 weeks as specified in the Time and Events Schedules until documented disease progression.

Pre-PD Follow-Up (FU) visits need to be scheduled as indicated below:

First Pre-PD FU visit:

- if patient is on treatment arm: 8 weeks after the last dose of any component of the treatment regimen

- if patient is on Observation arm: 8 weeks after the last Maintenance/Observation phase visit

The second and subsequent Pre-PD Follow-up visits will be performed every 12 weeks until documented disease progression.

MRD assessment will be performed also every year during Pre-PD FU if the MRD remains negative (after W105 of maintenance/Observation visit or the last MRD assessment since D100). Thereafter subsequent anticancer treatment and response to treatment including date of subsequent progression (PFS2) will be recorded and survival status will be obtained.

In case the patient starts a new line of therapy without disease progression, Follow-Up visits will be performed every 12 weeks until disease progression, lost to follow-up or death. The assessments done will be as details below in the Survival Follow-up visits.

If disease progression occurs, Survival Follow-up visits will be planned:

- Survival Follow-Up 1 visit will be performed 8 weeks after PD: Patient reported outcome (EORTCQLQ-C30 and EQ-5D-5L) must be completed

- Survival Follow-Up 2 visit will be performed 16 weeks after PD: Patient reported outcome (EORTCQLQ-C30 and EQ-5D-5L) must be completed

- Subsequent Survival Follow-up visits will be performed every 4 months

In accordance with the 2011 IMWG consensus recommendations for the purposes of the study a line of therapy is defined as one or more cycles of a planned treatment program. The planned treatment approach of induction therapy followed by autologous stem cell transplantation, consolidation, and where applicable maintenance is considered one line of therapy.

A new line of therapy starts when a planned course of therapy is modified to include other treatment agents (alone or in combination) as a result of a disease progression, relapse, or toxicity. (Rajkumar, 2011[47]).

If the information is obtained via telephone contact, written documentation of the communication must be available for review in the source documents. If the subject has died, the date and cause of death will be collected and documented in the eCRF. Follow-up of subject data will continue until 350 subjects have died, or for a maximum of 5 years after the last subject is randomized in Part 2 for the maintenance phase, which will be considered the end of the study.

9.2. Safety Evaluations

Safety and tolerability is a secondary objective of this study, the study will be conducted under the supervision of an IDMC (refer to Section 11.9) until the unblinding of data. Safety evaluations will include adverse event monitoring, physical examinations, electrocardiogram (ECGs) monitoring, clinical laboratory parameters (hematology and chemistry), vital sign measurements, and ECOG performance status. All toxicities will be graded according to the NCI-CTCAE Version 4. Any clinically relevant changes occurring during the study must be recorded in the Adverse Event eCRF page. Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached.

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

Adverse Events

Adverse events (with the exception of progression of multiple myeloma) will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) from the time a signed and dated informed consent is obtained until 30 days following the last dose of any component of the treatment regimen, except for subjects randomized to Arm A (observation) in the Maintenance Phase. For these subjects, adverse events will be collected for 2 years after the second randomization, or upon disease progression, withdrawal of consent, or start of new anticancer therapy (whichever occurs first), even though no study drug is being administered. Adverse events will be followed by the investigator as specified in Section 12 Adverse Event Reporting.

For AE reporting during the transplant period, please see Section 9.1.3.

Infusion Related Reaction (IRR)

An IRR is defined as any adverse event (AE) occurring during or within the 24 hours after the Daratumumab infusion and assessed as related to Daratumumab infusion.

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 Adverse Event eCRF page. The laboratory reports must be filed with the source documents.

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

- Hematology Panel

-hemoglobin
-white blood cell (WBC) count
-absolute neutrophil count
-absolute lymphocyte count
- platelet count

- Serum Chemistry Panel

During induction and consolidation cycles:
-urea
-creatinine
-glucose
-AST
-ALT
-alkaline phosphatase
-lactic acid dehydrogenase (LDH)
-uric acid
-total and direct bilirubin
-total protein

During maintenance cycles:
-AST
-ALT
-total and direct bilirubin
-urea
-creatinine

- Other Laboratory Tests

-Serum pregnancy test: Women of childbearing potential only. Urine pregnancy test allowed if results from a serum pregnancy test will not be promptly available. Thalidomide is contraindicated for use during pregnancy, as even a single dose can induce a high frequency of severe and life-threatening birth defects. Guidelines presented in the Celgene thalidomide pregnancy prevention program must be followed. If pregnancy does occur, then study treatment should be discontinued immediately, and the subject should be referred to an obstetrician experienced in reproductive toxicity for further evaluation and counseling.
-Calcium and albumin adjusted calcium: These parameters will be part of the efficacy evaluations as specified in Section 9.6.4. Albumin will be analyzed by the central and local laboratories. Measurement of calcium and albumin should follow the schedule for disease assessments. Measurement of free ionized calcium is an acceptable alternative to corrected serum calcium for determining hypercalcemia.

Daratumumab Interference with Indirect Antiglobulin Test (IAT) results

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

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

a) Providing ABO/RhD compatible, phenotypically (standard or extended phenotyping prior to daratumumab administration) 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.

Stem Cell Harvest: For subjects who receive ASCT, record number of CD34+ cells collected, agents used for mobilization, and hematopoietic engraftment information.

Pulmonary Function Test: Subjects with known or suspected COPD or asthma must have a FEV_1 test during screening. Refer to Section 6.1.3.2 for details on subjects with higher risk of respiratory complications.

ECG: 12-lead ECGs will be performed as specified in the Time and Events Schedule. Whenever possible, ECGs should be taken immediately before chemistry and PK assessments. During the collection of ECGs, subjects should be in a quiet setting without distractions (eg, television, cell phones). Subjects should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. If blood sampling or vital sign measurement

is scheduled for the same time point as ECG recording, then the procedures should be performed in the following order: ECG(s), vital signs, blood draw.

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

Physical Examination: A complete physical examination (including neurological examination) should be performed during the Screening Phase. Thereafter, only a symptom directed physical examination is required. Abnormalities will be recorded in the appropriate section of the eCRF.

9.3. Immunogenicity Evaluations

9.3.1. Immunogenicity Assessments

Samples to assess the generation of antibodies to daratumumab (immunogenicity) and associated serum daratumumab concentration levels will be obtained from all subjects according to the Time and Events Schedule. At specified time points, venous blood samples (5 mL per sample) will be collected and the serum will be divided into 3 aliquots (1 aliquot for immunogenicity assessment, 1 aliquot for serum daratumumab concentration, and 1 aliquot as a back-up). Daratumumab concentration is evaluated at all immunogenicity time points to ensure appropriate interpretation of immunogenicity data and both analyses are performed on aliquots from the same blood draw; no additional sampling is required.

Procedures for sample collection, preparation, identification, storage, and shipment will be provided in the Laboratory Manual or equivalent document. The exact dates and times of blood sampling must be recorded. Collected samples must be stored under the specified and controlled conditions for the temperatures indicated in the Laboratory Manual. Samples collected for determining immunogenicity/serum concentrations of daratumumab in this study may be retained to address questions about drug characteristics that may arise at a later time point.

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

9.3.2. Analytical Procedures

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

For the immunogenicity assessments, serum samples will be screened for antibodies binding to daratumumab and serum titer will also be determined from confirmed positive samples. Other immunogenicity analyses (eg, assessment of neutralizing capabilities) may be performed to further characterize the immune responses that are generated.

9.4. Biomarker Evaluations

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

Biomarkers for MMY3006 will focus on the evaluation of MRD and immune profiling in bone marrow aspirates and on the assessment of clinical efficacy in high-risk molecular subgroups.

The use of sensitive methodology to detect MRD following a clinical response is being adopted by myeloma researchers as a supplemental criterion to define CR (Paiva 2011[43]). Monitoring MRD (clonal plasma cells still present in bone marrow) is important to detect residual disease after treatment and early relapse, to monitor the effects of treatment at low levels of disease, to measure the depth of response and how it correlates with outcome, and to continue to maintain a defined treatment. The most commonly used sensitive methods to monitor MRD include next generation sequencing (NGS), allele-specific oligonucleotide PCR, and multiparametric flow cytometry (Rawstron 2013[49], Sarasquete 2005[52]). Markers used to monitor multiple myeloma MRD may include CD138/CD38/CD45/CD56 and kappa/lambda light chains.

Residual disease would be indicated by the presence of clonal plasma cells in a subject. MRD will be monitored by NGS and in selected patients, by flow cytometry using collected marrow aspirate samples.

A portion of the baseline bone marrow aspirate will also be utilized for assessment of high-risk molecular subgroups by RNA/DNA sequencing of CD138+ MM cells. Specific high-risk markers to be analyzed may include t(4;14), t(14;16), 1q21, and del17p, as well as GEP-70 and other signatures associated with poor prognosis. In addition, if feasible, a bone marrow aspirate will be collected at disease progression to monitor for mechanisms of resistance to daratumumab.

Next-Generation Sequencing (NGS) Analyses will be performed on screening blood samples aliquots a posteriori, using the same methodology as the one used for MRD detection in bone marrow after treatment initiation.

In addition to evaluating MRD and clinical efficacy in high-risk subgroups, biomarker assessments will also monitor changes in immune cell subpopulations after induction, transplant, and consolidation. The immune system related parameters to be analyzed may include the determination of the frequency and activity of immune effector cells including T cells (cytotoxic,

regulatory, memory T cells subsets), B cells, NK cells, myeloid derived suppressor cells (MDSC), macrophages, and dendritic cells, as these cells are involved in immune mediated tumor lysis. The initial values of all these parameters and the relative changes during therapy will be correlated with the quality and the duration of the clinical response. For these immune monitoring studies, flow cytometry or CyTOF may be performed. CyTOF uses transition element isotopes as labels for antibodies, thereby providing the opportunity to measure multiple markers simultaneously on every cell that is analyzed, with no requirements for compensation of spectral overlap. Samples may also be collected at time of relapse, to monitor changes in immune subpopulations that lead to resistance. These immune profiles will be analysed for associations with clinical data (quality of response, MRD status and depth, PFS, OS) as well as with MM sequencing data.

Other exploratory biomarker analyses may include assessment of copy number variation (CNV) and single nucleotide polymorphisms (SNP) in genes associated with daratumumab mechanism of action (CD38, complement inhibitory proteins CD46, CD55, CD59, complement, Fcgamma receptors, KIR, etc.). In addition, exploratory analyses may be performed to monitor complement proteins, cytokines indicative of immune response, and unbiased evaluation of protein.

9.5. Sample Collection and Handling

If blood samples are collected via an indwelling cannula, an appropriate amount (1 mL) of serosanguineous fluid slightly greater than the dead space volume of the lock will be removed from the cannula and discarded before each blood sample is taken. Refer to the Time and Events Schedule for the timing and frequency of all sample collections.

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

9.6. Efficacy

9.6.1. Evaluations

Assessment of tumor response and disease progression will be conducted in accordance with the IMWG response criteria. Efficacy evaluations will include measurements of tumor burden/residual disease, myeloma proteins, bone marrow examinations, skeletal surveys, extramedullary plasmacytomas, and serum calcium corrected for albumin.

9.6.1.1. Response Categories

Disease evaluations must be performed as outlined in the Time and Events Schedules on the scheduled assessment day (±3 days). Disease evaluations scheduled for treatment days should be collected before study drug is administered. Disease evaluations will be performed by a central laboratory (unless otherwise specified).

This study will use the IMWG consensus recommendations for multiple myeloma treatment response criteria (Durie 2007[13], Rajkumar 2011[47]) presented in Table 13. For quantitative immunoglobulin at baseline, M-protein, and immunofixation measurements in serum and 24-hour urine, the investigator will use results provided by the central laboratory.

For subjects with suspected daratumumab interference on SPEP and IFE, a reflex assay will be performed to distinguish daratumumab from any remaining endogenous M protein in the patient's serum. Subjects with confirmed daratumumab interference who meet all other clinical criteria for CR or sCR will be considered CR/sCR.

Table 13: International Uniform Response Criteria Consensus Recommendations

Response	Response Criteria
Stringent complete Response (sCR)	• CR as defined below, *plus* • Normal FLC ratio, *and* • Absence of clonal PCs by immunohistochemistry, immunofluorescence[a] or 2- to 4-color flow cytometry
Complete response (CR)*	• Negative immunofixation on the serum and urine, *and* • Disappearance of any soft tissue plasmacytomas, *and* • <5% PCs in bone marrow
Very good partial Response (VGPR)*	• Serum and urine M-component detectable by immunofixation but not on • electrophoresis, *or* • ≥90% reduction in serum M-protein plus urine M-protein <100 mg/24 hours
Partial response (PR)	• ≥50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥90% or to <200 mg/24 hours • If the serum and urine M-protein are not measurable, a decrease of ≥50% in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria • If serum and urine M-protein are not measurable, and serum free light assay is also not measurable, ≥50% reduction in bone marrow PCs is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥30% • In addition to the above criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required.
Stable disease (SD)	• Not meeting criteria for CR, VGPR, PR, or progressive disease
Progressive disease (PD)†	Increase of 25% from lowest response value in any one of the following: • Serum M-component (absolute increase must be ≥0.5 g/dL), • Urine M-component (absolute increase must be ≥200 mg/24 hours), • Only in subjects without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL) • Only in subjects without measurable serum and urine M-protein levels and without measurable disease by FLC levels, bone marrow PC percentage (absolute percentage must be ≥10%) • Bone marrow plasma cell percentage: the absolute percentage must be >10% • Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas • Development of hypercalcemia (corrected serum calcium >11.5 mg/dL) that can be attributed solely to the PC proliferative disorder
FLC = free light chain; PC = plasma cell	

All response categories (CR, sCR, VGPR, PR, and PD) require 2 consecutive assessments made at any time before the institution of any new therapy; CR, sCR, VGPR, PR, and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable on serum, urine, both, or neither.

Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. For PD, serum M-component increases of more than or equal to 1 g/dL are sufficient to define relapse if starting M-component is ≥5 g/dL.

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

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

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

Clinical Relapse

Clinical relapse is defined using the definition of clinical relapse in the IMWG criteria (Durie 2006[13], Rajkumar 2011[47]). In the IMWG criteria, clinical relapse is defined as requiring one or more of the following direct indicators of increasing disease or end-organ dysfunction that are considered related to the underlying plasma cell proliferative disorder:

1. Development of new soft tissue plasmacytomas or bone lesions on skeletal survey, magnetic resonance imaging, or other imaging
2. Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion
3. Hypercalcemia (>11.5 mg/dL; >2.875mM/L)
4. Decrease in hemoglobin of more than 2 g/dL (1.25 mM) or to less than 10 g/dL
5. Rise in serum creatinine by more than or equal to 2 mg/dL (≥177 mM/L)
6. Hyperviscosity

In some subjects, bone pain may be the initial symptom of relapse in the absence of any of the above features. However, bone pain without imaging confirmation is not adequate to meet these criteria in studies.

Disease progression must be consistently documented across clinical study sites using the criteria in Table 13. It is important that instances of disease progression be reported to the sponsor as soon as possible.

Patients will continue in the last confirmed response category until there is confirmation of progression or improvement to a higher response status; patients cannot move to a lower response category.

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

Serum free light chain assay test results will be analyzed by the central laboratory for the assessment of sCR, according to the most recently published IMWG criteria (Durie 2007[13]). Freelite ® or another validated assay will be utilized for this assessment.

9.6.2. Central Confirmation of stringent Complete Response (sCR)

Subjects who are believed have attained a stringent Complete Response (sCR) will have this confirmed centrally by a minimum of 4 color flow cytometry. A fresh bone marrow aspirate is

required for flow cytometry as outlined in the Time and Events Schedules or whenever it will be required to assess sCR.

9.6.3. Myeloma Protein Measurements in Serum and Urine

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

- Serum quantitative immunoglobulins (QIgs)
  - All subjects will be evaluated for IgG, IgA, IgM and IgE at Screening. During the study, subjects with IgD or IgE disease will be evaluated for IgG, IgA, IgM and IgE and subjects with IgG, IgA, or IgM disease will be evaluated for IgG, IgA, and IgM
- Serum M-protein quantitation by electrophoresis (SPEP)
- Serum immunofixation at screening and thereafter when M-protein is non-quantifiable up to confirmation of CR
- 24-hour urine M-protein quantitation by electrophoresis (UPEP)
- Urine immunofixation at screening and thereafter when a M-protein is non-quantifiable up to confirmation of CR
- Free light chain assessment for subjects with light chain only myeloma and IgD myeloma (IgD<0,5g/dL at screening); also for all subjects to confirm sCR

Blood and 24-hour urine samples will be collected as specified in the Time and Events Schedule until the development of confirmed disease progression. 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 immunofixation test will be performed at screening and thereafter when serum or 24-hour urine M-protein electrophoresis [by SPEP or UPEP] is negative or non-quantifiable. For subjects with light chain multiple myeloma, both serum and urine immunofixation test will be performed at every cycle.

As an IgG1 kappa immunoglobulin, Daratumumab has been shown to interfere with serum protein electrophoresis (SPE) and immunofixation (IFE) (McCudden 2010[33]). This detection of daratumumab can be mitigated through a reflex assay using the anti-idiotype antibody to bind daratumumab, shift it on SPE and IFE, and confirm interference. This reflex assay will be implemented as part of response criteria. For those subjects who meet all other clinical criteria for CR/sCR, with confirmed daratumumab interference on SPE/IFE, will be considered CR/sCR.

9.6.4. Albumin and Serum Calcium Corrected for Albumin

Blood samples for calculating serum calcium corrected for albumin will be collected and analyzed locally, as specified in the Time and Events Schedule until the development of confirmed disease progression. Development of hypercalcemia (corrected serum calcium >11.5 mg/dL or 2.8 mmol/L) can indicate disease progression or relapse if it is not attributable to any other cause (see disease response criteria in Table 13). 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.

9.6.4.1. β2-microglobulin and Albumin

Blood samples for β2 microglobulin and albumin are to be collected at Screening and will be analyzed by the central laboratory.

9.6.5. Bone Marrow Examination

Bone marrow aspirate and/or biopsy will be performed at screening for clinical staging (morphology, cytogenetics, and immunohistochemistry [IHC] or immunofluorescence or flow cytometry), to establish baseline multiple myeloma clonality to monitor for MRD, and to perform molecular subtyping to monitor daratumumab activity in high-risk molecular subgroups. Clinical staging may be performed locally; however, a portion of the bone marrow aspirate/biopsy must be sent to the central lab for analysis of MRD and molecular subtyping. A fresh bone marrow aspirate at screening is required. A core bone marrow biopsy/aspirate will be performed to confirm sCR and CR. If a bone marrow core biopsy cannot be obtained or is not available, morphologic review of the bone marrow aspirate smear may be reviewed by the local laboratory for confirmation of CR. Bone marrow aspirates are acceptable for determination of relapse from CR (IHC or immunofluorescence) and to monitor for MRD. If feasible, a bone marrow aspirate may be collected from subjects at disease progression to evaluate mechanisms of daratumumab resistance.

9.6.6. 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 (see the disease response criteria in Table 13). If a radionucleotide 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 radionucleotide 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 x-rays

are necessary. In instances where changes may be more subtle, a repeat x-ray may be performed in 1 to 3 weeks per investigator discretion.

9.6.7. Documentation of Extramedullary Plasmacytomas

Sites of known extramedullary plasmacytomas must be documented during the Screening Phase. Clinical examination or MRI may be used to document extramedullary sites of disease. CT scan evaluations are an acceptable alternative if there is no contraindication to the use of intravenous contrast. Positron emission tomography (PET) 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%, from the smallest measurable size during the study and new plasmacytomas must not have developed (see the disease response criteria in Table 13). 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.

9.7. Patient Reported Outcomes

It is anticipated that the addition of daratumumab will provide benefits in terms of symptom reduction, improved functioning, and improved utilities. To measure functional status, well-being, and symptoms, the EORTC QLQ-C30 and the EQ-5D-5L instruments will be used. Both questionnaires will be completed at the timepoints outlined in the Time and Events Schedule before any other study procedures scheduled for the same day.

The EORTC QLQ-C30 includes 30 items resulting in 5 functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), 1 Global Health Status scale, 3 symptom scales (fatigue, nausea and vomiting, and pain), and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). The recall period is 1 week (the past week). The EORTC QLQ-C30 has been widely used among cancer patients. Scores are transformed to a 0 to 100 scale. Administration time is approximately 11

minutes. Reliability, validity, and clinically meaningful change have been demonstrated in patients with multiple myeloma (Wisloff 1996[57], Wisloff 1997[58]). The focus of the PRO assessment will be the global health scale which is designated as a secondary endpoint. The remaining domains are included as exploratory endpoints.

The **EQ-5D-5L** is a generic measure of health status. For purposes of this study, the EQ-5D-5L will be used to generate utility scores for use in cost effective analyses. The EQ-5D-5L is a 5 item questionnaire that assesses 5 domains including mobility, self-care, usual activities, pain/discomfort and anxiety/depression plus a visual analog scale rating "health today" with anchors ranging from 0 (worst imaginable health state) to 100 (best imaginable health state) (Herdman 2011[22]). The scores for the 5 separate questions are categorical and are cannot be analyzed as cardinal numbers. However, the scores for the 5 dimensions are used to compute a single utility score ranging from zero (0.0) to 1 (1.0) representing the general health status of the individual.

9.8. Medical Resource Utilization

Medical resource utilization (MRU) data, principally number of hospitalizations and use of permitted therapies, will be derived from data reported in the eCRF for all subjects throughout the study. Hospitalization or prolongation of hospitalization related to Daratumumab administration reaction and/or SAE must to be reported in e-CRF.

10. SUBJECT COMPLETION/WITHDRAWAL

10.1. Completion

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

10.2. Discontinuation of Study Treatment

The Treatment Phase will be conducted in 2 parts and will extend from Cycle 1 Day 1 until treatment discontinuation due to progressive disease, unacceptable toxicity, ineligibility for second randomization, or 2 years of maintenance therapy/observation. The Follow-up Phase will extend from treatment discontinuation until death, loss to follow-up, withdrawal of consent, or study end, whichever occurs first.

If a subject's study treatment must be discontinued before the end of the treatment regimen, **this will <u>not</u> result in automatic withdrawal of the subject from the study.** After treatment discontinuation, the subject will move into the Follow-up Phase. Follow-up visit assessments should continue as specified in the Time and Events Schedule. 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.

A subject's study treatment must be discontinued if:

- The investigator believes that for safety reasons (eg, adverse event) it is in the best interest of the subject to discontinue study treatment
- The subject becomes pregnant
- The subject (or the subject's legally acceptable representative) withdraws consent for administration of study drug
- The subject initiates treatment with a prohibited medication (Section 8.3)
- The subject received concurrent (non-protocol) treatment for multiple myeloma
- The subject experiences unacceptable toxicity, including infusion-related reactions described in Section 6.1.4
- The subject's dose is held for more than 28 days (unless Sponsor approves continuation)
- The subject is not eligible for randomization to Part 2
- The subject experiences disease progression (please see below). Relapse from CR is not considered as disease progression

A subject who experiences a second primary malignancy, that can be treated by surgery alone may continue to receive the assigned study treatment and should continue to be followed for subsequent progression of multiple myeloma.

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

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

10.3. Withdrawal From the Study

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

- Lost to follow-up
- Withdrawal of consent for study participation
- Death
- Sponsor terminates the study
- Screening failure

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 consent for study participation before completing the study, the reason for withdrawal is to be documented in the eCRF 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.

Withdrawal From the Use of Samples in Future Research

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

11. STATISTICAL METHODS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined in this section.

11.1. Subject Information

Analysis of primary and secondary efficacy variables will be based on the intent-to-treat (ITT) population, which includes all subjects randomized in the first randomization. In addition, maintenance-specific analyses will use the maintenance-specific intent-to-treat population (ITT-m), which will include all subjects who are randomized in the second randomization.

All safety analyses will be based on the safety analysis set. The safety population will be defined separately for the induction/ASCT/consolidation and maintenance stages. These populations will include all subjects randomized at each stage who received at least 1 dose of study drugs at the respective stage.

11.2. Sample Size Determination

The sample size of this study takes into consideration the statistical power for the primary comparisons in both stages of the study. For Part 2 (maintenance phase), it is assumed that median PFS from the second randomization is 45 months for observation, and daratumumab maintenance will decrease the risk of progression or death by 25% (HR=0.75; estimated median PFS of 60 months for daratumumab maintenance). To achieve 80% power with a significance level of 0.05, 390 PFS events are needed. Assuming a 36 months accrual and 45 months of additional follow-up, approximately 800 subjects (400/arm) will be randomized in the second randomization (daratumumab maintenance vs. observation).

Assuming that 75% of subjects in the induction/ASCT/consolidation stage are eligible to be randomized for maintenance, which takes into account the expected response rate as well as potential dropouts, 1080 subjects (540/arm) will be randomized in the first randomization (daratumumab in combination with VTD induction/ASCT/VTD consolidation vs. VTD induction/ASCT/VTD consolidation). This sample size would provide at least over 85% power to detect an improvement in sCR rate from 25% to 35% at a 2-sided α of 0.05.

11.3. Efficacy Analyses

The study is designed to evaluate daratumumab treatment at 2 stages of first-line treatment, one concerning daratumumab in combination with VTD (D-VTD) as induction/consolidation, the other daratumumab maintenance, in ASCT-eligible myeloma subjects. Therefore, a separate Type I error rate (alpha) will be assigned at the level of 0.05 for each of the 2 distinct hypotheses of interest (induction/ASCT/consolidation, maintenance).

11.3.1. Endpoints

Part 1: Induction/ASCT/Consolidation Phase

Primary Endpoint

Stringent Complete Response (sCR), by end of consolidation therapy, defined as the percentage of subjects achieving CR in addition to having a normal serum FLC ratio and an absence of clonal cells in bone marrow by immunohistochemistry, immunofluorescence or 2- to 4-color flow cytometry. Subjects who demonstrate all criteria for sCR, but have confirmed daratumumab interference on SPEP and IFE, will be considered sCR.

Major Secondary Endpoints

- PFS (from first randomization), defined as time from the initial randomization to either confirmed progressive disease (PD) per the IMWG criteria or death, whichever comes first. It is noted that the PFS events (PD or death) may include those that occur in the maintenance phase.
- Time to progression (TTP) (from first randomization), defined as time from the initial randomization to confirmed progressive disease (PD) per the IMWG criteria, or death due to progressive disease, whichever occurs first. It is noted that the events (PD or death due to PD) may include those that occur in the maintenance phase.
- Post-ASCT/ consolidation CR rate, defined as the proportion of subjects who have achieved CR or better by the end of consolidation per the IMWG criteria.
- Post-ASCT/consolidation MRD negative rate, defined as the proportion of subjects who have achieved MRD negative status by the end of consolidation per the IMWG criteria.
- Post-induction sCR rate, defined as the proportion of subjects who have achieved sCR prior to high-dose therapy/ASCT per the IMWG criteria.
- PFS2 (from first randomization), defined as the time from initial randomization to time of subsequent progression on next line of therapy after disease progression on study treatment.
- OS (from first randomization), measured from the date of initial randomization to the date of the subject's death. If the subject is alive or the vital status is unknown, then the subject's data will be censored at the date the subject was last known to be alive.

Other Secondary Endpoints

- Post-induction overall response rate (ORR) and rate of VGPR or better, defined as the proportions of subjects who have achieved PR or better by the end of induction per the IMWG criteria.
- Duration of CR and sCR will be calculated from the date of the initial documentation of a CR or sCR to the date of the first documented evidence of relapse of CR or disease progression, as defined in the IMWG criteria, whichever occurs first. For subjects who have not relapsed nor progressed, data will be censored at the last disease evaluation.
- Impact of D-VTD compared to VTD on patient-reported perception of global health

Part 2: Maintenance Phase

Primary Endpoint

Progression Free Survival (PFS) post completion of maintenance therapy, defined as the duration from the date of re-randomization to either progressive disease, according to the IMWG criteria, or death, whichever occurs first.

Major Secondary Endpoints

- TTP (from second randomization), defined as time from the second randomization to confirmed progressive disease (PD) per the IMWG criteria, or death due to progressive disease, whichever occurs first.
- Overall CR rate, defined as the proportion of subjects who have achieved CR or better during the study per the IMWG criteria.
- Overall MRD negative rate, defined as the proportion of subjects who have achieved MRD negative status by the end of study.
- PFS2 (from second randomization), defined as the time from the second randomization to time of subsequent progression on next line of therapy after disease progression on study treatment.
- OS (from second randomization), defined as the time from the second randomization to the date of death.

Other Secondary Endpoints

- Rate of improved response during maintenance, defined as the proportion of subjects who have achieved a better category of response during maintenance compared to the response status at the end of consolidation (up to the second randomization). This is to be evaluated among the group of subjects who not achieved sCR by the second randomization.
- Rate of MRD negative conversion during maintenance, defined as the proportion of subjects who have achieved de novo MRD negative status during maintenance.
- ORR rate, defined as the proportion of subjects who have achieved PR or better by the end of study.

11.3.2. Efficacy Analysis for Induction/ASCT/Consolidation Phase

The primary comparison of the 2 randomized induction/consolidation treatments will be made with respect to sCR rate using the Cochran-Mantel-Haenszel chi square test in the ITT population. A Mantel-Haenszel odds ratio, along with its 2-sided 95% confidence interval, will be calculated. All binary secondary endpoints for the induction/ASCT/consolidation stage will be analyzed similarly as the primary endpoint (sCR rate).

The statistical comparison between the 2 induction regimens with respect to PFS from the first randomization will need to take into consideration subsequent maintenance assignment (daratumumab maintenance or observation). A usual “as-randomized”-type of intent-to-treat

analysis that compares the 2 induction treatments with respect to PFS without considering maintenance treatment has been shown to produce potentially biased estimates of treatment effects. As such, 2 appropriate intent-to-treat (ITT)-type of induction comparisons of particular interest, 1 specific to each maintenance treatment (daratumumab maintenance or observation), will be conducted:

- daratumumab+VTD (D-VTD) induction/consolidation followed by daratumumab maintenance vs. VTD induction/consolidation followed by daratumumab maintenance, and
- daratumumab+VTD (D-VTD) induction/consolidation followed by observation vs. VTD induction/consolidation followed by observation

For each of the 2 comparisons, the analysis will include any subjects who are randomized in the first randomization and are then subsequently randomized to the specific maintenance treatment as well as those subjects who are randomized in the first randomization but are not randomized in the second randomization. A stratified Cox regression analysis with inverse probability weighting will be performed (Lokhnygina 2007[30]), which yields unbiased estimates of treatment effects and maintains Type I error rate. The overall comparison of induction treatments will be made treating these 2 comparisons as 2 strata with the variance estimated using the robust variance estimator (the sandwich estimate). These 3 comparisons will all be tested with the significance level of 0.05 (2-sided) following the closed testing procedure. Essentially, the statistical significance is established for each of the 2 maintenance-specific comparisons if both itself and the overall induction comparison are significant at the 2-sided level of 0.05. Other time-to-event endpoints, except for duration of response, will be analyzed similarly. Duration of response will be presented descriptively using the weighted Kaplan-Meier estimates by Miyahara and Wahed 2010[36].

11.3.3. Efficacy Analysis for Maintenance Phase

The primary comparison of the 2 randomized maintenance treatments (daratumumab maintenance and observation) will be made with respect to PFS from the second randomization using a stratified log-rank test in the ITT-m population. The Kaplan-Meier method will be used to estimate the distribution of PFS from the second randomization for each treatment. The treatment effect (hazard ratio) and its 2-sided 95% confidence intervals are to be estimated using a stratified Cox regression model with maintenance treatment as the sole explanatory variable. In addition, the interaction between induction/consolidation and maintenance will be tested at a 2-sided significance level of 0.05 by a stratified Cox regression model that includes the interaction term between maintenance treatment and induction/consolidation treatment. All secondary time-to-event endpoints in the maintenance stage will be analyzed similarly as for the primary endpoint (PFS from the second randomization).

The comparison of the 2 randomized maintenance arms on binary secondary endpoints will be made using the Cochran-Mantel-Haenszel chi square test in the population of all subjects that are randomized in the second randomization. The observed rate of the binary outcome will be provided along its 2-sided 95% CIs. A Mantel-Haenszel odds ratio, along with its 2-sided 95% confidence interval, will be calculated.

11.3.4. Other Efficacy Analyses

The 2-stage randomization design of this study allows comparison of all 4 sequences of induction/ASCT/consolidation and maintenance treatments:

- D-VTD induction/consolidation followed by daratumumab maintenance
- D-VTD induction/consolidation followed by observation
- VTD induction/consolidation followed by daratumumab maintenance
- VTD induction/consolidation followed by observation

The distribution of PFS, TTP, and OS for these 4 sequences will be estimated using the weighted Kaplan-Meier estimates [Miyahara and Wahed 2010[36]]. Pairwise comparisons of these 4 comparisons will be made by a stratified Cox regression analysis with inverse probability weighting (Lokhnygina 2007[30]), except for the 2 pairwise comparisons: D-VTD followed by daratumumab maintenance vs. D-VTD followed by observation, and VTD followed by daratumumab maintenance vs. VTD followed by observation, which reduces to the 2 maintenance comparisons specific to a particular induction regimen.

11.4. Daratumumab Immunogenicity Analyses

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

11.5. Biomarker Analysis

Biomarker studies are designed to identify markers predictive of response (or resistance) to daratumumab. Analyses will be performed and stratified by clinical covariates or molecular subgroups using the appropriate statistical methods (eg, parametric or non-parametric, univariate or multivariate, analysis of variance, or survival analysis, depending on the endpoint). Correlation of baseline expression levels or changes in expression levels with response or time to-event endpoints will identify responsive (or resistant) subgroups in addition to genes and pathways attenuated following treatment with daratumumab. In order to remove any confounding influence of prognostic factors, any predictive biomarker identified in this study could be verified in a prospective clinical study with a control treatment arm.

Any biomarker measures will be listed, tabulated, and where appropriate, plotted. Subjects will be grouped by prescribed dose. Complete responders will be utilized to investigate the prognostic effect of MRD on PFS. MRD analysis will include evaluation of data from other studies to determine if decreased MRD is seen with daratumumab + bortezomib based chemotherapy regimen compared with the bortezomib based chemotherapy alone.

Results of biomarker and pharmacodynamic analyses may be presented in a separate report. Planned analyses are based on the availability of clinically valid assays and may be deferred if emerging study data show no likelihood of providing useful scientific information.

In addition, due to the small sample sizes of high-risk subgroups within the multiple myeloma patient population, a meta-analyses may be performed across daratumumab Phase 3 studies to evaluate clinical efficacy of daratumumab with standard of care agents in pre-specified subgroups of multiple myeloma patients. The meta-analysis protocol will pre-specify the objective of the meta-analysis, the criteria for inclusion and exclusion of studies, the hypotheses and endpoints, and statistical methods including a method for investigation of heterogeneity. This meta-analytic approach, supported by high-quality data from the individual trials, should be able to provide definitive evidence on the effectiveness of daratumumab in the subpopulation of multiple myeloma subjects with high-risk molecular abnormalities. In a similar fashion, a meta-analysis examining MRD negativity in daratumumab treated patients in frontline, newly diagnosed multiple myeloma (MMY3006, MMY3007, and MMY3008 studies) may also be performed.

11.6. Patient Reported Outcomes

EORTC QLQ-C30 domain scores will be summarized at each time point as indicated in the Time and Events Schedule. The relationship between clinical response and change in domain scores will be explored. EQ-5D-5L scores will be summarized at each time point.

11.7. Safety Analyses

Safety analyses will be conducted after 100 subjects have completed consolidation therapy and at 6 monthly intervals under the direction of the independent monitoring committee (IDMC) until the unblinding of data.

Adverse Events

The verbatim terms used in the eCRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). In general, adverse events that occurred during the induction/consolidation and maintenance stages will be summarized separately. Treatment-emergent adverse events for each stage will be defined as events that occur or worsen after administration of the first dose of during that stage and through 30 days after the last dose of study drug in that stage and before the next phase of treatment begins. Adverse events will be summarized by system organ class and preferred terms, NCI toxicity grade, and by action taken with study treatment.

Summaries, listings, datasets, or subject narratives will 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 will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point. Changes from baseline results will be presented in pre- versus post treatment cross-tabulations (with classes for below, within, and above normal ranges). Worst toxicity grade during treatment presented, according to NCI CTCAE Version 4. 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.

Vital Signs

Descriptive statistics of pulse, temperature, 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.

Descriptive statistics for electrocardiogram data 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.

11.8. Interim Analysis

Two primary analyses are planned, one for each stage. The first primary analysis is specific to the induction/ASCT/consolidation stage, and its main purpose is to evaluate the effectiveness of the 2 induction/consolidation treatments with respect to the stringent complete response (sCR) rate, which will be performed after all subjects have completed the induction/ASCT/consolidation treatment phase. No interim analysis is planned for Part 1.

The second primary analysis is specific to the maintenance stage, and its main purpose is evaluate the 2 maintenance arms with response for PFS, which will be performed when approximately 390 PFS events have been observed in the population of subjects who are re-randomized in the maintenance stage. An interim analysis is planned for the maintenance stage after 273 (70%) PFS events are observed in the population of subjects who are re-randomized. The significance level at this interim analysis will be determined based on the observed number of PFS events at the time of the analysis, using the O'Brien-Fleming boundaries as implemented by the Lan-DeMets alpha spending method. Assuming 273 PFS events are observed, the alpha to be spent in this interim analysis will be 0.0147 (2-sided) and will be 0.0455 (2-sided) for the final analyses. In case the Interim analysis for PFS meets the pre-defined boundary this interim analysis reflects the primary analysis for PFS. No PFS analysis at 390 PFS events will be done.

11.9. Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will be formed to review data including those from interim analyses of overall safety. The IDMC members will be independent of the trial and familiar with the methodology of hematological oncology trials. The IDMC will include a fixed number of permanent members with experience of clinical studies in hematological oncology including at least one statistician. They must be aware of the implications of the conclusions based on immature data and agree with the design and objectives of this protocol.

The first IDMC meeting will take place after the first 100 subjects have completed consolidation therapy (first safety analysis) and subsequently approximately every six months - either face-to-face or via teleconference – to review accrual, study conduct (including treatment withdrawals), patient safety (adverse events presented according to assigned treatment), and disease-related event until the unblinding of data. In addition, the IDMC will evaluate efficacy and toxicity of the

peripheral stem cell mobilization. This will include data concerning stem cell yield and whether any additional agents were required for peripheral stem cell mobilization (for example plerixifor).

Relevant safety data for review by the IDMC will include:

- AEs (NCI-CTC AE version 4.0) and SAEs
- AEs requiring dose reduction or modification
- AEs associated with stem cell mobilization.

After each meeting, the IDMC will provide the Study Steering Committee with its recommendation. At the part 2 interim analysis, the primary endpoint was met, and the study data was unblinded. No new safety signals were observed. No further IDMC meetings will be scheduled. Safety data will be reviewed by regular Pharmacovigilance aggregate data review.

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 sponsors and are mandated by regulatory agencies worldwide. The sponsor and Janssen have established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor, Janssen, or their 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 interventions and/or 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 12.3.1 for time of last adverse event recording).

Serious Adverse Event

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

- Results in death

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

* Overnight stays at the hospital because of slow infusion times should not be reported as a serious adverse event

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

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

Unlisted (Unexpected) Adverse Event/Reference Safety Information

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

Adverse Event Associated With the Use of the Drug

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

An IRR is defined as any adverse event (AE) occurring during or within the 24 hours after the daratumumab infusion and assessed as related to daratumumab infusion.

12.1.2. Attribution Definitions

Not Related

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

Doubtful

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

Possible

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

Probable

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

Very Likely

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

12.1.3. Severity Criteria

The severity assessment for an adverse event or serious adverse event should be completed using the NCI CTCAE Version 4. Any adverse event or serious adverse event not listed in the NCI CTCAE Version 4 will be graded according to investigator clinical judgment by using the standard grades as follows:

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

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

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

Grade 4: Life-threatening of disabling adverse event

Grade 5: Death related to the adverse event

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

12.2. Special Reporting Situations

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

- Overdose of study drug. No MTD has been reached for daratumumab. However, if the dose exceeds the maximum tested dose of 24 mg/kg, then it will be considered as overdose in this study.
- Suspected abuse/misuse of a study drug
- Inadvertent or accidental exposure to study drug
- Medication error involving daratumumab (with or without subject/patient exposure to daratumumab, eg, name confusion)
- Any adverse event leading to treatment discontinuation and assessed as related to Daratumumab or any part of the VTD backbone regimen.
- All events of secondary malignancies will be notified to sponsor as SAE. These events will be followed and reported to the sponsor throughout the study (including the Follow up phase).

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

12.3. Procedures

12.3.1. All Adverse Events

All adverse events and special reporting situations, whether serious or non-serious, must be reported from the time a signed and dated ICF is obtained until 30 days after the last dose of any component of the treatment regimen, until the subject withdraws consent for study participation, or until the subject starts subsequent anticancer therapy. However, for subjects randomized to Arm A (observation) in the Maintenance Phase, adverse events will continue to be collected for 2 years after the second randomization, or upon disease progression, withdrawal of consent, death or start of new anticancer therapy (whichever occurs first in the Maintenance Phase), even though no study drug is being administered. The only exception is for subjects who have withdrawn informed consent for study participation or for subjects who have received additional treatment with therapeutic intent for multiple myeloma within 30 days after the last dose of any component of the treatment regimen.

For subjects who have received additional treatment with therapeutic intent for multiple myeloma during the adverse event reporting period, only adverse events that are considered to be possibly, probably, or definitely related to study drug (Daratumumab) or any part of the VTD backbone treatment regimen must be reported (unless the subject has been withdrawn from the study).

Serious adverse events, including those spontaneously reported to the investigator within 30 days of the last dose of any component of the treatment regimen, and those that are considered related to daratumumab occurring within the Follow-up Phase, must be reported using the Serious Adverse Event Form. The sponsor and Janssen will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Adverse Events, Serious Adverse Event, including pregnancy, will be followed by the investigator.

Disease progression should not be recorded as an adverse event or serious adverse event term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the serious adverse event definition (refer to Section 12.1.1). Death should not be recorded as an adverse event or serious adverse event, but as the outcome of an adverse event. The event that resulted in the death should be reported as a serious adverse event. During the mobilization and stem cell transplantation procedures, AEs related to the planned procedures need to be reported as AEs; any toxicity related to daratumumab exposure should be reported.

During the transplant period (that is to say the period from the first day of ASCT hospitalization to the day before C5D1), neutropenia and thrombocytopenia resulting from bone marrow aplasia will not be recorded as AEs in the eCRF.

Only the following have to be recorded in the eCRF:
✓ any evolution of ongoing AE
✓ any new AE related, or that appears to be related, to Daratumumab
✓ any new infection from at least grade 3
✓ any new oral mucositis from at least grade 3.

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

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

Subjects (or their designees, if appropriate) 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:

- Subject's name
- Study number

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

12.3.2. Serious Adverse Events

All serious adverse events occurring during the study must be reported to the appropriate sponsor's 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 and Janssen pharmacovigilance using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site, and transmitted to the appropriate sponsor's delegated contact person within 24 hours. The initial and follow-up reports of a serious adverse event should be made by facsimile (fax) and or e-Mail. The appropriate sponsor's delegated contact person will review the SAE reports for completeness and accuracy before sending to Janssen Pharmacovigilance team within 24 hours from reception.

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; elective procedures for a condition unrelated to multiple myeloma, respite care)
- Surgery or procedure planned before entry into the study (must be documented in the eCRF). Note: Hospitalizations that were planned before the signing of the ICF; or hospitalizations due to planned mobilization and transplant, and where the underlying

condition for which the hospitalization was planned has not worsened, will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.

12.3.3. Pregnancy

All initial reports of pregnancy must be reported to the appropriate sponsor's contact person by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. The appropriate sponsor's delegated contact person will review the pregnancy reports for completeness and accuracy before sending to Janssen Pharmacovigilance team within 24 hours from reception. Abnormal pregnancy outcomes (eg, spontaneous abortion, stillbirth, and congenital anomaly) are considered serious adverse events and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must discontinue further study treatment and promptly be withdrawn from the study. The subject should be referred to a physician experienced in teratology for evaluation and advice. Investigators should follow the local label for guidance on subject education and ensure that all subjects adhere to the thalidomide pregnancy prevention program. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

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

12.4. Contacting Sponsor

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

13. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, i.e., any dissatisfaction relative to the identity, quality, durability, or reliability of the study drug, 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. Janssen, the manufacturer of daratumumab, 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 Janssen 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, then the study-site personnel must report the PQC to Janssen according to the serious adverse event reporting timelines (refer to Section 12.3.2). A sample of the suspected product should be maintained for further investigation if requested by Janssen.

13.2. Contacting Janssen Regarding Product Quality

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

14. DARATUMUMAB INFORMATION

14.1. Physical Description of Daratumumab

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

14.2. Packaging

Daratumumab will be supplied to the site/pharmacy in glass vials containing daratumumab at a concentration of 20 mg/mL.

14.3. Labeling

Daratumumab 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

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

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

14.5. Drug Accountability

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

Daratumumab 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 daratumumab must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to Janssen of unused daratumumab will be documented on the IP destruction form. When the study site is an authorized destruction unit and daratumumab supplies are destroyed on-site, this must also be documented on the IP

destruction 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.

Daratumumab should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Daratumumab will be supplied only to subjects participating in the study. Returned daratumumab must not be dispensed again, even to the same subject. Daratumumab may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the daratumumab 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:

- Study Protocol
- Investigator's Brochure
- Investigational Product Manual
- Laboratory Manual
- Electronic data capture (eDC) Manual
- Sample ICF
- Subject diary for recording of post infusion medications self-administered at home

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

The primary safety profile of daratumumab is consistent with infusion-related reactions. 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.

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. Note

that as specified in Section 16.2.3, a legally acceptable representative may provide consent on behalf of the subject.

The total blood volume for the study is estimated at approximately 50 mL during screening, 400 mL in Part 1 (Induction/ASCT/Consolidation Phase), and approximately 500 mL in Part 2 (2-year Maintenance Phase). The total blood volume to be collected is considered to be acceptable for subjects participating in a cancer clinical study and reasonable 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/sponsor representative where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

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

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

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

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

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

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

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

16.2.3. Informed Consent

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

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

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

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

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

16.2.4. Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study. These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

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

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

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

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

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

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

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Subjects may withdraw their consent for their samples to be stored for research (refer to Section 10.3).

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

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

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

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

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

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

17.2.2. Required Prestudy Documentation

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

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

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

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

- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

17.3. Subject Identification, Enrollment, and Screening Logs

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

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

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

17.4. Source Documentation

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

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

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

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

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

17.5. Case Report Form Completion

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

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

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

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

All eCRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel. If necessary, queries will be generated in the eDC tool.

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

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

17.6. Data Quality Assurance/Quality Control

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

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

17.7. Record Retention

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

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

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

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

If it becomes necessary for the sponsor, Janssen 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

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

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

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

The study is considered completed 5 years after the last subject is randomized in Part 2 for the maintenance phase, or 350 subjects have died, whichever occurs first.

17.9.2. Study Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed. The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

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

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

17.10. On-Site Audits

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

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

17.11. Use of Information and Publication

All information, including but not limited to information regarding daratumumab or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not

previously published, and any data, including exploratory biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

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

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

or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of Clinical Studies and Disclosure of Results

Where appropriate the study sponsor or Janssen LLC on behalf of the sponsor will register and disclose the existence of and the results of clinical studies as required by law.

REFERENCES

1. Attal M, Harousseau JL, Stoppa AM, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Francais du Myelome. N Engl J Med. 1996;335:91-97.
2. Attal M, Harousseau JL, Marit G, et al. Lenalidomide after autologous transplantation for myeloma: first analysis of a prospective, randomized study of the Intergroupe Francophone Du Myelome (IFM 2005 02). Blood (ASH Annual Meeting Abstracts). 2009;114:Abstract 529.
3. Attal M, Lauwers-Cances V, Marit G. Lenalidomide Maintenance after Stem-Cell Transplantation for Multiple Myeloma. N Engl J Med. 2012; 366:1782-91.
4. Blade J, Esteve J, Rives S, et al. High-dose therapy autotransplantation/intensification vs continued standard chemotherapy in multiple myeloma in first remission. Results of a non-randomized study from a single institution. Bone Marrow Transplantation 2000;26:845-849.
5. Burtis CA, Ashwood ER. Tietz textbook of clinical chemistry, 3rd ed. Philadelphia; WB Saunders, 1998.
6. Cavo M, Pantani L, Petrucci MT, et al. Bortezomib-thalidomide-dexamethasone is superior to thalidomide-dexamethasone as consolidation therapy after autologous hematopoietic stem cell transplantation in patients with newly diagnosed multiple myeloma. Blood. 2012;120(1):9-19.
7. Cavo M, Tacchetti P, Patriarca F, et al. Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study. Lancet. 2010;376:2075-2085.
8. Chanan-Khan AA and Giralt S. Importance of achieving a complete response in multiple myeloma, and the impact of novel agents. J Clin Oncol 2010;28:2612-2624.
9. Chapuy, C, Nicholson R, Aguad MD, et al. Resolving the daratumumab interference with blood compatibility testing. Transfusion. 2015; 55:1545-1554.
10. Child JA, Morgan GJ, Davies FE, et al. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. N Engl J Med. 2003;348:1875-1883.
11. de Weers M, Tai YT, van der Veer MS, Bakker JM, Vink T, Jacobs DC, et al. Daratumumab, a novel therapeutic human CD38 monoclonal antibody, induces killing of multiple myeloma and other hematological tumors. J Immunol. 2011;186(3):1840-1848.
12. Dimopoulos MA, Richardson PG, Schlag R, et al. VMP (Bortezomib, Melphalan, and Prednisone) Is Active and Well Tolerated in Newly Diagnosed Patients With Multiple Myeloma With Moderately Impaired Renal Function, and Results in Reversal of Renal Impairment: Cohort Analysis of the Phase III VISTA Study. J Clin Oncol. 2009;27(38):6086-6093.
13. Durie BG, Harousseau JL, Miguel JS, et al. International uniform response criteria for multiple myeloma. Leukemia. 2006;20:1467–73. Corrigenda/Erratum in: Leukemia. 2007;21:1134-1135.
14. Engelhardt M, Terpos E, Kleber M, et al. European Myeloma Network recommendations on the evaluation and treatment of newly diagnosed patients with multiple myeloma. Haematologica 2014;99(2):232-242.
15. Gay F, Larocca A, Wijermans P, et al. Complete response correlates with long-term progression-free and overall survival in elderly myeloma treated with novel agents: analysis of 1175 patients. Blood 2011;117:3025-3031.
16. Giralt S, Stadtmauer EA, Harousseau JL, et al. International myeloma working group (IMWG) consensus statement and guidelines regarding the current status of stem cell collection and high-dose therapy for multiple myeloma and the role of perixfor (AMD 3100). Leukemia 2009;23(10):1904-1912.
17. Harousseau J-L, Attal M, and Avet-Loiseau H. The role of complete response in multiple myeloma. Blood 2009;114:3139-3146.
18. Harousseau J-L and Moreau P. Autologous Hematopoietic Stem-Cell Transplantation for Multiple Myeloma. N Engl J Med 2009;360:2645-54.

19. Harousseau J-L, Palumbo A, Richardson PG, et al. Superior outcomes associated with complete response in newly diagnosed multiple myeloma patients treated with non-intensive therapy; analysis of the Phase 3 VISTA study of bortezomib plus melphalan-prednisone versus melphalan-prednisone. Blood. 2010c;116(19):3743-50.

20. Harousseau JL, Attal M, Avet-Loiseau H, et al. Bortezomib Plus Dexamethasone Is Superior to Vincristine Plus Doxorubicin Plus Dexamethasone As Induction Treatment Prior to Autologous Stem-Cell Transplantation in Newly Diagnosed Multiple Myeloma: Results of the IFM 2005-01 Phase III Trial. J Clin Oncol.2010b; 28:4621-4629.

21. Harousseau JL, Moreau P. Autologous hematopoietic stem-cell transplantation for multiple myeloma. N Engl J Med. 2009;360:2645–2654.

22. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of the EQ-5D (EQ-5D-5L). Qual Lif Res. 2011;20:1727-1736.

23. Kapoor P, Kumar SK, Dispenzieri A, et al. Importance of Achieving Stringent Complete Response After Autologous Stem-Cell Transplantation in Multiple Myeloma. J Clin Oncol 2013;31:4529-4535.

24. Kumar S, Flinn I, Richardson PG, et al. Randomized, multicenter, Phase 2 study (EVOLUTION) of combinations of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide in previously untreated multiple myeloma. Blood. 2012b; 119:4375-4382.

25. Kyle RA, Gertz MA, Witzig TE, et al. Review of 1027 patients with newly diagnosed multiple myeloma. Mayo Clin Proc. 2003;78(1):21-33.

26. Kyle RA, Remstein ED, Therneau TM, et al. Clinical course and prognosis of smoldering (asymptomatic) multiple myeloma. N Engl J Med. 2007;356(25):2582-2590.

27. Ladetto M, Pagliano G, Ferrero S. Major Tumor Shrinking and Persistent Molecular Remissions After Consolidation With Bortezomib, Thalidomide, and Dexamethasone in Patients With Autografted Myeloma. J Clin Oncol. 2010; 28(12): 2077-84.

28. Lahuerta JJ, Mateos MV, Martinez-Lopez J, et al. Influence of pre- and post-transplantation responses on outcome of patients with multiple myeloma: sequential improvement of response and achievement of complete response are associated with longer survival. J Clin Oncol 2008;26:5575-5782.

29. Leleu X, Fouquet G, Hebraud B, et al. Consolidation with VTd significantly improves the complete remission rate and time to progression following VTd induction and single autologous stem cell transplantation in multiple myeloma. Leukemia 2013;27:2242-2244.

30. Lokhnygina Y, Helterbrand JD. Cox regression methods for two-stage randomization designs. Biometrics 2007; 63: 422-428.

31. Ludwig H, Durie BM, McCarthy P, et al. IMWG consensus on maintenance therapy in multiple myeloma. Bloo 2012;119:3003-3015.

32. McCarthy PL, Kouros O, Hofmeister CC. Lenalidomide after Stem-Cell Transplantation for Multiple Myeloma. N Engl J Med. 2012; 366: 1770-1781.

33. McCudden 2010 McElwain TJ, Powles RL. High-dose intravenous Melphalan for plasma-cell leukaemia and myeloma.Lancet 1983; 2(8354): 822-824.

34. McElwain TJ, Powles RL. High-dose intravenous Melphalan for plasma-cell leukaemia and myeloma.Lancet 2(8354): 822-824, 1983

35. Mellqvist U-H, Westin J, Gimsing P, et al. Improved Response Rate with Bortezomib Consolidation after High Dose Melphalan: First Results of a Nordic Myeloma Study Group Randomized Phase III Trial. Blood (ASH Annual Meeting Abstracts). 2009. 114: Abstract 530.

36. Miyahara S and Wahed AS. Weighted Kaplan-Meier estimators for two-stage treatment regimes. Stat Methods 2010;10:2581-91.

37. Moreau P, Avet-Loiseau H, Facon T, et al. Bortezomib plus dexamethasone versus reduced-dose bortezomib, thalidomide plus dexamethasone as induction treatment before autologous stem cell transplantation in newly diagnosed multiple myeloma. Blood. 2011b; 118(22): 5752-58.

38. Moreau P, San Miguel J, Ludwig H, et al. Multiple myeloma: ESMO clinical practice guidelines for diagnosis, treatment, and follow-up. Annals of Oncol 2013;24(Supplement 6):vi133-vi137.

39. Morgan GJ, Walter MG, Faith ED. The role of maintenance thalidomide therapy in multiple myeloma: MRC Myeloma IX results and meta-analysis. Blood. 2012;119(1):7-15.

40. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Multiple Myeloma, version 2.2013. Fort Washington, PA: National Comprehensive Cancer Network.

41. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649-655.

42. Overdijk MB, Verploegen S, Bogels M, et al. Phagocytosis is a potent mechanism of action for the therapeutic human monoclonal antibody daratumumab in lymphoma and multiple myeloma. Submitted to Blood. 13 May 2013.

43. Paiva B, Martinez-Lopez J, Vidriales M-B, et al. Comparison of immunofixation, serum free light chain, and immunophenotyping for response evaluation and prognostication in multiple myeloma. J Clin Oncol 2011;29:1627-1633.

44. Palumbo A, Facon T, Sonneveld P, et al. Thalidomide for treatment of multiple myeloma: 10 Years later. Blood. 2008c;111(8):3968-3977.

45. Palumbo A, Anderson K. Multiple myeloma. N Engl J Med. 2011;364(11):1046-1060.

46. Palumbo A, Sezer O, Kyle R, et al. International Myeloma Working Group guidelines for the management of multiple myeloma patients ineligible for standard high-dose chemotherapy with autologous stem cell transplantation. Leukemia; 2009:23:1716-1730.

47. Rajkumar SV, Harousseau J-L, Durie B, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. Blood. 2011; 114:4691-4695.

48. Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol. 2014;15:e538-e548.

49. Rawstron AC, Child JA, de Tute RM, et al. Minimal residual disease assessed by multiparameter flow cytometry in multiple myeloma: impact on outcome in the Medical Research Council Myeloma IX Study. J Clin Oncol. 2013;31(20):2540-7, doi: 10.1200/JCO.2012.46.2119.

50. Reeder CB, Reece DE, Kukreti V, et al. Cyclophosphamide, bortezomib and dexamethasone induction for newly diagnosed multiple myeloma: high response rates in a Phase II clinical trial. Leukemia. 2009;23:1337-1341.

51. Rosiñol L, Oriol A, Teruel AI, et al. Superiority of bortezomib, thalidomide, and dexamethasone (VTD) as induction pretransplantation therapy in multiple myeloma: a randomized phase 3 PETHEMA/GEM study. Blood. 2012;120(8);1589-1596.

52. Sarasquete ME, Garcia-Sanz R, Gonzalez D, et al. Minimal residual disease monitoring in multiple myeloma: a comparison between allelic-specific oligonucleotide real-time quantitative polymerase chain reaction and flow cytometry. Haematologica 2005;90:1365-1372.

53. Smith A, Wisloff F, Samson D. Guidelines on the diagnosis and management of multiple myeloma 2005. Br J Haematol. 2005;132:410-451.

54. Sonneveld P, Goldschmidt LR, Blade J, et al. Bortezomib-Based Versus Non-bortezomib-Based Induction Treatment Before Autologous Stem-Cell Transplantation in Patients With Previously Untreated Multiple Myeloma: A Meta-Analysis of Phase III Randomized, Controlled Trials. J Clin Oncol. 2013. Epub ahead of print. 10.1200/JCO.2012.48.4626.

55. Terragna C, Zamagni E, Petrucci MT, et al. Molecular remission after bortezomib-thalidomide dexamethasone compared with thalidomide dexamethasone as consolidation therapy after double autologous transplantation for multiple myeloma: results of a qualitative and quantitative analysis. Blood. (ASH Annual Meeting Abstracts). 2010;116:Abstract 861.

56. Van de Velde H, Liu X, Chen G, et al. Complete response correlates with long-term survival and progression-free survival in high-dose therapy in multiple myeloma. Hematologica 2007;92:1399-1406.

57. van der Veer M, de Weers M, van Kessel B. Towards effective immunotherapy of myeloma: enhanced elimination of myeloma cells by combination of lenalidomide with the human CD38 monoclonal antibody daratumumab. Haematol. 2011b:96(2):284-290.

58. Wisloff F, Eika S, Hippe E, et al. Measurement of health-related quality of life in multiple myeloma. Nordic Myeloma Study Group. Br J Haematol. 1996;92:604-613.

59. Wisloff F, Hjorth M. Health-related quality of life assessed before and during chemotherapy predicts for survival in multiple myeloma. Nordic Myeloma Study Group. Br J Haematol .1997;97:29-37.

ATTACHMENT 1: DIAGNOSTIC CRITERIA FOR MULTIPLE MYELOMA

Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma[1] AND any one or more of the following myeloma defining events:

Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:

- Hypercalcemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than ULN or >2.75 mmol/L (>11 mg/dL)
- Renal insufficiency: creatinine clearance[2] <40mL/min or serum creatinine >177 μmol/L (>2 mg/dL)
- Anemia: hemoglobin >2 g/dL below the lower limit of normal or hemoglobin <10 g/dL
- Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT[3]

Any one or more of the following biomarkers of malignancy:

- Clonal bone marrow plasma cell percentage[1] ≥60%
- Involved: uninvolved serum free light chain ratio[4] ≥100
- >1 focal lesion[5] on MRI studies

Footnotes:

1. Clonality should be established by showing κ/λ light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and the core biopsy, the highest value should be used.
2. Measured or estimated by validated equations.
3. 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.
4. These values are based on the serum Freelite assay (The Binding Site Group, Birmingham UK). The involved free light chain must be ≥100mg/L.
5. Each focal lesion must be 5mm or more in size.

Reference: Rajkumar 2014.

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 1982[41]

ATTACHMENT 3: CALCULATED CREATININE CLEARANCE (COCKCROFT & GAULT FORMULA)

$$eC_{Cr} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times [0.85 \; if \; Female]}{72 \times \text{Serum Creatinine (in mg/dL)}}$$

When serum creatinine is measured in µmol/L:

$$eC_{Cr} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times Constant}{\text{Serum Creatinine (in } \mu\text{mol/L)}}$$

Where *Constant* is *1.23* for men and *1.04* for women.

ATTACHMENT 4: SERUM CALCIUM CORRECTED FOR ALBUMIN

If calcium is expressed in mg/dL and albumin is expressed in g/L:
Corrected calcium (mg/L) =
serum calcium (mg/L) + 0.8•(40 - serum albumin [g/L])

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

Source: Burtis 19985

ATTACHMENT 5: ASTHMA GUIDELINES

Components of Severity		Classification of Asthma Severity											
					Persistent								
		Intermittent			Mild			Moderate			Severe		
		0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs
Impairment	Symptoms	≤ 2 days/week			≤ 2 days/week but not daily			Daily			Throughout the day		
	Nighttime awakenings	0	≤ 2x/month		1-2x/ month	3-4x/month		3-4x/ month	> 1x/week but not nightly		> 1x/ month	Often 7x/week	
	SABA use for symptom control (not prevention of EIB)	≤ 2 days/week			≤ 2 days/week but not daily		>2 days/ week but not daily, and not more than 1x on any day	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 FEV_1 FEV_1/FVC	N/A	Normal FEV_1 between exacerbations > 80% > 85%	Normal FEV_1 between exacerbations > 80% Normal	N/A	> 80% > 80%	> 80% Normal	N/A	60-80% 75-80%	60-80% Reduced 5%	N/A	< 60% < 75%	< 60% Reduced 5%
Risk	Exacerbations requiring oral systemic corticosteroids	0-1/year			≥ 2 exacerbations in 6 months requiring oral steroids or >4 wheezing episodes/1 year lasting >1 day and risk factors for persistent asthma	≥ 2/year Relative annual risk may be related to FEV_1.	≥ 2/year Relative annual risk may be related to FEV_1.	≥ 2 exacerbations in 6 months requiring oral steroids or >4 wheezing episodes/1 year lasting >1 day and risk factors for persistent asthma	≥ 2/year Relative annual risk may be related to FEV_1.	≥ 2/year Relative annual risk may be related to FEV_1.	≥ 2 exacerbations in 6 months requiring oral steroids or >4 wheezing episodes/1 year lasting >1 day and risk factors for persistent asthma	≥ 2/year Relative annual risk may be related to FEV_1.	≥ 2/year Relative annual risk may be related to FEV_1.
		← Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category. →											
Recommended Step for Initiating Treatment		Step 1			Step 2			Step 3 and consider short course of oral steroids	Step 3: medium dose ICS and consider short course of oral steroids	Step 3 and consider short course of oral steroids	Step 3 and consider short course of oral steroids	Step 3: medium dose ICS OR Step 4 and consider short course of oral steroids	Step 4 or 5 and consider short course of oral steroids
		In 2-6 weeks, evaluate level of asthma control that is achieved. 0-4 years: If no clear benefit is observed in 4-6 weeks, stop treatment and consider alternate diagnosis or adjusting therapy. 5-11 and 12+ years: adjust therapy accordingly.											

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

ATTACHMENT 6: CONVERSION TABLE FOR GLUCOCORTICOSTEROID DOSE

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

ATTACHMENT 7: BODY SURFACE AREA CALCULATION

BSA should be calculated using the Mosteller Formula (shown below); however, the DuBois Formula can be used as an alternative.

$$\text{BSA} = \sqrt{\frac{Ht(inches) \times Wt(lbs)}{3131}}$$

or

$$\text{BSA} = \sqrt{\frac{Ht(cm) \times Wt(kg)}{3600}}$$

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.

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): _____

Institution: _____

Signature: _____ Date: _____

(Day Month Year)

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

PROTOCOL – SPONSOR VALIDATION FORM

Intergroupe Francophone du Myelome (IFM)
in Collaboration with
Dutch-Belgian Cooperative Trial Group for Hematology Oncology (HOVON)
And Janssen Research & Development

Clinical Protocol

Study of Daratumumab (JNJ-54767414 (HuMax® CD38) in Combination with Bortezomib (VELCADE), Thalidomide, and Dexamethasone (VTD) in the First Line Treatment of Transplant Eligible Subjects with Newly Diagnosed Multiple Myeloma.

Protocol IFM 2015-01 /HO131/54767414MMY3006; Phase 3
Initial Version dated 14 January 2015
AMENDMENT 4 dated 14 January 2021

JNJ-54767414 (daratumumab)

Sponsor's Representatives Sign.: _____ date: _____
IFM

_____ date: _____

LAST PAGE