Janssen Research & Development*

Clinical Protocol

A Phase 3, Randomized, Controlled, Open-label Study of VELCADE (Bortezomib) Melphalan-Prednisone (VMP) Compared to Daratumumab in Combination with VMP (D-VMP), in Subjects with Previously Untreated Multiple Myeloma who are Ineligible for High-dose Therapy

Protocol 54767414MMY3007; Phase 3
Amendment 5

JNJ-54767414 Daratumumab

*Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen Pharmaceutica NV; Janssen, Inc; Janssen Sciences Ireland UC; or Janssen Research & Development, LLC. The term "sponsor" is used throughout the protocol to represent these various legal entities; the sponsor is identified on the Contact Information page that accompanies the protocol.

EudraCT NUMBER: 2014-002272-88

Status: Approved
Date: 14 February 2018
Prepared by: Janssen Research & Development, LLC
EDMS number: EDMS-ERI-83878417, 10.0

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

TABLE OF CONTENTS

LIST OF ATTACHMENTS

LIST OF IN-TEXT TABLES AND FIGURES

TABLES

FIGURES

PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	26 June 2014
Amendment 1	24 November 2014
Amendment 2	05 November 2015
Amendment 3	26 July 2016
Amendment 4	11 November 2016
Amendment 5	14 February 2018

Amendments are listed beginning with the most recent amendment.

Amendment 5 (14 February 2018)

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

The overall reason for the amendment: Based on the Independent Data Monitoring Committee (IDMC) recommendation following review of data from the second interim analysis, the study is being amended to allow subjects in Arm A (VELCADE [bortezomib]-melphalan-prednisone [VMP] alone) access to daratumumab after sponsor confirmation of disease progression (PD) per International Myeloma Working Group criteria.

Applicable Section(s)	Description of Change(s)
Rationale: Subjects randomized to Arm A (VMP) who have sponsor-confirmed disease progression may have the option to receive daratumumab provided by the sponsor (in any subsequent line of therapy) if recommended by the investigator. Eligibility for and administration of daratumumab must be in accordance with local prescribing information and local regulations.	
8.4. Subsequent Therapies	A new section has been added.
Rationale: To update statistical text following positive findings for the second interim analysis.	
Synopsis, Overview of Study Design; Synopsis, Statistical Methods; 3.1. Overview of Study Design; 9.2.2. Endpoints	Details of IDMC reviews have been removed from the Synopsis, Overview of Study Design. Details of IDMC reviews, the 2 planned interim analyses, and the primary progression-free survival (PFS) analysis have been incorporated within the Synopsis, Statistical Methods. It is explained that the interim PFS analysis will function as the primary analysis of this endpoint, as the superiority of daratumumab plus VMP (D-VMP) over VMP alone is established at the second interim analysis.
Synopsis, Overview of Study Design; Synopsis, Statistical Methods; Time and Events Schedule; 3.1. Overview of Study Design	Removed text which referred to reduced data collection as described in Section 9.1.4. Where appropriate, added references to subject monitoring as described in the new Sections 9.1.5 (following positive second interim analysis of PFS) and 9.1.6 (following overall survival [OS] interim analysis).
Synopsis, Overview of Study Design; 3.1. Overview of Study Design	Added a statement that as the superiority of daratumumab combined with VMP over VMP alone with respect to PFS was established at the second interim analysis, the interim PFS analysis will serve as the primary PFS analysis.

Applicable Section(s)	Description of Change(s)
Synopsis, Overview of Study Design; 3.1. Overview of Study Design; 11.10. Interim Analysis	Described that an interim analysis of OS is now planned to be conducted when 200 deaths (60% of all planned events) have been accumulated, with the final analysis of OS to be conducted when 330 deaths are accumulated.
Time and Events Schedule; 9.2.2. Endpoints	Removed text which referred to disease evaluations not being required after the clinical cutoff date.
9.1.4. Follow-up Phase	Removed the following text: A clinical cut-off will be established after the primary PFS analysis (360 PFS events). Following the clinical cut-off date, disease assessments will no longer be required and data collection will be limited to the following: • For subjects still receiving study treatment: study treatment administration, AEs, SAEs, laboratory data associated with SAEs • For all subjects: all subsequent anticancer treatment, PFS2 (per investigator judgment), second primary malignancies, and survival follow-up
9.1.5. Assessments Following the Positive Second Interim Analysis of PFS	A new section has been added.
9.1.6. Assessments Following the OS Interim Analysis	A new section has been added.
11.3. Efficacy Analyses	Described that the analysis of OS may be confounded by subjects from Arm A receiving daratumumab after their study treatment was stopped. Exploratory analysis may be performed to adjust for the effect daratumumab exposure may have on OS for the subjects who were randomized to Arm A (VMP).
11.3. Efficacy Analyses	Text describing secondary endpoints was revised to align with the secondary endpoints which were planned to be sequentially tested at the second interim analysis.
Rationale: To clarify/emphasize the requirement to wait until confirmed PD prior to starting subsequent anti-myeloma therapy.	
Synopsis, Overview of Study Design; 3.1. Overview of Study Design	It is emphasized that for both Arm A (VMP) and Arm B (D-VMP), subjects entering the Follow-up Phase 'should not be started on subsequent anti-myeloma therapy without confirmed disease progression'.
8.3. Prohibited Therapies	Clarified that the prohibition on concomitant administration of any other antineoplastic therapy for the intention of treating multiple myeloma applies prior to confirmation of disease progression.
Synopsis, Overview of Study Design; 3.1. Overview of Study Design; 9.1.4. Follow-up Phase; 9.2.1.1. Response Categories	Cross-references to the new Section 8.4 Subsequent Therapies have been added.

Applicable Section(s)	Description of Change(s)
Rationale: Clarification of the IDMC's role in data review following database lock for the primary analysis.	
Synopsis, Statistical Methods; 3.1. Overview of Study Design; 11.11. Data Monitoring Committee	It is noted that the IDMC will no longer review study data after the database lock for the primary analysis has been completed.
Rationale: To clarify the daratumumab pharmacokinetics (PK) and immunogenicity assessments specific to Arm B (D-VMP).	
Synopsis, Pharmacokinetic and Immunogenicity Evaluations; 9.3.1. Evaluations; 9.3.4. Immunogenicity Assessments (Antibodies to daratumumab)	Added text stating that in the Follow-up Phase, for all subjects in Arm B (D-VMP), samples for PK and immunogenicity assessments are to be collected 8 weeks after the last dose of daratumumab, regardless of whether there has been confirmed disease progression.
Time and Events Schedule	Within the rows describing daratumumab PK and immunogenicity assessments, the 'Prior to PD' and 'After PD' cells under Follow-up Phase have been merged. Samples are to be collected 8 weeks after the last dose of daratumumab, regardless of whether there has been confirmed disease progression. Within the rows describing daratumumab PK and immunogenicity assessments, text has been added to emphasize that these assessments apply only to subjects in Arm B.
Rationale: To clarify quantitative immunoglobulin (Ig) assessments.	
Time and Events Schedule	Within the quantitative Ig row, the 'Cycle 10+' text has been revised to replace 'C12D1 and every 3 cycles thereafter until PD' with 'every 4 months until PD'. It is emphasized that assessments of quantitative Ig for Cycle 10+ apply to Arm B (D-VMP) only. Within this same row, within the Follow-up Phase/Prior to PD cell, the following text has been added: 'Every 3 months in Year 1, then every 4 months after Year 1 until PD'.
Rationale: To clarify that Eastern Cooperative Oncology Group (ECOG) and patient-reported outcomes (PRO) assessments that occur at Week 8 and Week 16 post-PD should be scheduled relative to the date of confirmation of disease progression.	
9.1.4. Follow-up Phase	Text in **bold** has been added: 'Every 16-week follow-up contacts**, as well as Week 8 post-PD and Week 16 post-PD ECOG and ePRO assessments,** should be scheduled from the date of confirmed progression **(ie, the date of the confirmatory laboratory assessment, not the date of confirmation by the sponsor)**.'
Rationale: Replaced time qualifier of '1-3 weeks later' because in urgent situations, a repeat investigation may be needed sooner. 'At least 1 day later' is used to make clear that the confirmatory test cannot happen on the same day as the initial test.	
9.2.1.2. Myeloma Protein Measurements in Serum and Urine	Text in ~~strikethrough~~ has been deleted, text in **bold** has been added: 'Disease progression based on 1 of the laboratory tests alone must be confirmed by ~~at least 1~~ **a** repeat investigation performed **at least 1 day** ~~1 to 3 weeks~~ later'.

Applicable Section(s)	Description of Change(s)
Rationale: To clarify that sites should continue to monitor extramedullary plasmacytomas for PD following complete response (CR).	
9.2.1.8. Documentation of Extramedullary Plasmacytomas	Text in ~~strikethrough~~ has been deleted: 'Assessment of measurable sites of extramedullary disease will be performed and evaluated locally every 6 weeks (by physical examination) or every 12 weeks by imaging (if required) 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.'
Rationale: To clarify required chemistry assessments at End-of-Treatment.	
9.8. Safety Evaluations	Text in **bold** has been added: 'Screening, Cycles 1-9 **and End-of-Treatment**'
Rationale: To clarify definitions for study end.	
10.1. Completion	Text added that the study end is defined as when 330 deaths have occurred or 5 years after the last subject is randomized, whichever comes first.
Rationale: To clarify definitions for completion of treatment.	
10.1. Completion	Separate definitions are provided for treatment completion for Arm A (VMP) and Arm B (D-VMP).
Rationale: Alignment of text with recent protocol template changes.	
Title page	Added 'Janssen Pharmaceutica NV' to the list of legal entities.
10.3. Withdrawal from the Study	Revised the text related to subjects withdrawing from the study.
12.3.1. All Adverse Events	Added a sentence related to sponsor's responsibility for reporting anticipated events.
12.3.3. Pregnancy	Deleted text related to the unknown effect of study drug on sperm, and consolidated to a single paragraph the guidance for all initial reports of pregnancy in female subjects or partners of male subjects.
17.3. Subject Identification, Enrollment, and Screening Logs	Added '(as allowed by local regulations)' following 2 instances of 'date of birth'.
17.11. Use of Information and Publication	Added the text in bold: 'key assessment parameters of the study will be used to determine a coordinating investigator **for the study'**. Changed the time for submitting combined results from the completed study for publication from 'within 12 months of the availability of the final data (tables, listings, graphs)' to '**within 18 months after study end date'**. Revised the text beginning 'Authorship of publications...'
Abbreviations	ICMJE has been added to the list of abbreviations.
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.
Throughout the protocol	'anticancer' has been replaced with 'anti-myeloma'

Applicable Section(s)	Description of Change(s)
6.3.1.1. Daratumumab-Related Toxicity Management	Added 'other' to describe 'components of the chemotherapy regimen'.
9.2.1.5. Bone Marrow Examination, Table 10 Bone Marrow Testing	Within the cell that describes local testing for CR, stringent CR (sCR), the text in **bold** has been added, to clarify that a separate biopsy is not needed: 'If sCR is not met, repeat local testing for sCR with subsequent bone marrow examinations will be done **at the time of the next protocol-required bone marrow examination**'.
10.3. Withdrawal from the Study	'When a subject withdraws before completing the study' has been revised to 'When a subject withdraws from the study'.

Amendment 4 (11 November 2016)

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

The overall reason for the amendment: The International Myeloma Working Group (IMWG) has recently defined new categories of MRD–negativity and has clarified several aspects of disease response assessment along with clinical trial endpoints (Kumar, 2016). In order for Protocol MMY3007 to be aligned with the new categories of MRD-negativity, the time points for collection of bone marrow for MRD assessment must be revised.

Applicable Section(s)	Description of Change(s)
Rationale: Addition of Kumar 2016 reference to support IMWG recommendations for multiple myeloma treatment response criteria.	
Amendment table; 9.2.1.1 Response Categories; References	Reference added to Amendment table, Section 9.2.1.1, and References
Rationale: Clarification of the minimal residual disease (MRD) secondary objective for cross protocol consistency.	
Synopsis, Secondary Objectives; 2.1 Secondary Objectives	Text modified to clarify objective to be the assessment of MRD negativity rate. Text moved to clinical outcome objective and text noting time point of "after treatment" was deleted.
Rationale: Inclusion of objective "time to response" for cross-protocol consistency.	
Synopsis, Secondary Objectives; 2.1 Secondary Objectives	"Time to response" included under clinical outcomes objective.
Rationale: New objective added to provide cross protocol consistency and to explore durability of MRD negativity.	
Synopsis, Exploratory Objectives; 2.1 Exploratory Objectives; 9.2.2 Endpoints	Exploratory objective added to assess durability of MRD negativity.

Applicable Section(s)	Description of Change(s)
Rationale: Whole blood samples for MRD assessment obtained with bone marrow aspirates will no longer be collected.	
Synopsis, Overview of Study Design; Time and Event Schedule: Disease: Evaluations: Blood sample for MRD; 3.1 Overview of Study Design ;9.2.1.6 Minimal Residual Disease Assessment	Text and requirement for whole blood samples to be obtained at 14, 20, and 26 months (+/-1 month) for MRD assessment deleted.
Rationale: Revision of endpoint presentation for protocol consistency.	
Synopsis, Efficacy Evaluation/Endpoints; 9.2.2 Endpoints	Secondary efficacy endpoint for sCR rate moved below overall response rate endpoint.
Rationale: Revision of the definition of MRD negativity required to align with IMWG.	
Synopsis, Efficacy Evaluation/Endpoints; 9.2.2 Endpoints	Text modified to define the MRD negativity rate as the proportion of subjects with negative MRD at any time point after the date of randomization. Text defining rate as measurement of subjects who achieve CR/sCR at 14, 20, and 26 months after first dose deleted.
Rationale: Text correction to include exploratory endpoints to align with exploratory endpoints in Section 9.2.2.	
Synopsis, Efficacy Evaluation/Endpoints	Exploratory endpoints added to synopsis.
Rationale: Text correction to include a time to response secondary efficacy endpoint to align with secondary objectives.	
Synopsis, Efficacy Evaluation/Endpoints; 9.2.2 Endpoints	Time to response, defined as the time between the randomization and the first efficacy evaluation that the subject has met all criteria for PR or better" included as secondary efficacy endpoint.
Rationale: Clarification of use for collected whole blood samples.	
Synopsis, Biomarker Evaluation; 9.5 Biomarkers	Text modified to indicate that whole blood samples will be collected to process to plasma and PBMCs. Text indicating use for assessment of MRD deleted.
Rationale: Modification of disease evaluation prior to PD time points in the Follow-up Phase to align with evaluation time points in the Treatment Phase.	
Time and Events Schedule: Follow-up Phase	Every 4-week designation for follow-up prior to PD deleted.
Rationale: Addition of ±2 weeks window to allow for flexible scheduling for follow-up visits after PD.	
Time and Events Schedule: Follow-up Phase	Visit window of ±2 weeks added to the every-16 week visit after PD in the Follow-up Phase.

Applicable Section(s)	Description of Change(s)
Rationale: Clarification of visit time points to ensure consistent timing of assessments for both ECOG and ePRO.	
Time and Events Schedule: ECOG, Disease Evaluations, PRO	Text modified to define 'every 3 months' as 'every 12 weeks' in Year 1 and 'every 6 months thereafter' as 'every 24 weeks thereafter'.
Rationale: Reinstatement of the 2-hour collection window for the pre-infusion daratumumab PK sample for subjects in Arm B.	
Time and Events Schedule: Laboratory Assessment: Daratumumab PK	Text added to clarify that collection of the pre-infusion daratumumab PK sample is allowed up to 2 hours prior to the start of infusion.
Rationale: Align bone marrow aspirate/biopsy collection time points in the Time and Events Schedule with new MRD guidelines and across daratumumab protocols.	
Time and Events Schedule: Disease: Evaluations: Bone marrow aspirate/biopsy	Text modified to indicate that for subjects with CR/sCR, additional bone marrow samples will be obtained 12, 18, 24, and 30 months (+2 months) after first dose. Text added indicating information including time points located in Section 9.2.1.5 and Table 10.
Rationale: Inclusion of antihistamine medication listing to align with daratumumab protocols.	
Time and Events Schedule for Study Treatment, Cycle 1; Time and Events Schedule for Study Treatment, Cycles 2-9; Time and Events Schedule for Study Treatment, Cycle 10+; 6.1.3.1 Pre-infusion Medication	Text indicating inclusion of new attachment included in Time and Events Schedules and Section 6.1.3.1. Listing provided in Attachment 5. Previous Attachments 5-8 renumbered throughout protocol.
Rationale: Clarification that order of combination drug administration applies to subjects in Arm B only.	
6 Dosage and Administration	Text added to clarify that the protocol-specified order of study drugs given in combination is applicable to subjects in Arm B only.
Rationale: Clarification that criteria required for VMP administration are applicable for Cycles 2-9 only. Minor text modifications to align with VELCADE SmPC.	
6 Dosage and Administration	Text added to clarify that criteria required for VMP administration are applicable for Cycles 2-9 only. Text wording "must" replaced with "should" for VELCADE SmPC alignment.
Rationale: Clarification that text within Table 4 is applicable to "within cycle" administration only.	
6.3.1.1 Daratumumab-Related Toxicity Management, Table 4	Text added to clarify that the information for Table 4 "Daratumumab-Related Toxicity Management" is applicable to "within cycle" administration only and not Day 1. The dose on Day 1 can be delayed but may not be skipped.

Applicable Section(s)	Description of Change(s)
Rationale: Clarification of VELCADE dose reduction.	
6.3.2 Dose Reductions (VELCADE, Melphalan, and Prednisone)	Text added to clarify that VELCADE dose reduction is only required in cases of held doses due to VELCADE-related toxicity.
Rationale: Clarification of text regarding re-escalation of melphalan after dose reduction post toxicity to align with melphalan dose-modification guidelines.	
6.3.2 Dose Reductions (VELCADE, Melphalan, and Prednisone)	Text added to indicate that re-escalation after dose reduction post toxicity is permitted for melphalan following recovery of renal function.
Rationale: Clarification of toxicity guidelines provided for the administration of VELCADE, Melphalan, and Prednisone.	
6.3.3 Dose Modification Guidelines for VELCADE, Melphalan, and Prednisone Related Toxicities	Text added to indicate that protocol provided management guidelines are applicable for toxicities deemed related to the administration of VELCADE, melphalan, and prednisone.
Rationale: Clarification of dose modification category for Grade 3 or Grade 4 neutropenia.	
6.3.3 Dose Modification Guidelines for VELCADE, Melphalan, and Prednisone Related Toxicities, Table 8 Hematological	Text revised to emphasize that this dose modification is applicable to Grade 3 neutropenia with associated fever and to all Grade 4 neutropenia (with or without associated fever).
Rationale: Dose modification for melphalan in the event of Grade 3 thrombocytopenia should be implemented in the subsequent treatment cycle.	
6.3.3 Dose Modification Guidelines for VELCADE, Melphalan, and Prednisone Related Toxicities, Table 8 Hematological	Text indicating that reduction of melphalan by 1 dose-level for the remainder of the cycle has been deleted.
Rationale: Prophylaxis text revision to align with daratumumab label	
8.1.4 Prophylaxis for Herpes Zoster Reactivation	Text providing detailed information on herpes zoster prophylaxis deleted. Prophylaxis recommended during Treatment Phase as per institutional guidelines.

Applicable Section(s)	Description of Change(s)
Rationale: Clarification of the use of study drug during or after emergency orthopedic surgery or radiotherapy.	
8.3 Prohibited Therapies	Text modified to indicate use of study drug or components of VMP regimen during or after emergency orthopedic surgery or radiotherapy are for conditions related to multiple myeloma. Text indicating "subject benefit" deleted.
Rationale: Clarification to provide additional scheduling flexibility for subject follow-up visits after PD and to clarify follow-up intervals for subjects not continuing disease evaluations after PD.	
9.1.4 Follow-up Phase	Time points from Time and Events schedule added. Text added to expand the protocol-specified information collection period after PD to every 16 weeks (±2 weeks). Clarification included indicating that in subjects not continuing disease evaluation, an every-16-week follow-up visit should be scheduled from the date of the End of Treatment visit.
Rationale: Highlight that increases in serum free light chains or the FLC ratio alone do not meet IMWG criteria for progressive disease in patients with measurable disease by SPEP and/or UPEP at baseline.	
9.2.1.1 Response Categories	Text modified to indicate that for patients with measurable disease by SPEP and/or UPEP at baseline, increases in serum free light chains or the FLC ratio alone do not meet criteria for progressive disease.
Rationale: Inclusion of text for protocol consistency to Section 9.1.4.	
9.2.1.1 Response Categories	Text "lost to follow-up" included in "For subjects who discontinue study treatment before disease progression, disease evaluations should continue to be performed per the Time and Events Schedule until confirmed disease progression, death, the start of a new treatment for multiple myeloma, withdrawal of consent for study participation, **lost to follow-up,** or the end of study, whichever occurs first" to be consistent with text in Section 9.1.4.
Rationale: Bone Marrow Examination Table modified to align with new MRD guidelines and daratumumab protocols.	
9.2.1.5 Bone Marrow Examination, Table 10	Text modifications: <u>CR/sCR</u> • Local testing: Text modified to indicate preference of 2-4 color flow cytometry for detection of kappa/lambda ratio. Immunohistochemistry and immunofluorescence allowed but a kappa/lambda ratio from ≥100 plasma cells required to confirm sCR. Subjects who achieved CR but not sCR will have additional sCR evaluations to coincide with MRD bone marrow time points until sCR is achieved. • Central testing: For subjects with CR/sCR additional samples to be obtained at 12, 18, 24, and 30 months after first dose. A window of 2 months **after** the 12, 18, 24 and 30-month time points is allowed. <u>Maintained CR/sCR</u>: • Text deleted <u>Disease Progression:</u> • Text modified to indicate that a bone marrow sample is requested from subjects in both treatment arms at disease progression to evaluate mechanism of resistance.
Rationale: Revision of time points for bone marrow collection for MRD assessment.	
9.2.1.6 Minimal Residual Disease Assessment	Text indicating collection time points of baseline, CR confirmation, 14, 20 and 26 months (+/-1 month) deleted. Please see Table 10 for updated time points.

Applicable Section(s)	Description of Change(s)
Rationale: Clarification of collection points for the Serum Chemistry Panel.	
9.8 Safety Evaluations: Clinical Laboratory Tests	Text added to indicate that the serum chemistry panel is to be obtained at Screening and Cycles 1-9. Text added to clarify that sodium and potassium, added in Amendment 2, will be retrospectively evaluated from the date of subject consent if collected as part of routine care. Urea added to the serum chemistry panel for Cycles 10+.
Rationale: Addition of Chapuy 2016 reference to support processes to eliminate daratumumab IAT interference.	
9.8 Safety Evaluations: Daratumumab Interference with Indirect Antiglobulin Test (IAT) Results; References	Reference added to Section 9.8 and References
Rationale: Although vital signs are performed at multiple time points as specified in the Time and Events Schedule, only vital signs obtained at Screening or associated with an adverse event are captured in the eCRFs.	
9.8 Safety Evaluations; References: Vital Signs	Text modified to indicate that only vital signs obtained at Screening or associated with an AE will be entered in the eCRF; all measurements will be recorded in the source documents.
Rationale: Clarification that subjects do not have to discontinue all components of the VMP regimen if only one component requires a third dose reduction for toxicity.	
10.2 Discontinuation of Study Treatment	Text modified to indicate that subjects do not have to discontinue all components of the VMP regimen if only one component requires a third dose reduction for toxicity. Bullet outlining discontinuation of study treatment if any component of VMP requires dose reduction for the third time deleted.
Rationale: Realignment of the testing order of the major secondary endpoints for the control of familywise type 1 error during the second interim analysis.	
11.3 Efficacy Analyses, Secondary Endpoints	Text modifications • Major secondary endpoints revised as TTP, CR rate, MRD negativity rate, PFS2, and OS. • Secondary time to event efficacy endpoints: time to treatment added as endpoint.
Rationale: Changes from baseline cannot be summarized since vital signs are only captured in the eCRF at Screening and when associated with an adverse event.	
11.9 Safety Analysis	Text modified to indicate that descriptive statistics for baseline temperature, heart rate, and blood pressure will be summarized. Text indicating providing changes from baseline for these parameters deleted.
Rationale: Inclusion of anticipated adverse events guidelines to align daratumumab protocols.	
12.3.1 All Adverse Events; Attachment 10	Text added to Section 12.3.1 indicating inclusion of new attachment. New guidelines provided in Attachment 10.

Applicable Section(s)	Description of Change(s)
Rationale: Alignment of text with recent protocol template changes.	
12.3.1 All Adverse Events	Text modified to indicate that the sponsor will report incidences of suspected unexpected serious adverse events to the investigator. Text added to indicate that the sponsor will periodically evaluate the data independent of the investigator and will, in the event of a drug-related serious anticipated event, submit appropriate documentation to the investigator.
Rationale: Alignment of text with recent protocol template changes.	
17.5 Case Report Form Completion	Text specifying that all data related to the study must be recorded on eCRFs prepared by the sponsor was deleted.
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 3 (25 July 2016)

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union, in that it does not significantly impact the safety or physical/mental integrity of subjects, nor the scientific value of the study.

The overall reason for the amendment: The Safety Evaluations included in Protocol Amendment 2 (dated 05 Nov 2015) for the chemistry panel (ie, the analysis of sodium and potassium levels) will require the collection of results to be done retrospectively from the date of subject consent for the duration of the study, if collected as part of routine care. The baseline data, if available, are needed in order to effectively analyze safety with respect to changes in sodium/potassium levels while on treatment with respect to the investigational agent daratumumab in this combination with VMP in the frontline setting of treatment for multiple myeloma in an elderly population. This does not require any additional testing nor does it require a change to the Informed Consent Form or the request for additional consent from the subjects.

Applicable Section(s)	Description of Change(s)
Rationale: This nonsubstantial amendment is required to include a clarification statement regarding collection of sodium and potassium. No changes to the text have been made.	

Amendment 2 (05 November 2015)

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

The overall reason for the amendment: To provide updated guidance with respect to VELCADE dose modifications (per the Summary of Product Characteristics [SmPC] and United Sates Package Insert [USPI]) and to align with the VELCADE label regarding dose modifications, to incorporate investigator feedback into the protocol, and to revise operational aspects of the study and provide clarifications on study procedures.

Applicable Section(s)	Description of Change(s)
Rationale: To provide updated guidance with respect to VELCADE dose modifications (per SmPC and USPI) and to add a window for within-cycle VELCADE and daratumumab treatments for site and subject convenience	
Time and Events Schedules for Study Treatment, Cycle 1 (VMP treatment Phase) and Cycle 2 to 9 (VMP Treatment Phase); 6.2.2 VELCADE Administration	VELCADE doses **should** ~~must~~ be at least 72 hours apart. Doses that need to be withheld are skipped and will not be made up later in the cycle. **Individual doses within a cycle have a ±1 day window.**
6 Dosage and Administration; 9.1.3 Treatment Phase	Text has been added or revised as follows: **Before initiating a new cycle of therapy, subjects must meet the following criteria:** • **Platelet count ≥70 x 10^9/L** • **ANC ≥1.0 x 10^9/L** • **Non-hematological toxicities resolved to Grade 1 or baseline** The start of each cycle may occur within ±3 days of the scheduled day in order to accommodate the schedule of the site or subject. **If the start of a cycle is delayed, Day 1 of subsequent cycles should be adjusted accordingly to maintain the 42-day cycle duration. In Cycles 1 through 9, weekly or every-three-week daratumumab infusions may be given within ±1 day of the scheduled day in order to accommodate the schedule of the site or subject. Additionally, weekly or twice weekly VELCADE doses may be given within ±1 day of the scheduled day in order to accommodate the schedule of the site or subject. Changes to within-cycle dosing should not impact Day 1 of the next cycle.** ~~The start of each cycle should be scheduled relative to Cycle 1 Day 1 and should not change if visits have shifted within the allowed window.~~
6.3.2 Dose Reductions (VELCADE, Melphalan, and Prednisone)	**VELCADE will be reduced or discontinued according to the guidelines presented in Table 5. In addition to the VELCADE dose modification guidelines presented in Section 6.3.3, Table 8, if several VELCADE doses in a cycle are withheld (≥3 doses during twice weekly administration or ≥2 doses during weekly administration), VELCADE dose should be reduced by 1 dose level. Once reduced due to toxicity, doses of VELCADE, melphalan, or prednisone should not be re-escalated.**
6.3.3 Dose Modification Guidelines for VELCADE, Melphalan, and Prednisone	Moved all footnotes in Table 8 to the end of the table. Updated Table 8 to align with VELCADE SmPC and USPI.

Applicable Section(s)	Description of Change(s)
Rationale: To allow flexibility in the administration of pre-infusion medications, to clarify allowable pre-infusion medications, and to be consistent with other daratumumab protocols.	
Time and Events Schedules for Study Treatment, Cycle 1 (VMP treatment Phase) and Cycle 2 to 9 (VMP Treatment Phase), and Cycle 10+ (Dara treatment Phase, Arm B only)	Administer pre-infusion medications approximately 1 hour before daratumumab infusion. Pre-infusion medications given by mouth (PO) may be administered within 3 hours before the infusion.
Time and Events Schedules for Study Treatment, Cycle 1 (VMP treatment Phase) and Cycle 2 to 9 (VMP Treatment Phase); and Cycle 10+ (Dara treatment Phase, Arm B only); 6.1.3.1 Pre-infusion Medication	Because it is acceptable to give dexamethasone PO or intravenously (IV) regardless of availability of IV dexamethasone, text was revised for clarity: Dexamethasone 20 mg IV or PO. To specify that only equivalent H1 blockers are acceptable, clarified: An antihistamine (diphenhydramine 25-50 mg IV or PO, or equivalent **H1 blocker**)
Time and Events Schedules for Study Treatment, Cycle 1 (VMP Treatment Phase); 6.1.3.1 Pre-infusion Medication	Added allowance of administration of leukotriene inhibitor, montelukast 10 mg PO or equivalent, at C1D1 approximately 1 hour or less before the daratumumab infusion.
6.1.3.2 Post-Infusion Medication	Added leukotriene inhibitor (montelukast or equivalent) as allowable post-infusion medication
Attachment 5 Conversion Table for Glucocorticosteroid Dose	Revised table to remove hydrocortisone, as it's a short acting corticosteroid and should not be used as a pre-infusion medication substitute for dexamethasone. Added the allowance of bethamethasone (0.6 mg), which can be used as a substitute for dexamethasone pre-infusion medication.
Rationale: To provide additional guidance as to acceptable methods of bone marrow preparation and indicate that flow cytometry is also an acceptable method of confirming multiple myeloma diagnosis.	
Time and Events Schedule	For screening (up to 42 days before randomization) fresh aspirate or biopsy preferred. If not available, obtain non-decalcified slides **(bone marrow aspirate, touch preparation or clot selection)** or FFPE block **(clot section only, no bone marrow biopsy**).
9.2.1.5 Bone Marrow Examination	Updated Table 10 to provide additional guidance on the acceptable methods of bone marrow preparation.

Applicable Section(s)	Description of Change(s)
Rationale: To clarify assessments and procedures, and timing thereof, and allow flexibility, as applicable, for some assessments and procedures, in relation to Screening.	
Time and Events Schedule; 9.1.2 Screening Phase; 9.2.1.8 Documentation of Extramedullary Plasmacytomas	Disease evaluations, including chest X-ray **(or full chest CT scan),** 12-lead ECG, lytic disease assessment, and extramedullary plasmacytomas are performed as part of SOC, are acceptable to be used for screening, as long as the assessments are done within 42 days before randomization. For subjects with history of plasmacytomas assessed by physical exam, a repeat assessment should be performed on C1D1 if not done within 14 days prior to randomization
Time and Events Schedule	12-lead ECG assessments can be performed within **±7 days** of the planned assessment date. Hematology and chemistry values are acceptable for screening to meet CRAB criteria, if performed as part of SOC within 42 days before randomization but must be performed within 21 days before randomization for other eligibility requirements. Clarification for analysis of daratumumab PK. For Arm B only, on daratumumab infusion days, 1 sample is to be collected before the start of infusion, and 1 sample is to be collected after the end of infusion (up to 2 hours after the end of infusion). Clarified that for SPEP and IFE, 24-hour UPEP and IFE; serum FLC; and calcium and albumin that the time frame is based on when the samples were collected, not when results were received. Clarified timing of assessments for Quantitative Ig to indicate that during Cycles 1-9, assessments are at C3D1, C5D1, C7D1, and C9D1. For Cycles 10+, assessments are at C12D1 and every 3 cycles thereafter until PD.
Rationale: Modified language and guidance pertaining to the indirect antiglobulin test (IAT).	
Time and Events Schedule	Added text indicating that a wallet card is to be given to all subjects (in Arm A and in Arm B) at C1D1.
4.3 Prohibitions and Restrictions	Removed the Blood Type IAT results language, as this is now limited to Section 9.8 Safety Evaluations.
9.8 Safety Evaluations	Updated the daratumumab IAT results text to align with other daratumumab protocols.
12.3.1 All Adverse Events	Added text specifying that wallet cards must be carried for the duration of the study by subjects in Arm A and for at least 6 months after the study treatment is discontinued for subjects in Arm B.
Rationale: To clarify inclusion and exclusion criteria.	
Synopsis, Subject Population; 4.1 Inclusion Criteria, Criterion #2.2	Eligible subjects must satisfy **the calcium elevation, renal insufficiency, anemia, and bone abnormalities (CRAB)** diagnostic criteria, **monoclonal plasma cells in the bone marrow ≥10% or presence of a biopsy proven plasmacytomas**, and measurable **secretory** disease, as **assessed by the central laboratory**.

Applicable Section(s)	Description of Change(s)
4.2 Exclusion Criteria, Criterion 12.2	Because subjects with pacemakers, which is classified as NCI CTCAE Grade 3 atrial fibrillation, are eligible for the study, criterion was revised to clarify: "Subjects are to be excluded if they have uncontrolled cardiac arrhythmia ~~(NCI CTCAE Version 4 Grade ≥2)~~ or clinically significant ECG abnormalities", because subjects with pacemakers, which is classified as NCI-CTCAE Grade 3 atrial fibrillation, are allowed to be enrolled in the study. As the intent is to exclude any subjects with prolonged QT and not to have sites converting ECG output using different correction formulas, criterion was revised to state "screening 12-lead ECG showing a baseline **corrected** QT interval ~~as corrected by Fridericia's formula (QTcF)~~ **(QTc)**>470 msec.
Rationale: To align with updated Investigator's Brochure (IB) and risk language wording, updated the timeframe associated with birth control use.	
4.2 Exclusion Criteria, Criterion #16.1	Subject is a woman who is pregnant, or breast-feeding, or planning to become pregnant while enrolled in this study or within **3 months** ~~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 **3 months** ~~4 months~~ after the last dose of any component of the treatment regimen.
4.3 Prohibitions and Restrictions, #1 and #2	1. For women of childbearing potential, adequate contraception as specified in Section 4.1 must continue during the Treatment Phase, during any dose interruptions, and for **3 months** ~~4 months~~ after the last dose of daratumumab. In addition, women must not donate ova during the study and for **3 months** ~~4 months~~ after the last dose of daratumumab. 2. A man who is sexually active with a woman of childbearing potential must always use a latex or synthetic condom during the study and for **3 months** ~~4 months~~ after discontinuing daratumumab. All men must not donate sperm during the study and for **3 months** ~~4 months~~ after the last dose of daratumumab.
Rationale: To clarify if assessments are to be analyzed by the local or central laboratory and to provide the reference for determination of ISS Stage.	
Synopsis, Overview of the Study Design; Time and Events Schedule; 5 Treatment Allocation and Blinding; 9.2.1.4 β2 Microglobulin and Albumin	Eligible subjects will be stratified by International Staging System (I vs II vs III **based on central laboratory results at Screening**).
Time and Events Schedule	Indirect Antiglobulin Test (IAT) **is to be assessed locally**. Randomization based on SPEP and IFE and 24-hour UPEP and IFE is **based on central laboratory values**.
New Attachment 8 International Staging System (ISS) Staging	

Applicable Section(s)	Description of Change(s)
Rationale: To update recommended and prohibited therapies.	
8.1 Recommended Therapies	Removed Section 8.1.1 Prevention of Deep Vein Thrombosis because none of the study treatments are associated with increased incidence of veno-thromboembolic disease.
8.1.1 Bisphosphonate Therapy	After Cycle 1, investigators should not prescribe bisphosphonates to subjects who have not received **them** before ~~as this would be considered a sign of disease progression~~, **unless approved by the sponsor after confirming that the subject does not have disease progression at the time of bisphosphonate initiation**.
8.3 Prohibited Therapies	Nonsteroidal anti-inflammatory agents should be **used with caution** ~~avoided~~ in order to prevent myeloma-related kidney disease.
Rationale: To update serum chemistry panel assessments to allow urea to be performed instead of BUN as some centers do not assess BUN; to add sodium and potassium to the chemistry panel; and to clarify that direct bilirubin assessment is only necessary if total bilirubin is >1.5xULN.	
9.8 Safety Evaluations	Cycles 1-9 Blood urea nitrogen (BUN) **or urea** total bilirubin **(direct bilirubin if total bilirubin >1.5xULN)** **sodium** **potassium** Cycle 10+ **Sodium** **Potassium**
Rationale: Clarify procedure for management of infusion-related reactions.	
6.1.4 Management of Infusion-related Reactions	Subjects in Arm B should be carefully observed during daratumumab infusions. Trained study staff at the clinic should be prepared to intervene in case of any infusion-related reactions occurring, and resources necessary for resuscitation (eg, agents such as epinephrine and aerosolized bronchodilator, also medical equipment such as oxygen tanks, ~~tracheostomy equipment,~~ and a defibrillator) must be available~~ at the bedside~~. Attention to staffing should be considered when multiple subjects will be dosed at the same time. If an infusion-related reaction develops, then the infusion should be temporarily interrupted~~ or slowed down~~. If an infusion is paused~~ or the infusion rate is decreased~~, then a longer-than-anticipated infusion time may occur.
Rationale: To align with updated protocol template language.	
4 Subject Population	Specified that "…the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a subject in the study. Waivers are not allowed."
Rationale: Miscellaneous updates and clarifications made throughout the protocol.	
Synopsis, Objectives and Hypothesis; 2.1 Objectives; 9.2.2 Endpoints	Clarified that ORR includes all subjects with PR or better (not just those with CR and PR).
Synopsis, Objectives and Hypothesis; 2.1 Objectives	Clarified secondary objective as "very good partial response (VGPR) or better **rate**.
Synopsis, Overview of Study Design; 3.1 Overview of Study Design	Measures to prevent **infusion-related reactions** ~~cytokine release syndrome~~ will include...

Applicable Section(s)	Description of Change(s)
Synopsis, Overview of Study Design; 3.1 Overview of Study Design; 9.3.3 Pharmacokinetic Parameters	Blood samples will be drawn for assessment of pharmacokinetic**s** and immunogenicity ~~parameters~~. Changes were made to further clarify the pharmacokinetic data analysis plans.
Synopsis, Efficacy Evaluations and Endpoints; 9.2.1.2 Myeloma Protein Measurements in Serum and Urine; 9.2.2 Endpoints	Updated the DIRA interference language to specify "For those subjects with negative **or low SPEP (≤0.2 g/L)** and suspected daratumumab interference on immunofixation, a reflex assay using anti-idiotype antibody will be utilized…" For subjects with suspected daratumumab interference on **SPEP and/or** serum IFE…
Time and Events Schedule; 9.8 Safety Evaluations	Removed asthma as a condition for measurement of FEV1, as subjects with asthma are excluded from study participation.
Time and Events Schedule	Added that it is allowable to accept results of a FEV1 assessment that was done as part of SOC within 42 days before randomization and not require repeat assessment within 21 days before randomization. Also, clarified the timing of the ECOG assessments in year 1.
Time and Events Schedules for Study Treatment, Cycle 1 (VMP treatment Phase) and Cycle 2 to 9 (VMP Treatment Phase)	Clarified that hematology and chemistry assessments are required for subjects in both treatment arms. Testing may be performed for up to 2 days before other treatment days, and results of hematology tests must be evaluated before treatment. Vital signs assessments are required for subjects in both treatment arms; additional vital sign assessments before, during, and after the daratumumab infusion are required for subjects in Arm B only.
3.1 Overview of Study Design	Updated Figure 3 to accurately reflect that in the Follow-up Phase, prior to PD, disease evaluations will be conducted as per the T&E schedule (rather than q4wks).
6.1.3.2 Post-Infusion Medication	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** ~~salbutanol~~± inhaled corticosteroids for subjects with COPD)
6.3.1.1 Daratumumab-Related Toxicity Management	Updated Table 4 to specifically refer to "Cycle 1" and "Cycles 2-9" and delete "VMP" clarifier.
9.2.1.8 Documentation of Extramedullary Plasmacytomas	Correct erroneous text to indicate that to quality for PR, the sum of products of the perpendicular diameters of the existing extramedullary plasmacytomas must have decreased by at least 50% ~~or 25%, respectively,~~ and new plasmacytomas must not have developed.
9.3.2 Analytical Procedures	Due to the evolving need for pharmacokinetic/immunogenicity data in this study to support daratumumab program decisions, it is not necessary to specify bioanalysis timing in the protocol, so removed text describing the specific detailed timing of the bioanalysis.
12.3.1 All Adverse Events	Reiterated statement that only clinically relevant laboratory abnormalities (ie, those causing a treatment intervention or need for concomitant therapy) should be recorded on the adverse event eCRF. All other laboratory abnormalities need not be recorded as adverse events.

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

Amendment 1 (24 November 2014)
This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: To incorporate investigator feedback into the protocol, to further clarify MRD monitoring, to clarify safety reporting requirements for sites in Japan, to incorporate updated IMWG criteria

Applicable Section(s)	Description of Change(s)
Rationale: To align the definition of multiple myeloma with the updated IMWG criteria (Lancet Oncol 2014; 15: e538–48.	
Attachment 1	Replaced contents of Attachment with new guidelines adapted from the newly published criteria
Rationale: To provide instructions for preventing interference of daratumumab in determining blood type for future transfusions.	
Time and Events Schedule, 12.3.1, All Adverse Events	Blood type and IAT results will be included on wallet card for subjects in Arm B.
4.3, Prohibitions 9.8, Safety Evaluations	Added text to explain daratumumab interference and recommendations for which tests to perform.
Rationale: To clarify details of bone marrow collection for MRD monitoring.	
Time and Events Schedule, 9.2.1.5, Bone Marrow Examination 9.2.1.6, MRD Assessment	Clarified that a fresh bone marrow aspirate or biopsy is preferred at screening, and a fresh aspirate or biopsy (or both) required to confirm CR/sCR; changed timing of bone marrow sample and blood sample to 14, 20, and 26 months after first dose.
9.2.1.5, Bone Marrow Examination	Revised text and put it into table format.
Rationale: To clarify that the secondary objective and secondary endpoint is to assess the MRD negative rate	
Synopsis, 2.1, Objectives	To assess minimal residual disease (MRD) negative rate after treatment
Synopsis, 9.2.2, Endpoints	Assess MRD negative rate, as measured in subjects who achieve CR/sCR, at 14, 20, and 26 months after first dose.

Applicable Section(s)	Description of Change(s)
Rationale: To clarify PRO and ECOG collection procedures	
Time and Events Schedule	Clarified that both PRO questionnaires and ECOG performance status must be administered and completed prior to any other study procedures or assessments for that study visit
Time and Events Schedule; 9.6, PRO 15, Study-specific Materials	All PRO measures will be collected via an electronic device (ePRO).
17.6, Data QA/QC	PRO data will be transmitted to the ePRO vendor database and then to the sponsor's database.
Rationale: Removed 2-hr post infusion collection of vital signs on Cycle 1 Day 1, in absence of safety signal and in response to investigator request.	
Time and Events Schedule for Study Treatment, Cycle 1	On Cycle 1 Day 1: immediately before the start of dara infusion; at 0.5, 1, 1.5, 2, 3.5 hr after start of infusion; at end of infusion; 0.5,1, ~~2~~ hr after end of infusion.
Rationale: Align inclusion criteria with other daratumumab protocols.	
4.1, Inclusion Criteria	#2: Added "without measurable disease in the serum or urine" to light chain myeloma #5: Added cutoff for Gilbert syndrome "direct bilirubin ≤1.5xULN" #5: Aligned creatinine clearance with new guidelines: "creatinine clearance ≥40 mL/min, may be calculated or measured according to local practice (if calculated, MDRD or CKD-EPI formulae preferred)" #5: corrected serum calcium to "<=14" mg/dL ("<=3.5" mmol/L); or free ionized calcium "<=6.5" mg/dL ("<=1.6" mmol/L) #7: changed screening pregnancy test to within 14 days prior to randomization
Rationale: Align exclusion criteria with other daratumumab protocols.	
4.2, Exclusion Criteria Attachment 4	#9: revised entire criterion for subjects with COPD or asthma, and added asthma guidelines as Attachment 4 #10: rewrote criteria for hepatitis B and hepatitis C #12: specified only subjects with uncontrolled cardiac arrhythmia should be excluded #17: specified vertebroplasty not considered to be major surgery
Rationale: Improve instructions for pre-infusion medications	
6.1.3.1, Pre-infusion Medication	specified administration "approximately" 1 hour before daratumumab infusion, deleted infusion of antihistamine 12 hours before first daratumumab infusion on C1D1, clarified that dexamethasone PO is only if IV not available
Rationale: Provide examples of subjects at higher risk of respiratory complications for post-infusion medications.	
6.1.3.2, Post-Infusion Medication	Specified subjects with higher risk of respiratory complications (eg, **subjects with mild asthma, or subjects with COPD**

Applicable Section(s)	Description of Change(s)
Rationale: Improve guidelines for delay of daratumumab infusions	
6.3.1.1, Daratumumab Toxicity Management	To emphasize the criteria when to stop daratumumab, bolded and underlined the following sentence: **ONLY if any of the following criteria are met, and the event cannot be ascribed to components of the chemotherapy regimen, the daratumumab infusion must be held to allow for recovery from toxicity** The following changes were made to the criteria for dose delay to: • Added: Grade 4 hematologic toxicity • Revised: Febrile neutropenia
Rationale: Clarify criteria for discontinuation of treatment after Cycle 9 due to dose delays.	
6.3.1.1, Daratumumab Toxicity Management 6.3.1.2, Daratumumab Interruption 10.2, Discontinuation of Treatment	Added wording that, after Cycle 9, if a subject misses 2 consecutive planned doses (rather than 4 weeks) then treatment should be discontinued.
Rationale: To allow prednisolone to substitute for prednisone in countries where prednisone is not available.	
6.2.3, Melphalan and Prednisone Admin	Prednisolone may be substituted for prednisone in countries where prednisone is not available.
Rationale: Updated investigational product characteristics and handling according to new guidelines	
14.1,Description of Study Drug 14.4, Preparation, Handling, Storage	Updated physical description of study drug, revised instructions for preparation and handling to refer to Investigational Product Preparation Instructions or SIPPM
Rationale: Revisions to improve accuracy and consistency	
Time and Events Schedule	Reorganized disease evaluations and specify window for SPEP, UPEP, IFE, and β-2 microglobulin to within 14 days of C1D1.
3.1, Overview of Study Design	Revised definition of Treatment Phase
3.1, Overview of Study Design 5, Treatment Allocation	Changed International Scoring System to International Staging System
6.2.2, VELCADE Administration	Added sentence that VELCADE dose may be delayed up to 48 hours, as stated in Time and Events Schedule.
6.3.3, Dose Modification Guidelines	Removed hepatic criteria from guidelines for melphalan dose adjustment for renal impairment
8.3, Prohibited Therapies	Added interferon and clarithromycin as prohibited therapies
9.1.2, Screening Phase	Added provision that Sponsor will review eligibility, specified assessments that do not need to be repeated on Cycle 1 Day 1 if done within the prior 14 days, extended window for pregnancy test to 14 days, provided instruction for measurement or calculation of creatinine clearance

Applicable Section(s)	Description of Change(s)
9.1.4, Follow-up Phase	Clarified reasons to stop disease evaluations and timing of visits after PD
9.2.1.2, Myeloma Protein Measurements	Revised testing of quantitative IgD and IgE to only subjects with IgD or IgE myeloma.
9.2.1.7, Assessment of Lytic Disease	Deleted text regarding use of radionucleotide scan as it is no longer relevant
11.11, Data Monitoring Committee	Corrected IDMC to consist of 2 clinicians and 1 statistician
11.4, PK Analyses 11.6, PK/PD Analyses	Removed redundancy between sections and consolidated into Section 11.6
Attachment 3	Deleted attachment for measuring creatinine clearance
Rationale: In response to PMDA comments, additional safety monitoring for Japanese subjects is added via an Attachment (and cross-references to the amendment in main text).	
Synopsis (Safety Evaluations)	During Cycle 1 at Japanese sites, an enhanced reporting, monitoring, and review of pre-specified safety events that occur for Japanese subjects in Arm B will be performed until a minimum of 3 subjects in Arm B have completed Cycle 1.
12.4. Reporting, Monitoring, and Review of Safety Events in Japanese Subjects in Arm B; Attachment 7	Section and attachment added to describe the enhanced reporting, monitoring, and review of pre-specified safety events for Japanese subjects in Arm B (minimum of 3 subjects).
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

SYNOPSIS

A Phase 3, Randomized, Controlled, Open-label Study of VELCADE (Bortezomib) Melphalan-Prednisone (VMP) Compared to Daratumumab in Combination with VMP (D-VMP), in Subjects with Previously Untreated Multiple Myeloma who are Ineligible for High-dose Therapy

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 Objective

The primary objective is to determine if the addition of daratumumab to VMP will prolong PFS compared with VMP.

Secondary Objectives

The secondary objectives are:

- To determine if the addition of daratumumab to VMP will improve clinical outcome as measured by:
  - Time to disease progression (TTP)
  - CR rate
  - Minimal residual disease (MRD) negativity rate
  - PFS2 (defined as time from randomization to progression on the next line of therapy or death, whichever comes first)
  - Time to next treatment
  - Overall response rate (partial response [PR] or better)
  - Stringent CR (sCR) rate
  - Very good partial response (VGPR) or better rate
  - Time to response
  - Duration of response
  - Overall survival
- To assess patient-reported outcomes and heath economic/resource utilization
- To determine the pharmacokinetics and immunogenicity of daratumumab
- To assess the safety and tolerability of daratumumab when administered in combination with VMP
- To evaluate clinical efficacy of daratumumab when added to VMP in high risk molecular subgroups

Exploratory Objectives

- To explore biomarkers predictive of response and resistance to therapy
- To assess durability of MRD negativity

Hypothesis

The hypothesis of the study is that daratumumab continued until disease progression, in combination with 9 cycles of VMP, will improve PFS compared with 9 cycles of VMP alone.

OVERVIEW OF STUDY DESIGN

This is a randomized, open-label, parallel-group, controlled, multicenter study in subjects at least 18 years of age with previously untreated multiple myeloma who are ineligible for high dose therapy. A target of up to 700 subjects will be enrolled in this study with 350 subjects planned per treatment arm.

Subject participation will include a Screening Phase, a Treatment Phase, and a Follow-up Phase. The Screening Phase will be up to 21 days before randomization. All subjects will receive up to 9 cycles of the VMP regimen (1 cycle = 6 weeks) with or without daratumumab.

The Treatment Phase will extend from Day 1 of Cycle 1 to discontinuation of all study treatment. Eligible subjects will be stratified by International Staging System (I vs II vs III based on central laboratory results at Screening), region (Europe vs Other), and age (<75 vs ≥75) and then randomized in a 1:1 ratio. Subjects in both treatment arms will receive 1.3 mg/m^2 VELCADE by subcutaneous injection (SC) twice weekly (Weeks 1, 2, 4, and 5) in Cycle 1 followed by once weekly (Weeks 1, 2, 4, and 5) in Cycles 2 to 9. Melphalan PO at 9 mg/m^2 and prednisone PO at 60 mg/m^2 will be self-administered on Day 1-4 of each VELCADE cycle. For subjects randomized to the Treatment Arm B, 20 mg of dexamethasone will substitute for the planned dose of prednisone on Day 1 of each cycle. In this setting, dexamethasone will be utilized as the treatment dose of steroid for that particular day, as well as the required pre-medication prior to daratumumab infusion. Daratumumab 16 mg/kg will be administered to subjects in Treatment Arm B by IV infusion once every week for 6 weeks (Cycle 1; 1 VELCADE cycle); then once every 3 weeks for 16 additional doses (Cycles 2-9). Measures to prevent infusion-related reactions (IRRs) will include pre-infusion medication with dexamethasone, paracetamol, and antihistamine before each daratumumab infusion.

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

After completion of the VMP cycles, subjects in Arm A will enter the Follow-up Phase and should not be started on subsequent anti-myeloma therapy without confirmed disease progression. Subjects in Arm B will continue to receive daratumumab every 4 weeks until documented progression, unacceptable toxicity, or the study ends (see below for definition). Subjects who need to discontinue treatment with any one component of study treatment (VELCADE, melphalan, prednisone, or daratumumab) may continue to receive treatment with the other components of study treatment, as assigned. Upon discontinuation of daratumumab, subjects in Arm B will also enter the Follow-up Phase and should not be started on subsequent anti-myeloma therapy without confirmed disease progression.

In the Follow-up Phase, subjects who discontinue treatment before disease progression must continue to have disease evaluations according to the Time and Events Schedule until confirmed PD (see Section 8.4, Subsequent Therapies), subsequent anti-myeloma treatment, death, withdrawal of consent, lost to follow-up, or the end of the study. After disease progression is documented, follow-up will be obtained at least every 16 weeks. Subsequent anti-myeloma treatment, PFS2 (per investigator judgment), second primary malignancies, and survival will also be recorded.

Two interim analyses are planned. The first interim analysis, with a purpose to evaluate safety, will be performed after a total of approximately 100 subjects have been treated for at least 2 cycles or discontinued the study treatment. The second interim analysis, with a purpose to evaluate cumulative interim safety and efficacy data, will be performed when approximately 216 PFS events have been accumulated. Investigators will be informed when each interim analysis is to occur. As the superiority of daratumumab combined with VMP over VMP alone with respect to PFS was established at the second interim analysis, the interim PFS analysis will serve as the primary PFS analysis, which otherwise was to occur when approximately 360 PFS events had been observed. As planned in the original protocol, two interim OS analyses will be performed at the time of the interim PFS (216 events) and the primary PFS (360 events) prior to the final OS analysis at 330 deaths. The second interim OS will occur when 200 deaths (60% of all planned deaths) have been accumulated which about the same time of the primary PFS analysis as if it would have occurred. All available data prior to that time will be included in each of the respective analyses. An Independent Data Monitoring Committee (IDMC) will be commissioned for this study to review efficacy and safety results at the 2 planned interim analyses and to perform periodic reviews of safety data.

The end of the study will occur when 330 subjects have died, or 5 years after the last subject is randomized, whichever comes first. The sponsor will ensure that subjects benefiting from treatment with daratumumab will be able to continue treatment after the end of the study.

As a result of the positive second interim analysis, that established the superiority of daratumumab combined with VMP over VMP alone with respect to the primary endpoint (PFS), and consistent with the IDMC's recommendation, the sponsor will ensure that access to daratumumab is provided for subjects randomized to Arm A (VMP) who have sponsor-confirmed disease progression (see Section 8.4, Subsequent Therapies).

SUBJECT POPULATION

Key eligibility criteria include the following: subjects who are ≥18 years of age (or legal age of consent), have a confirmed diagnosis of symptomatic multiple myeloma satisfying the calcium elevation, renal insufficiency, anemia, and bone abnormalities (CRAB) diagnostic criteria; monoclonal plasma cells (PCs) in the bone marrow ≥10% or presence of a biopsy proven plasmacytomas; and measurable secretory disease, as assessed by the central laboratory; an Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2, must be newly diagnosed and not considered candidates for high-dose chemotherapy with stem cell transplantation.

DOSAGE AND ADMINISTRATION

Daratumumab (16 mg/kg) will be administered to subjects in Arm B by IV infusion initially once every week for 6 weeks (Cycle 1; 1 VELCADE cycle); then once every 3 weeks for an additional 16 doses (Cycles 2-9); then once every 4 weeks thereafter (post-VMP Treatment Phase), until documented progression, unacceptable toxicity, or study end.

Subjects will receive 1.3 mg/m^2 VELCADE as a SC injection twice weekly (Weeks 1, 2, 4, and 5) for one 6-week cycle (Cycle 1; 8 doses per cycle) followed by once weekly (Weeks 1, 2, 4, and 5) administrations for eight 6-week cycles (Cycles 2 to 9; 4 doses per cycle).

Melphalan will be administered at 9 mg/m^2 and prednisone will be administered at 60 mg/m^2 on Day 1 to 4 of each VELCADE cycle. Both melphalan and prednisone will be administered orally. For subjects randomized to the Treatment Arm B, 20 mg dexamethasone will substitute for the planned dose of prednisone on Day 1 of each cycle. In this setting, dexamethasone will be utilized as the treatment dose of steroid for that particular day, as well as the required pre-medication prior to daratumumab infusion.

EFFICACY EVALUATIONS/ENDPOINTS

Disease evaluations must be performed every 3 weeks during the first year, every 4 weeks during the second year, and every 8 weeks thereafter until disease progression (or other reasons as per Section 10 of the protocol). A window of ±7 days is allowed. If treatment has been delayed for any reason, the disease evaluations must be performed according to the original schedule, regardless of any changes to the dosing regimen.

The primary endpoint is PFS, which is defined as the duration from the date of randomization to either progressive disease or death, whichever comes first. Disease progression will be determined according to the IMWG criteria (Durie 2006, Rajkumar 2011)[8,37].

The secondary efficacy endpoints include:

- Time to disease progression (TTP) is defined as the time from the date of randomization to the date of first documented evidence of PD, as defined in the IMWG criteria. For subjects who have not progressed, data will be censored at the date of the disease evaluation before the start of any subsequent anti-myeloma therapy.
- CR rate, defined as the percentage of subjects achieving CR, as defined by:
  - Negative immunofixation of serum and urine, and
  - Disappearance of any soft tissue plasmacytomas, and
  - <5% PCs in bone marrow
  - For those subjects with negative or low SPEP (≤0.2 g/L) and suspected daratumumab interference on immunofixation, a reflex assay using anti-idiotype antibody will be utilized to confirm daratumumab interference and rule out false positive immunofixation. Subjects who have confirmed daratumumab interference, but meet all other clinical criteria for CR or sCR, will be considered CR/sCR.
- MRD negativity rate, defined as the proportion of subjects who have negative MRD at any time point after the date of randomization.
- Progression-free Survival on Next line of Therapy (PFS2), defined as the time from randomization to progression on the next line of treatment or death, whichever comes first. Disease progression will be based on investigator judgment. Subjects who are still alive and not yet progressed on the next line of treatment will be censored on the last date of follow-up.
- Time to next treatment, defined as the time from randomization to the start of the next-line treatment.
- Overall response rate (ORR), defined as the proportion of subjects who achieve PR or better according to the IMWG criteria, during or after the study treatment.
- sCR rate, defined as the percentage of subjects achieving CR in addition to having a normal FLC ratio and an absence of clonal cells in bone marrow by immunohistochemistry, immunofluorescence, 2-4 color flow cytometry**.**
- Proportion of subjects who achieve VGPR or better, defined as the proportion of subjects achieving VGPR and CR (including sCR) according to the IMWG criteria during or after the study treatment at the time of data cutoff.
- Time to response, defined as the time between randomization and the first efficacy evaluation that the subject has met all criteria for PR or better. For subjects without response, data will be censored either at the date of progressive disease or, in the absence of progressive disease, at the last disease evaluation before the start of subsequent anti-myeloma therapy.

- Duration of response, calculated from the date of initial documentation of a response (CR or PR) to the date of first documented evidence of progressive disease, as defined in the IMWG criteria. For subjects who have not progressed, data will be censored at the last disease evaluation before the start of any subsequent anti-myeloma therapy.
- OS, measured from the date of 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.
- Impact of D-VMP compared to VMP on patient-reported perception of global health.
- Clinical efficacy of D-VMP in high risk molecular subgroups compared to VMP alone.

Exploratory endpoints include:

- Biomarkers predictive of response or resistance to daratumumab
- Durability of MRD negativity

PHARMACOKINETIC AND IMMUNOGENICITY EVALUATIONS

Samples to assess both the serum concentration (pharmacokinetics) of daratumumab and the generation of antibodies to daratumumab (immunogenicity) will be obtained from all subjects in the D-VMP group according to the Time and Events Schedule. In the Follow-up Phase, for all subjects in Arm B (D-VMP), samples are to be collected 8 weeks after the last dose of daratumumab, regardless of whether there has been confirmed disease progression. At specified time points, venous blood samples (5 mL per sample) will be collected and the serum will be divided into 3 aliquots (1 aliquot for pharmacokinetic analysis, 1 aliquot for immunogenicity assessment [when appropriate], and 1 aliquot as a back-up).

BIOMARKER EVALUATIONS

Bone marrow aspirates will be collected at screening and following treatment as outlined in the Time and Events Schedule. Baseline bone marrow aspirate samples will be subjected to DNA and RNA sequencing in order to classify subjects into high-risk molecular subgroups and to establish the myeloma clone for MRD monitoring.

In addition to planned bone marrow aspirate assessments, a whole blood sample will be collected from subjects as outlined in the Time and Events Schedule for processing to plasma and PBMCs.

SAFETY EVALUATIONS

Safety will be measured by adverse events, laboratory test results, ECGs, vital sign measurements, physical examination findings, and assessment of ECOG performance status score.

During Cycle 1 at Japanese sites, an enhanced reporting, monitoring, and review of pre-specified safety events that occur for Japanese subjects in Arm B will be performed until a minimum of 3 subjects in Arm B have completed Cycle 1.

STATISTICAL METHODS

The sample size calculation is performed based on the assumption that the median PFS for the VMP group in this study is estimated to be 21 months. Assuming that the addition of daratumumab can reduce the risk of the disease progression or death by 27.6%, ie, assuming the hazard ratio (VMP vs. D-VMP) of 0.724, which translates into a median PFS of 29 months for the D-VMP group, a total of 360 PFS events is needed to achieve a power of 85% to detect this hazard ratio with a log-rank test (two-sided alpha = 0.05). With a 20-month accrual period and an additional 21-month follow-up, the total sample size needed for the study is approximately 700 (350/treatment group) subjects. The sample size calculation has taken into consideration an annual dropout rate of 5%.

Long-term survival follow-up will continue until 330 deaths have been observed. Therefore, this study will achieve more than 80% power to detect a 27% reduction in the risk of death (hazard ratio=0.73) with a log-rank test (two-sided alpha=0.05).

Response to study treatment and progressive disease will be evaluated by a validated computer algorithm. For the primary endpoint of PFS, the primary analysis will consist of a stratified log-rank test for the comparison of the PFS distribution between the 2 treatment groups. The Kaplan-Meier method will be used to estimate the distribution of overall PFS for each treatment. The treatment effect (hazard ratio) and its two-sided 95% confidence intervals are to be estimated using a stratified Cox regression model with treatment as the sole explanatory variable.

Details of the 2 planned interim analyses are provided in Synopsis, Overview of Study Design. After each interim review, the IDMC will make recommendations regarding the continuation of the study. In addition, the IDMC may also review cumulative safety data every 6 months besides the 2 interim analyses. The IDMC will no longer review study data after the database lock for the primary analysis has been completed.

As the superiority of daratumumab combined with VMP over VMP alone with respect to PFS was established at the second interim analysis, the interim PFS analysis will serve as the primary PFS analysis, which otherwise was to occur when approximately 360 PFS events had been observed. The date established for the primary PFS analysis (12 June 2017) will serve as the primary clinical cutoff date, after which subject monitoring will be conducted according to Section 9.1.5 of the protocol. After the OS interim analysis (ie, when 200 deaths have occurred) subject monitoring will be conducted according to Section 9.1.6.

TIME AND EVENTS SCHEDULE

	Notes	Screening Phase	Treatment Phase			Follow-up Phase	
		within 21 days before randomization	**Cycle 1-9** VMP Treatment (6wk cycles), **Arm A and Arm B**	**Cycle 10+** Dara Treatment (4wk cycles), **Arm B ONLY**	**EOT** 30 days after last dose	Prior to PD	After PD (Q16wks ±2 weeks)
Study treatment should be initiated within 72 hours after randomization. The start of each cycle may occur ±3 days of the scheduled day in order to accommodate the schedule of the site or subject. After EOT, subjects in both treatment arms prior to PD will continue to return for disease evaluations. After PD is documented, subjects will be followed for survival, PFS2, second primary malignancy, and subsequent anti-myeloma therapy. After the primary clinical cutoff date (12 June 2017), subject monitoring will be conducted as per Section 9.1.5. After the OS interim analysis, subject monitoring will be conducted according to Section 9.1.6.							
Procedures							
Informed consent	ICF must be signed before any study related procedures						
Eligibility criteria		X					
Demography/ Medical History		X					
Height		X					
Chest X-ray (or full chest CT scan)	Acceptable for screening if performed as part of SOC within 42 days before randomization	X					
Spirometry	FEV1 measured for subjects with COPD; acceptable for screening if performed as part of SOC within 42 days before randomization	X					
ECOG	Prior to any other study procedures planned for the same day	X	Q3mo in year 1 (ie, every 12 weeks from C1D1), thereafter Q6mo (ie, every 24 weeks thereafter) until PD, post PD Wk8, Wk16 (window ±14 days)				
12-lead ECG	Acceptable for screening if performed as part of SOC within 42 days before randomization	X	C3D1, C6D1 (±7 days)		X		
Physical exam	including neurological exam	X	Symptom and disease directed exam as clinically indicated				
Vital signs, weight		X	Please see following table for details		X		
Blood type and Indirect AntiglobulinTest	ABO, Rh, and IAT to be assessed locally. Results will be included on wallet card for subjects in Arm B.		C1D1, Arm B only				
Wallet Card	To be given to all subjects (in Arm A and in Arm B)		C1D1				
Laboratory Assessments							
Pregnancy test	For women of childbearing potential only, serum or urine pregnancy test within 14 days of randomization.	X	additional serum or urine pregnancy tests as clinically indicated				

	Notes	Screening Phase	Treatment Phase			Follow-up Phase	
		within 21 days before randomization	**Cycle 1-9** VMP Treatment (6wk cycles), **Arm A and Arm B**	**Cycle 10+** Dara Treatment (4wk cycles), **Arm B ONLY**	**EOT** 30 days after last dose	Prior to PD	After PD (Q16wks ±2 weeks)
Hematology	Acceptable for screening to meet CRAB criteria if performed as part of SOC within 42 days before randomization, but must also be performed within 21 days before randomization for other eligibility requirements.	X	Please see following table for details		X		
Serum chemistry	Acceptable for screening to meet CRAB criteria if performed as part of SOC within 42 days before randomization, but must also be performed within 21 days before randomization for other eligibility requirements.	X	Please see following table for details		X		
Daratumumab PK	Arm B only. On dara infusion days, 1 sample is to be collected before the start of infusion (up to 2 hours before the start of the infusion) and 1 sample is to be collected after the end of infusion (up to 2 hours after the end of infusion). Samples to be sent to central laboratory.		C1D1, C3D1, C6D1 **Arm B ONLY**		X **Arm B ONLY**	8 wks after last dara dose **Arm B ONLY**	
Daratumumab immunogenicity	Arm B only. No additional sample needed; will be taken from PK sample. If an infusion reaction occurs, obtain unscheduled blood sample as soon as possible.		C1D1 predose **Arm B ONLY**		X **Arm B ONLY**	8 wks after last dara dose **Arm B ONLY**	
Whole blood	Plasma and PBMC biomarker assessments		C1D1 predose		X		
Disease Evaluations: Every effort should be made to conduct disease evaluations as per schedule (window ±7 days, ePRO window ±14 days). Refer to Section 9.2 for details on efficacy evaluations							
SPEP and IFE, 24-hour UPEP and IFE	Sample to be sent to central laboratory. Randomization based on central laboratory values. After Cycle 1, IFE only when endogenous M-protein is 0 or nonquantifiable.	X	Q3wk in year 1, Q4wk in year 2, thereafter Q8wk until PD. Not required on C1D1 if screening values were obtained from samples collected within the prior 14 days				
Serum FLC	FLC to confirm CR and sCR. In addition, for subjects with light chain myeloma, perform according to schedule. Sample to be sent to central laboratory.	X	Q3wk in year 1, Q4wk in year 2, thereafter Q8wk until PD. Not required on C1D1 if screening values were obtained from samples collected within the prior 14 days				
Calcium, albumin	Sample to be sent to central laboratory. ISS staging based on central laboratory value.	X	Q3wk in year 1, Q4wk in year 2, thereafter Q8wk until PD. Not required on C1D1 if screening values were obtained from samples collected within the prior 14 days				
β2-microglobulin	Sample to be sent to central laboratory. ISS staging based on central laboratory value	X					
Bone marrow aspirate/biopsy	For screening (up to 42 days before randomization) fresh aspirate or biopsy preferred. If not available, obtain non-decalcified slides (bone marrow aspirate, touch preparation or clot selection) or FFPE block (clot section only, no bone marrow biopsy). Fresh biopsy or aspirate or both required to confirm CR/sCR. Samples for biomarker analysis to be sent to central laboratory.	X (Refer to Section 9.2.1.5 for required local bone marrow testing)	To confirm CR/sCR, assess MRD, and evaluate PD (if feasible). For subjects with CR/sCR, an additional bone marrow aspirate will be obtained 12, 18, 24 and 30 months (+2 months) after first dose. A portion of all bone marrow aspirates may be used for other biomarker assessments (see Section 9.2.1.5 and Table 10)				

	Notes	Screening Phase	Treatment Phase			Follow-up Phase	
		within 21 days before randomization	**Cycle 1-9** VMP Treatment (6wk cycles), **Arm A and Arm B**	**Cycle 10+** Dara Treatment (4wk cycles), **Arm B ONLY**	**EOT** 30 days after last dose	Prior to PD	After PD (Q16wks ±2 weeks)
Quantitative Ig	See Section 9.2.1.2	X	C3D1, C5D1, C7D1, C9D1	Every 4 months until PD **Arm B ONLY**	X	Every 3 months in Year 1, then every 4 months after Year 1 until PD	
Lytic disease assessment	Acceptable for screening if performed as part of SOC within 42 days before randomization	X	As clinically indicated, using the same methodology as used at screening				
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 Q6wks, by radiologic exam (if required) Q12wks, using the same methodology as used at screening. For subjects with history of plasmacytoma assessed by physical exam, repeat assessment on C1D1 if not done within 14 days prior to randomization.				
PRO	EORTC-QLQ-30, EQ-5D-5L, collected using an electronic device (ePRO)	X	Q3mo in year 1 (ie, every 12 weeks from C1D1), thereafter Q6mo (ie, every 24 weeks thereafter) until PD, post PD Wk8, Wk16 (window ±14 days); preferably to be completed prior to any other study procedures at that study visit				
Follow-up							
Survival, PFS2, second primary malignancy, subsequent anti-myeloma therapy							Q16wk
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					

Abbreviations to the Time and Events Schedules:
AE=adverse event; Arm A=VMP alone for nine 6-week cycles; Arm B=VMP + daratumumab for nine 6-week cycles, then daratumumab monotherapy until PD; C=cycle; COPD=chronic obstructive pulmonary disease; CR=complete response; CRAB=calcium elevation, renal insufficiency, anemia, and bone abnormalities; D=day; Dara=daratumumab; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=End-of-Treatment; FEV1=Forced Expiratory Volume (in 1 second); FFPE=formalin-fixed paraffin embedded; FLC=free light chain; hr=hour; ICF=informed consent form; IFE=immunofixation; Ig=immunoglobulin; ISS=International Staging System; MRD=minimal residual disease; MRI=magnetic resonance imaging; OS=overall survival; PBMC=peripheral blood mononuclear cell ; PD=disease progression; PFS2=time from randomization to progression on the next line of therapy or death, whichever comes first; PK=pharmacokinetics; PRO=patient-reported outcomes; Q(3)(6)mo=every (3)(6) months; Q(3)(4)(8)(16)wk=every (3)(4)(8)(16) weeks; Q(2)(3)cycle=every (2)(3) cycles; SAE=serious adverse event; SC=subcutaneous; sCR=stringent complete response; SIPPM=Site Investigational Product Procedures Manual (or equivalent document); SOC=standard of care; SPEP=serum M-protein quantitation by electrophoresis; UPEP=urine M-protein quantitation by electrophoresis; VMP=VELCADE-melphalan-prednisone; Wk=week.

TIME AND EVENTS SCHEDULE FOR STUDY TREATMENT, CYCLE 1 (VMP TREATMENT PHASE)

	Notes	Week 1				Week 2		Week 3	Week 4		Week 5		Week 6
		D1	D2	D3	D4	D8	D11	D15	D22	D25	D29	D32	D36
Study treatment should be administered in the following order: prednisone, daratumumab, VELCADE, and melphalan. Cycles are based on the administration of VELCADE. The start of each cycle may occur ±3 days of the scheduled day in order to accommodate the schedule of the site or subject													
Hematology	Local lab. Required for subjects in both treatment arms. For C1D1, no need to repeat tests if done within past 5 days. Testing may be performed up to 2 days before other treatment days. Results of hematology tests must be evaluated before administration of treatment. Perform at additional time points, as clinically indicated.	X				X		X	X		X		X
Clinical Chemistry		X							X				
Weight	If weight changes by more than 10% from baseline, the dose of all study treatments will be re-calculated	X											
Vital Signs	Vital signs (blood pressure, heart rate, temperature) measured in sitting position for subjects in both treatment arms. Additionally, for Arm B only, on Cycle 1 Day 1 before the start of dara infusion; at 0.5, 1, 1.5, 2, 3.5 hr after start of infusion; at end of infusion; 0.5,1 hr after end of infusion. For all other infusions, vital signs measured before start and at end of dara infusion.	X				X		X	X		X		X
Diary review	Accountability/exposure check					X							
Pre-infusion Medications, Arm B only													
Dexamethasone	Administer approximately 1 hour before dara infusion. PO pre-infusion medications may be administered within 3 hours before the infusion. • Dexamethasone 20 mg IV or PO. Substitutions for dexamethasone allowed, see Attachment 6. • An antihistamine (diphenhydramine 25-50 mg IV or PO, or equivalent H1 blocker), see Attachment 5 • Paracetamol (acetaminophen) 650-1000 mg IV or PO • Leukotriene inhibitor, montelukast 10 mg PO or equivalent, optional, C1D1	X				X		X	X		X		X
Antihistamine		X				X		X	X		X		X
Paracetamol		X				X		X	X		X		X
Leukotriene Inhibitor (optional)		X											

	Notes	Week 1				Week 2		Week 3	Week 4		Week 5		Week 6
		D1	D2	D3	D4	D8	D11	D15	D22	D25	D29	D32	D36
Study Treatment, Arm A and Arm B													
Prednisone	Dispense on Day 1 for self-administration. Prednisone taken on Day 1 in Arm A only (dexamethasone will be given on Day 1 in Arm B), taken on Day 2-4 in both Arms.	X	X	X	X								
VELCADE	Administer by SC injection. Dose may be delayed up to 48 hrs, however subsequent doses must be adjusted to account for delay as all VELCADE doses should be at least 72 hrs apart. Doses that need to be withheld are skipped and will not be made up later in the cycle. Individual doses within a cycle have a ±1 day window	X			X	X	X		X	X	X	X	
Melphalan	Dispense on Day 1 for self-administration.	X	X	X	X								
Study Treatment, Arm B only													
Daratumumab	Refer to SIPPM for recommendations on daratumumab infusion rate. Skip if infusion cannot be given within 3 days. Individual doses within a cycle have a ±1 day window.	X				X		X	X		X		X

TIME AND EVENTS SCHEDULE FOR STUDY TREATMENT, CYCLE 2 TO 9 (VMP TREATMENT PHASE)

	Notes	Week 1				Week 2		Week 3	Week 4		Week 5		Week 6
		D1	D2	D3	D4	D8	D11	D15	D22	D25	D29	D32	D36
Study treatment should be administered in the following order: prednisone, daratumumab, VELCADE, and melphalan. Cycles are based on the administration of VELCADE. The start of each cycle may occur ±3 days of the scheduled day in order to accommodate the schedule of the site or subject													
Hematology	Local lab. Required for subjects in both treatment arms. Testing may be performed up to 2 days before treatment day. Results of hematology tests must be evaluated before administration of treatment. Perform at additional time points, as clinically indicated.	X							X				
Clinical Chemistry		X							X				
Weight	If weight changes by more than 10% from baseline, the dose of all study treatments will be re-calculated	X											
Vital Signs	Vital signs (blood pressure, heart rate, temperature) measured in sitting position for subjects in both treatment arms. Additionally, for Arm B, vital signs before start and at end of dara infusion.	X							X				
Diary review	Accountability/exposure check					X							

	Notes	Week 1				Week 2		Week 3	Week 4		Week 5		Week 6
		D1	D2	D3	D4	D8	D11	D15	D22	D25	D29	D32	D36
Pre-infusion Medications, Arm B only													
Dexamethasone	Administer approximately 1 hour before dara infusion. PO pre-infusion medications may be administered within 3 hours before the infusion. • Dexamethasone 20 mg IV or PO. Substitutions for dexamethasone allowed, see Attachment 6. • An antihistamine (diphenhydramine 25-50 mg IV or PO, or equivalent H1 blocker), see Attachment 5 • Paracetamol (acetaminophen) 650-1000 mg IV or PO	X							X				
Antihistamine		X							X				
Paracetamol		X							X				
Study Treatment, Arm A and Arm B													
Prednisone	Dispense on Day 1 for self-administration. Prednisone taken on Day 1 in Arm A only (dexamethasone will be given on Day 1 in Arm B), taken on Day 2-4 in both Arms.	X	X	X	X								
VELCADE	Administer by SC injection. Dose may be delayed up to 48 hrs, however subsequent doses should be adjusted to account for delay 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. Individual doses within a cycle have a ±1 day window.	X				X			X		X		
Melphalan	Dispense on Day 1 for self-administration.	X	X	X	X								
Study Treatment, Arm B only													
Daratumumab	Refer to SIPPM for recommendations on daratumumab infusion rate. Skip if infusion cannot be given within 1 wk. Individual doses within a cycle have a ± 1 day window.	X							X				

TIME AND EVENTS SCHEDULE FOR STUDY TREATMENT, CYCLE 10+ (DARA TREATMENT PHASE, ARM B ONLY)

	Notes	Day 1 every 4 weeks
The start of each cycle may occur ±3 days of the scheduled day in order to accommodate the schedule of the site or subject.		
Hematology	Local lab. Testing may be performed up to 2 days before treatment day. Results of hematology tests must be evaluated before each infusion. Perform at additional time points, as clinically indicated. AST and ALT every 3 cycles.	X
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	Vital signs (blood pressure, heart rate, temperature) measured in sitting position before start and at end of daratumumab infusion.	X
Pre-infusion Medications, Arm B only		
Dexamethasone	Administer approximately 1 hour before dara infusion. PO pre-infusion medications may be administered within 3 hours before the infusion • Dexamethasone 20 mg IV or PO. Substitutions for dexamethasone allowed, see Attachment 6. • An antihistamine (diphenhydramine 25-50 mg IV or PO, or equivalent H1 blocker), see Attachment 5 • Paracetamol (acetaminophen) 650-1000 mg IV or PO	X
Antihistamine		X
Paracetamol		X
Study Treatment, Arm B only		
Daratumumab	Refer to SIPPM for recommendations on daratumumab infusion rate. Skip if infusion cannot be given within 2 wks.	X

ABBREVIATIONS

ADCC	antibody-dependent cell-mediated cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
AE	adverse event
ALT	alanine aminotransferase
ASCT	autologous stem cell transplantation
AST	aspartate aminotransferase
BM-MNC	bone marrow mononuclear cell
BSA	body surface area
BUN	blood urea nitrogen
CDC	complement-dependent cytotoxicity
CKD-EPI	chronic kidney disease epidemiology collaboration
CL	total systemic clearance
Cmax	maximum observed concentration
Cmin	minimum observed concentration
COPD	chronic obstructive pulmonary disease
CR	complete response
CRAB	calcium elevation, renal insufficiency, anemia, and bone abnormalities
CrCl	creatinine clearance
CT	computed tomography
dara	daratumumab
D_{LCO}	diffusing capacity of the lung for carbon monoxide
DLT	dose limiting toxicity
DTT	dithiothreitol
D-VMP	daratumumab plus VELCADE-melphalan-prednisone
EBMT	European Group for Blood and Marrow Transplantation
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
eDC	electronic data capture
EU	European Union
FEV1	forced expiratory volume (in 1 second)
FFPE	formalin fixed paraffin embedded
FISH	fluorescence in situ hybridization
FLC	free light chain
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
HIV	human immunodeficiency virus
HR	hazard ratio
IAT	indirect antiglobulin test (also known as indirect Coombs test)
ICF	informed consent form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFE	immunofixation
Ig	immunoglobulin
IHC	immunohistochemistry
IMiD	immunomodulatory agent
IMWG	International Myeloma Working Group
IRB	Institutional Review Board
IRR	infusion-related reaction
ISS	International Staging System
IV	intravenous
IWRS	interactive web response system
LDH	lactic acid dehydrogenase
LVEF	left ventricular ejection fraction

mAb	monoclonal antibody
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MP	melphalan-prednisone
MPT	melphalan-prednisone-thalidomide
MRD	minimal residual disease
MRI	magnetic resonance imaging
MRU	medical resource utilization
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next generation sequencing
NK	natural killer
OR	overall response
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PC	plasma cell
PD	disease progression
PFS	progression-free survival
PFS2	time from randomization to progression on the next line of therapy or death, whichever comes first
PI	proteasome inhibitor
PK	pharmacokinetics
PO	per oral
PQC	Product Quality Complaint
PR	partial response
PRO	patient-reported outcome(s)
QD	once daily
QIg	quantitative immunoglobulins
RBC	red blood cell
Rd	lenalidomide plus low-dose dexamethasone
SAE	serious adverse event
SC	subcutaneous injection
sCR	stringent complete response
SCT	stem cell transplantation
SIPPM	Site Investigational Product Procedures Manual (or equivalent document)
SPEP	serum M-protein quantitation by electrophoresis
TTP	time to progression
ULN	upper limit of normal
UPEP	urine M-protein quantitation by electrophoresis
US	United States
V	volume of distribution
VD	VELCADE-dexamethasone
VGPR	very good partial response
VISTA	“VELCADE as Initial Standard Therapy in multiple myeloma” study
VMP	VELCADE-melphalan-prednisone
VMPT	VELCADE-melphalan-prednisone-thalidomide
VP	VELCADE-prednisone
VT	VELCADE-thalidomide
VTD	VELCADE-thalidomide-dexamethasone
VTP	VELCADE-thalidomide-prednisone
WHO	World Health Organization

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 disease leads to progressive morbidity and eventual mortality by lowering resistance to infection and causing significant skeletal destruction (with bone pain, pathological fractures, and hypercalcemia), anemia, renal failure, neurological complications and hyperviscosity syndrome.

The majority of patients with multiple myeloma produce a monoclonal protein, also called paraprotein, M-protein or M-component, which is an immunoglobulin (Ig) or a fragment of one that has lost its function (Kyle 2009, Palumbo 2011).[19,33] Normal immunoglobulin levels are compromised, leading to susceptibility of infections. 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, neurologic symptoms, and bone resorption seen as diffuse osteoporosis or lytic lesions shown in radiographs (Kyle 2003).[18] Furthermore, hypercalcemia, renal insufficiency or failure, and detectable monoclonal protein in the serum or urine are frequently seen (Palumbo 2011).[33] A small minority of patients with multiple myeloma are non-secretory.

At the time of diagnosis, multiple myeloma is a heterogeneous disease, with a course that varies on the basis of both disease- and host-related factors (eg, age, renal function, stage, chromosomal abnormalities). Multiple myeloma causes significant morbidity and mortality. It accounts for approximately 1% of all malignancies and 13% of hematologic cancers. Approximately 50,000 patients per year are diagnosed with multiple myeloma in the EU and US, and 30,000 patients per year die due to multiple myeloma (ACS 2013, Ferlay 2010).[1,11]

1.1.2. Treatment Options for Multiple Myeloma

Treatment choices for multiple myeloma vary with age, performance status, comorbidity, the aggressiveness of the disease, and related prognostic factors (Palumbo 2011).[33] 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 autologous stem cell transplantation (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.

The availability of different efficacious multi-agent regimens has provided clinicians with the opportunity of tailoring treatment for each patient. Selection is based on patients' comorbidities and biologic age, while at the same time, taking into account the expected toxicity profiles of each treatment regimen (Gay 2011).[12]

1.1.3. Transplant-ineligible Population

In general, patients over the age of 65 or with significant comorbidities are usually not considered eligible for more intensive forms of first line therapy, and as a result the treatment approach often favors longer, less-intensive/toxic treatments (Gay 2011).[12] Treatment traditionally consists of systemic chemotherapy, with adjunctive use of radiation or surgery in selected cases associated with extramedullary disease (NCCN 2013, Palumbo 2009, Smith 2005).[30,36,40] For many years, the oral combination melphalan-prednisone (MP) was considered the standard of care for patients with multiple myeloma who were not eligible for ASCT (Gay 2011).[12] The advent of immunomodulatory agents (IMiD) and proteasome inhibitors (PI) has led to a multiplicity of new treatment options for newly diagnosed patients not considered suitable for transplant based therapy. In Europe, the standard of care are combinations such as melphalan-prednisone-thalidomide (MPT) (Fayers 2011)[10], or VELCADE-melphalan-prednisone (VMP) (San Miguel 2008).[39] VELCADE in combination with melphalan and prednisone are approved in this setting within numerous countries worldwide including the European Union and the US.

1.1.4. Treatment Until Progression in Transplant-ineligible Patients

There is growing evidence that continued treatment of multiple myeloma can prolong the period of remission; however, long-term treatment with current therapies is often compromised through unacceptable toxicity.

The VMP regimen is typically given for up to a year; the VISTA study (VELCADE as Initial Standard Therapy in multiple myeloma [VISTA]) demonstrated that complete responses continued to occur in the later cycles (Cycles 5-9) (Harousseau 2010).[14] Furthermore, the study demonstrated that the longer patients were on treatment, the better the outcomes.

VELCADE, given to disease progression, has been investigated in combination with other agents in the transplant-ineligible population. In a study of 178 elderly untreated patients who were initially treated with an induction combination regimen comprising either VMP or VELCADE-thalidomide-prednisone (VTP), patients were treated until progression with either VELCADE-thalidomide (VT) or VELCADE-prednisone (VP). Progression-free survival or OS was not significantly different between the 2 treatment groups, but both resulted in median PFS of 32 (VP) to 39 (VT) months and a 5-year OS over 50% in both arms (Mateos 2012).[27]

In another randomized comparison of VELCADE- melphalan-prednisone- thalidomide (VMPT) followed by continuous VT as maintenance, or VMP with no additional continuous therapy in 511 previously untreated patients who were not eligible for transplant (aged 65 years or older), the arm with VMPT induction followed by the continuous VT therapy showed superiority over the VMP alone arm. The 3-year estimates of PFS were 56% in patients receiving VMPT-VT and 41% in those receiving VMP (p=0.008) (Palumbo 2010).[35]

Further justification for continuous treatment until progression was demonstrated in a large, randomized Phase 3 study (MM-020/IFM 07-01) comparing 2 active-treatment arms consisting of different durations of lenalidomide plus low-dose dexamethasone (Rd) to a third active control arm of MPT in subjects newly diagnosed with multiple myeloma (Facon 2013).[9] In this study,

1,623 subjects who were ineligible for ASCT were randomized to receive continuous Rd until disease progression (Arm A); Rd for eighteen 28-day cycles (72 weeks) (Arm B); or MPT for up to twelve 42-day cycles (72 weeks) (Arm C). The primary endpoint of the study is PFS (Arm A vs Arm C). Secondary endpoints included OS, response rate, quality of life and safety. Continuous treatment with Rd significantly improved the primary endpoint of PFS compared with MPT. After a median follow-up of 37 months, the trial met the primary endpoint, demonstrating a 28% reduction in risk of progression or death (HR=0.72; p=0.00006). The preplanned interim analysis of OS demonstrated a 22% reduction in risk of death in favor of Arm A vs Arm C (HR=0.78, p=0.01685); however, the pre-specified boundary (p<0.0096) was not crossed. All other secondary endpoints (ORR [PR or better], OR, and PFS2) consistently showed improvement in favor of Arm A vs. Arm C. The safety profile of Rd was manageable, with reduced hematologic second primary malignancies compared with MPT.

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.

For the most comprehensive nonclinical and clinical information as well as Reference Safety Information regarding daratumumab, refer to the latest version of the Investigator's Brochure (IB Daratumumab 2013).[16]

1.2.1. Nonclinical Studies

Based on preclinical data, daratumumab may utilize multiple effector cell functions, resulting in immune mediated killing of tumor cells. In ex vivo experiments utilizing human bone marrow stromal cells co-cultured with primary multiple myeloma cells, 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).[6] 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).[6] Daratumumab has also been shown to induce antibody-dependent cellular phagocytosis (ADCP) in the presence of macrophages within 4 hours in vitro (Overdijk 2013).[32] The precise role of some or all of these effector functions in reducing tumor burden in patients is unknown.

In toxicology studies in cynomolgus monkeys and chimpanzees, the major observed toxicities were cytokine release syndrome and thrombocytopenia along with a minor decrease in red blood parameters. 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.

Preclinical evidence to support combining VMP with daratumumab is based on results of ex vivo flow cytometry-based assay platform, in which the addition of daratumumab to VMP significantly increased the treatment effect by almost doubling the bone marrow mononuclear cells lysis levels (van der Veer 2011a).[42]

In 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 VELCADE, even in samples from subjects that were refractory to lenalidomide and VELCADE treatment. Treatment of BM-MNC with lenalidomide or VELCADE resulted in 10% and 18% lysis, respectively. A combination of lenalidomide and VELCADE resulted in 25% lysis of BM-MNC. When daratumumab was added to either lenalidomide or VELCADE, a 2-fold increase in lysis was observed compared with lenalidomide or VELCADE alone. When daratumumab was added to combinations of dexamethasone, lenalidomide and VELCADE or to VELCADE, prednisone, and melphalan, the cell lysis was significantly increased ($p<0.001$) compared with the triple combination alone (no daratumumab) (van der Veer 2011a).[42] Refer to Figure 1 and Figure 2.

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

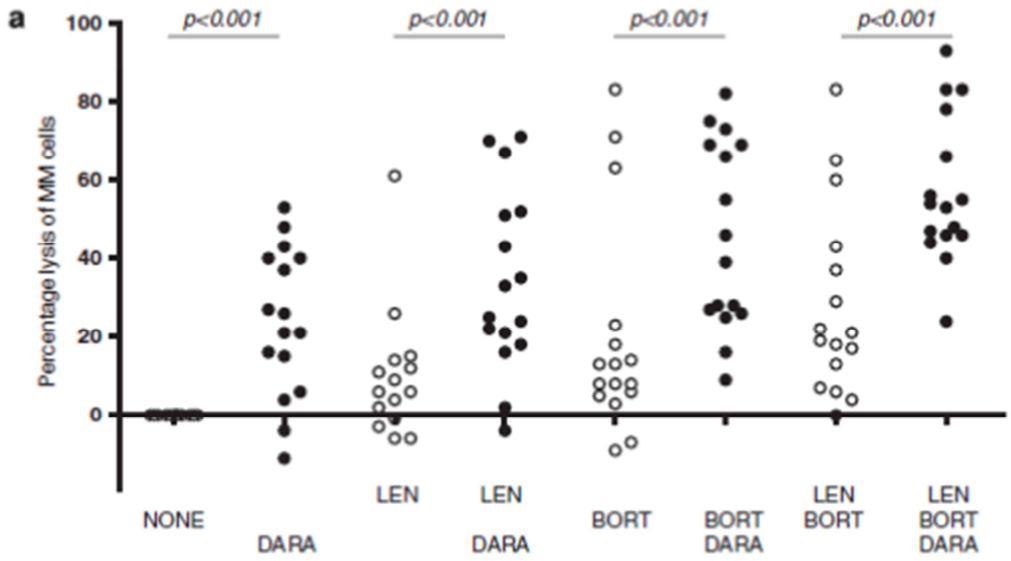
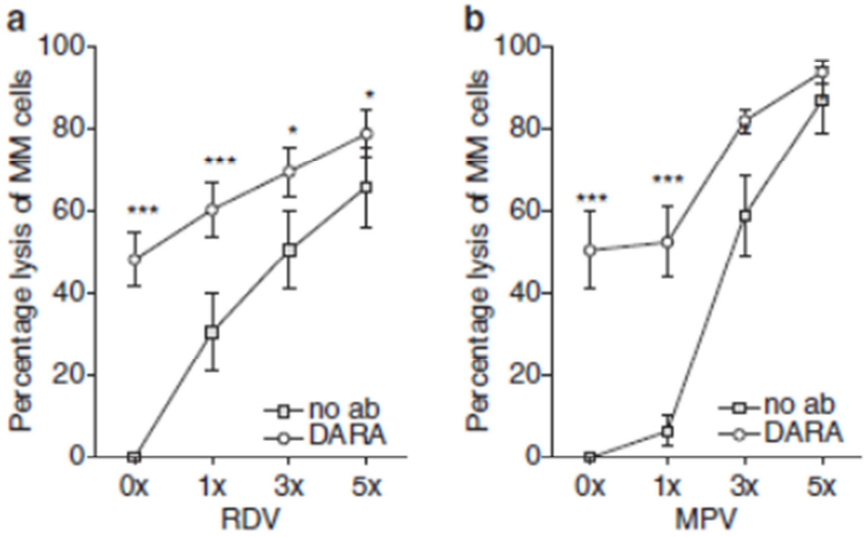


Figure 2: Dose-dependent Lysis of Multiple Myeloma cells in Triple Chemotherapy Treatments



1.2.2. Clinical Studies

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

Two single-agent studies with daratumumab are ongoing (Studies GEN501 and MMY2002), as described in Table 1.

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).

Table 1: Daratumumab Single-Agent Studies GEN501 and MMY2002

Study Number	Study Design	Number of subjects Treated/ Treatment Regimen	
GEN501	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	Part 1 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)	
		Part 2 n=51 total treated	
		8 mg/kg (n=30) Weekly for 8 weeks, followed by q2w for an additional 16 weeks, and monthly thereafter	16 mg/kg (n=21) 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 thereafter
MMY2002	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	n=34 total treated in Stage 1	
		8 mg/kg (n=18) q4w	16 mg/kg (n=16) qw for 8 weeks, then q2w for another 16 weeks, and then q4w thereafter

ASCT=autologous stem cell transplantation; IMiD=immunomodulatory agent; PI=proteasome inhibitor; q2w=every 2 weeks; q4w=every 4 weeks

1.2.2.2. Combination Daratumumab Studies

One study of daratumumab in combination with lenalidomide and dexamethasone (Study GEN503), and one study of daratumumab in combination with various backbone treatment regimens (Study MMY1001) are ongoing (Table 2).

Based on preliminary efficacy data, 15 of 20 subjects treated 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, 5 subjects have been enrolled to the VMP plus daratumumab cohort as of 21 May 2014. The same dose and schedule used in MMY1001 will be utilized in the present study. Emerging safety data will be communicated as appropriate.

Table 2: 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)	Phase 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 in combination with various backbone treatment regimens for multiple myeloma in either newly diagnosed or those who have received at least 2 prior therapies, depending on backbone treatment regimen	Daratumumab 16 mg/kg (initially, with possibility to de-escalate, if necessary) The backbone regimens to be combined with daratumumab include VELCADE-dexamethasone (VD), VMP, VTD, and Pom-dex	n=18 subjects treated VTD (n=6) VMP (n=5) Vd (n=1) Pom-dex (n=6) approximately 48 subjects planned; 12 per cohort
Pom-dex=pomalidomide-dexamethasone; VMP-VELCADE-melphalan-prednisone; VTD=VELCADE-thalidomide-dexamethasone			

Phase 3 combination studies include study MMY3003 comparing daratumumab, lenalidomide, and dexamethasone with Rd and study MMY3004 comparing daratumumab, VELCADE, and dexamethasone with Vd. Both ongoing studies are in patients with relapsed or refractory multiple myeloma.

1.3. Overall Rationale for the Study

Multiple myeloma remains incurable with standard chemotherapy, despite the availability of multi agent therapy. Strategies directed at improving and maintaining response for longer periods of time and new treatment options directed at alternative mechanisms are also urgently needed for patients with multiple myeloma.

The clinical utility of adding VELCADE to melphalan and prednisone (VMP) for the treatment of patients 65 years or older was investigated in the VISTA study (San Miguel 2008).[39] The study demonstrated significant improvements in both time to progression and overall survival compared to MP alone. In terms of response rate, 30% of patients in the VMP group had a complete response versus only 4% in the MP group ($p<0.001$). Median time to progression was 24.0 months in the VMP group compared to 16.6 months in the MP group (HR=0.48, $p<0.001$). Median time to subsequent myeloma therapy was 20.8 months in the MP group and was not reached in the VMP group ($p<0.001$). After a median follow-up of 16.3 months, 45 patients (13%) in the VMP group and 76 patients (22%) in the MP group had died (hazard ratio in the VMP cohort=0.61, p=0.008); median survival was not reached in either group. As a result, VMP is now established as a standard of care in numerous countries worldwide.

Recent studies have indicated that multiple drug combinations are superior over single- or double-agent combinations in treating multiple myeloma (van der Veer 2011a).[42] In particular, VELCADE-based treatment regimens have demonstrated significant improvements in response, progression-free survival (PFS), and overall survival (OS) compared with non-VELCADE-based therapy, both in newly diagnosed transplant ineligible patients and those suitable for induction and transplant (Sonneveld 2013, Dimopoulos 2009).[41,7]

Daratumumab's immediate and effective cell mediated (and potentially direct) cytotoxic effects against multiple myeloma cells, combined with the observed remarkable synergy with VELCADE (even in samples from patients who are refractory to VELCADE), may potentially improve the clinical outcome for patients with multiple myeloma when combined with a VELCADE-based combination regimens (van der Veer 2011a).[42] This study will explore the efficacy and safety of the combination of daratumumab and VMP in subjects who are not eligible for ASCT.

2. OBJECTIVES AND HYPOTHESIS

2.1. Objectives

Primary Objective

The primary objective is to determine if the addition of daratumumab to VMP will prolong PFS compared with VMP.

Secondary Objectives

The secondary objectives are:

- To determine if the addition of daratumumab to VMP will improve clinical outcome as measured by:
  - Time to disease progression (TTP)
  - CR rate
  - Minimal residual disease (MRD) negativity rate
  - PFS2 (defined as time from randomization to progression on the next line of therapy or death, whichever comes first)
  - Time to next treatment
  - Overall response rate (partial response [PR] or better)
  - Stringent CR (sCR) rate
  - Very good partial response (VGPR) or better rate
  - Time to response
  - Duration of response
  - Overall survival
- To assess patient-reported outcomes and heath economic/resource utilization
- To determine the pharmacokinetics and immunogenicity of daratumumab
- To assess the safety and tolerability of daratumumab when administered in combination with VMP
- To evaluate clinical efficacy of daratumumab when added to VMP in high risk molecular subgroups.

Exploratory Objective

- To explore biomarkers predictive of response and resistance to therapy.
- To assess durability of MRD negativity

2.2. Hypothesis

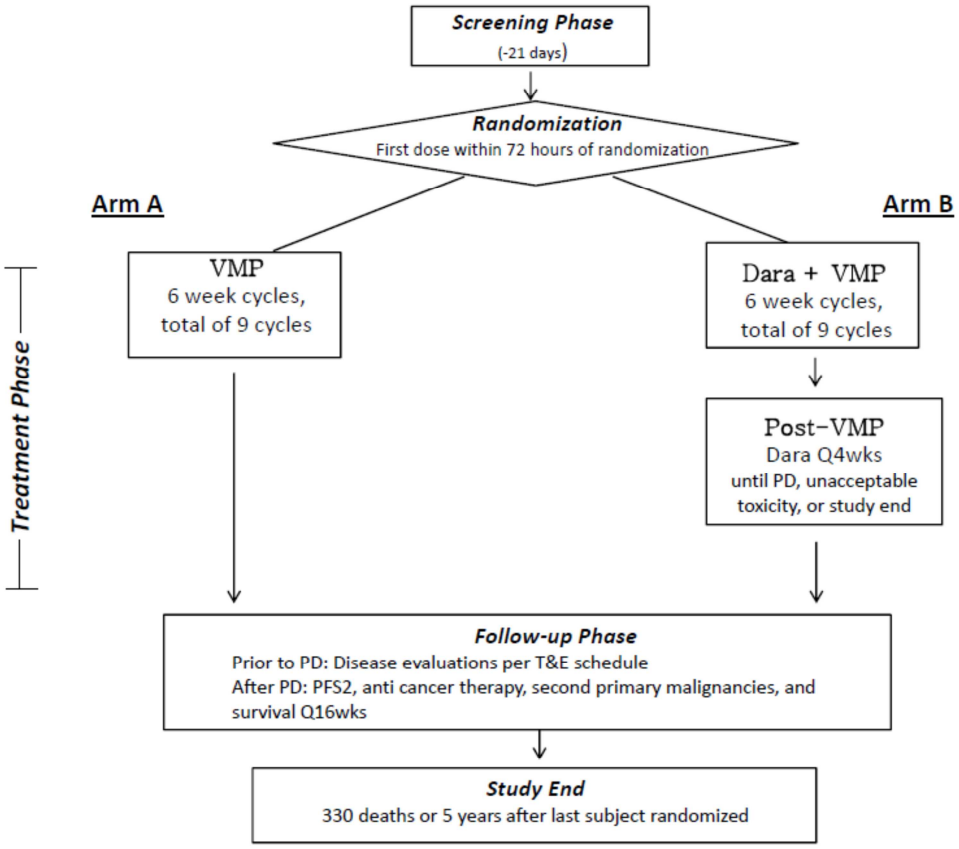
The hypothesis of the study is that daratumumab continued until disease progression, in combination with 9 cycles of VMP, will improve PFS compared with 9 cycles of VMP alone.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a randomized, open-label, parallel-group, controlled, multicenter study in subjects at least 18 years of age with previously untreated multiple myeloma who are ineligible for high dose therapy. A target of up to 700 subjects will be enrolled in this study with 350 subjects planned per treatment arm. A diagram of the study design is provided in Figure 3.

Figure 3: Schematic Overview of the Study



Dara=daratumumab; PD=disease progression; Q4wks=every 4 weeks; Q16wks=every 16 weeks; VMP=VELCADE-melphalan-prednisone

Subject participation will include a Screening Phase, a Treatment Phase, and a Follow-up Phase. The Screening Phase will be up to 21 days before randomization. All subjects will receive up to 9 cycles of the VMP regimen (1 cycle = 6 weeks) with or without daratumumab.

The Treatment Phase will extend from Day 1 of Cycle 1 to discontinuation of all study treatment. Eligible subjects will be stratified by International Staging System (I vs II vs III), region (Europe vs Other), and age (<75 vs ≥75) and then randomized in a 1:1 ratio. Subjects in both treatment arms will receive 1.3 mg/m^2 VELCADE by subcutaneous injection (SC) twice weekly (Weeks 1, 2, 4, and 5) in Cycle 1 followed by once weekly (Weeks 1, 2, 4, and 5) in Cycles 2 to 9. Melphalan PO at 9 mg/m^2 and prednisone PO at 60 mg/m^2 will be self-administered on Day 1-4

of each VELCADE cycle. For subjects randomized to the Treatment Arm B, 20 mg of dexamethasone will substitute for the planned dose of prednisone on Day 1 of each cycle. In this setting, dexamethasone will be utilized as the treatment dose of steroid for that particular day, as well as the required pre-medication prior to daratumumab infusion. Daratumumab 16 mg/kg will be administered to subjects in Treatment Arm B by IV infusion once every week for 6 weeks (Cycle 1; 1 VELCADE cycle); then once every 3 weeks for 16 additional doses (Cycles 2-9). Measures to prevent infusion related reactions (IRRs) will include pre-infusion medication with dexamethasone, paracetamol, and antihistamine before each daratumumab infusion.

After completion of the VMP cycles, subjects in Arm A will enter the Follow-up Phase and should not be started on subsequent anti-myeloma therapy without confirmed disease progression. Subjects in Arm B will continue to receive daratumumab every 4 weeks until documented progression, unacceptable toxicity, or the study ends (see below for definition). Subjects who need to discontinue treatment with any one component of study treatment (VELCADE, melphalan, prednisone, or daratumumab) may continue to receive treatment with the other components of study treatment, as assigned. Upon discontinuation of daratumumab, subjects in Arm B will also enter the Follow-up Phase and should not be started on subsequent anti-myeloma therapy without confirmed disease progression.

In the Follow-up Phase, subjects who discontinue treatment before disease progression must continue to have disease evaluations according to the Time and Events Schedule until confirmed PD (see Section 8.4, Subsequent Therapies), subsequent anti-myeloma treatment, death, withdrawal of consent, lost to follow-up, or the end of the study. After disease progression is documented, follow-up will be obtained at least every 16 weeks. Subsequent anti-myeloma treatment, PFS2 (per investigator judgment), second primary malignancies, and survival will also be recorded.

Two interim analyses are planned. The first interim analysis, with a purpose to evaluate safety, will be performed after a total of approximately 100 subjects have been treated for at least 2 cycles or discontinued the study treatment. The second interim analysis, with a purpose to evaluate cumulative interim safety and efficacy data, will be performed when approximately 216 PFS events have been accumulated. As the superiority of daratumumab combined with VMP over VMP alone with respect to PFS was established at the second interim analysis, the interim PFS analysis will serve as the primary PFS analysis, which otherwise was to occur when approximately 360 PFS events had been observed. The date established for the primary PFS analysis (12 June 2017) will serve as the primary clinical cutoff date, after which subject monitoring will be conducted according to Section 9.1.5 of the protocol. As planned in the original protocol, two interim OS analyses will be performed at the time of the interim PFS (216 events) and the primary PFS (360 events) prior to the final OS analysis at 330 deaths. The second interim OS will occur when 200 deaths (60% of all planned deaths) have been accumulated which is about the same time of the primary PFS analysis as if it would have occurred. After the OS interim analysis, subject monitoring will be conducted according to Section 9.1.6. Investigators will be informed when each interim analysis is to occur. All available data prior to that time will be included in each of the respective analyses.

The end of the study will occur when 330 subjects have died, or 5 years after the last subject is randomized, whichever comes first. The sponsor will ensure that subjects benefiting from treatment with daratumumab will be able to continue treatment after the end of the study.

An Independent Data Monitoring Committee (IDMC) will be commissioned for this study to review efficacy and safety results at the 2 planned interim analyses. After the interim review, they will make recommendations regarding the continuation of the study. In addition, the IDMC may also review cumulative safety data every 6 months besides the two interim analyses. The IDMC will no longer review study data after the database lock for the primary analysis has been completed.

As a result of the positive second interim analysis, that established the superiority of daratumumab combined with VMP over VMP alone with respect to the primary endpoint (PFS), and consistent with the IDMC's recommendation, the sponsor will ensure that access to daratumumab is provided for subjects randomized to Arm A (VMP) who have sponsor-confirmed disease progression (see Section 8.4, Subsequent Therapies).

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

3.2. Study Design Rationale

Choice of VELCADE Schedule

The most common side effect of VELCADE therapy is peripheral neuropathy. In an effort to manage this toxicity, a number of clinical investigators have made minor adaptations to the VELCADE schedule in order to reduce the incidence and severity of this AE, with the intention of keeping patients on therapy longer; thus ensuring that patients receive appropriate intensity and duration of treatment with corresponding positive effects on the length of remission. A study comparing 2 regimens, VMP versus VMPT, as up-front therapy for patients >65 years, showed that the weekly infusion of VELCADE significantly reduced the incidence of Grade 3-4 peripheral neuropathy (18% in the biweekly vs 9% in the weekly schedule for the VMPT arm, and 12% in the biweekly vs 3% in the weekly schedule for the VMP arm) (Table 3) without adversely influencing outcome (Palumbo 2008).[34] The once-weekly schedule of VELCADE resulted in a reduced discontinuation rate and prolonged the time on therapy: in both groups, patients received a median of 9 cycles, and the median cumulative delivered dose of VELCADE was similar, 40.1 mg/m^2 for twice-weekly and 39.4 mg/m^2 for once-weekly regimens-corresponding to a dose intensity of 59% for twice-weekly and 84% for once-weekly regimens (Bringhen 2010).[2]

Table 3: Complete responses, progression-free survival and peripheral neuropathy in all patients and in those who received weekly infusion of VELCADE

	VMPT (n=152)		VMP group (n=152)	
	All Patients (n=152)	Subgroup with VELCADE weekly infusion (n=90)	All Patients (n=152)	Subgroup with VELCADE weekly infusion (n=90)
CR rate (%)	31	28	16	10
2 year PFS (%)	84	87	76	78
Grade 3-4 peripheral neuropathy (%)	18	9	12	3
Source: (Palumbo 2008)[34]				

Similarly, the beneficial impact of a weekly administration schedule of VELCADE was also shown in a Spanish multicenter study comparing VMP with VELCADE-thalidomide-prednisone (VTP). This study showed that VELCADE-based regimens that use an intensive dosing of VELCADE twice-per-week in the first cycle followed by less intensive weekly dosing, are not only well-tolerated, but are also an active approach for elderly populations, with similar efficacy for VMP and VTP (Mateos 2010).[26]

In a recent paper, Mateos et al evaluated the safety and efficacy of 4 different VMP regimens (Mateos 2014).[25] The VISTA study was compared to the GIMEMA MM-03-05 study (both once- and twice-weekly Velcade groups) and the GEM2005MAS65 study (once-weekly Velcade, 6 cycles). The median cumulative dose of VELCADE was notably higher in patients receiving twice-weekly VELCADE. Overall response rate for VMP treatment was similar between all the regimens and averaged between 74% to 87%. Overall survival was similar across all studies, however PFS was slightly longer in the GEM2005MAS65 study likely secondary to extended VELCADE usage for up to 3 years (38 months vs 21-25 months). Although the efficacy was similar, Mateos and colleagues reported that the risk of peripheral neuropathy and discontinuation due to AEs was much higher in the studies that utilized twice-weekly VELCADE vs once-weekly VELCADE. For example, the rate of Grade 3/Grade 4 peripheral neuropathy was 13% in VISTA and 14% in the twice-weekly GIMEMA study, but was 2% to 7% in the once-weekly VELCADE studies. The authors concluded that regimens that predominantly use once-weekly VELCADE result in high efficacy, comparable to response rates seen in VISTA, with improved safety and tolerability.

This study will incorporate twice-weekly dosing of VELCADE in the first cycle, to obtain rapid reduction in plasma cell tumor burden, followed by once-weekly dosing in subsequent cycles for improved tolerability. The 54-week treatment duration is based on the accepted duration of treatment with melphalan-prednisone. Note that for ease of reading, the VMP “lite” regimen is referred to as “VMP” throughout the protocol.

Rationale for VELCADE Subcutaneous Administration

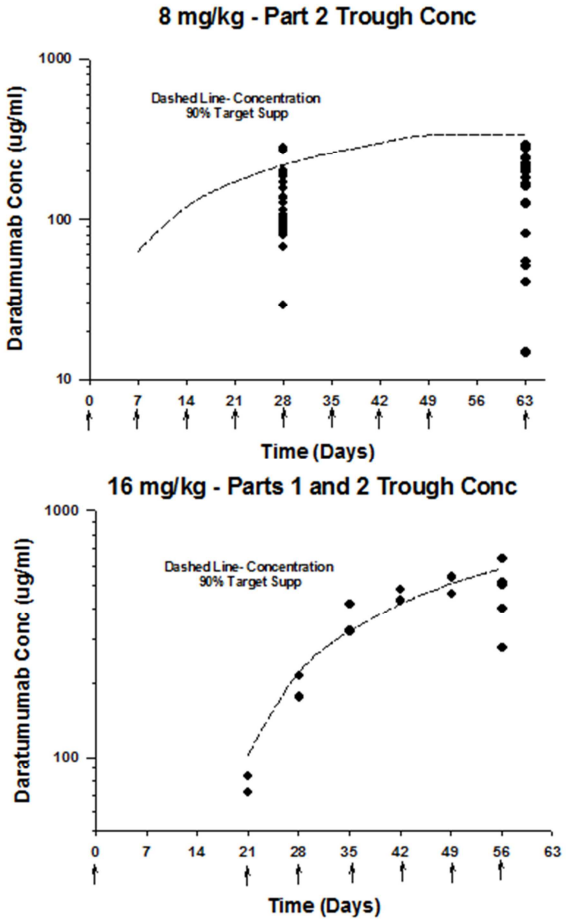
VELCADE is approved in the US and the EU for both IV and SC routes of administration for all labeled indications. In this study, VELCADE will be administered subcutaneously. In clinical studies, SC administration has been shown to be non-inferior to the standard IV route of delivery and appears to have an improved systemic safety profile, notably resulting in significantly lower rates of peripheral neuropathy, an important side effect of VELCADE (Moreau 2011).[29] Furthermore, SC administration is a useful alternative to IV administration, particularly for patients with poor venous access or with an increased risk of side effects and also affords greater flexibility for the site and convenience for the patient.

Therefore, in this study, subjects will receive 1.3 mg/m^2 VELCADE as a SC injection twice weekly (Weeks 1, 2, 4, and 5) for one 6-week cycle (Cycle 1; 8 doses per cycle) followed by once weekly (Weeks 1, 2, 4, and 5) administrations for eight 6 week cycles (Cycles 2 to 9; 4 doses per cycle).

Rationale for Daratumumab Dose

CD38, the target for daratumumab, is expressed on NK cells and clinical data has shown NK cell suppression to be a marker of on target drug activity. Clinical pharmacokinetic data have shown the 16 mg/kg dose to be the lowest dose that results in nearly complete target suppression at all time points. This dose and schedule continuously suppressed NK cells throughout dosing. Daratumumab maximal target suppression is presented in Figure 4.

Figure 4: Daratumumab Maximal Target Suppression



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

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

The ORR appeared higher for the 16 mg/kg dose compared with the 8 mg/kg dose, based on early preliminary data from Part 2 of Study GEN501 and from Study MMY2002 (both ongoing studies) as of a cutoff date of 24 January 2014. In Study GEN501, the ORRs (ie, PR or greater) were 11% and 40% for the 8 mg/kg (n=28) and 16 mg/kg (n=15) dose regimens, respectively. For Study MMY2002, the unconfirmed ORRs for the 8 mg/kg and 16 mg/kg dose regimens were similar to those observed in GEN501. In addition, VGPRs were observed for 7 of 30 subjects treated with the 16 mg/kg dose in the 2 studies. VGPR had not been observed at lower dose levels. These preliminary data support that full target saturation at the 16 mg/kg dose is needed to achieve higher and deeper response rates.

Rationale for DNA and Biomarker Collection

Biomarker samples will be collected to evaluate the depth of clinical response to daratumumab through evaluation of MRD, using DNA sequencing of immunoglobulin genes, and to determine response rates in specific molecular subgroups of multiple myeloma, using DNA/RNA sequencing of MM cells to allow for assessment of high–risk genomics such as deletion 17p, t(4;14), t(14;20), t(14;16), deletion13, GEP signatures such as UAMS-70, and mutations in p53, BRAF, FGFR, IGH, PI3K, or other molecular subtypes associated with disease progression. Other biomarker goals include evaluation of potential mechanisms of resistance, inter-individual

variability in clinical outcomes or identification of population subgroups that respond differently to treatment.

4. SUBJECT POPULATION

Screening for eligible subjects will be performed within 21 days before randomization.

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a subject in the study. Waivers are not allowed.

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

4.1. Inclusion Criteria

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

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

2. Criterion modified per Amendment 1

   2.1. Criterion modified per Amendment 2

   2.2 Subject must have documented multiple myeloma satisfying the calcium elevation, renal insufficiency, anemia, and bone abnormalities (CRAB) diagnostic criteria (see Attachment 1), monoclonal plasma cells in the bone marrow ≥10% or presence of a biopsy proven plasmacytomas, and measurable secretory disease, as assessed by the central laboratory, and defined by any of the following:

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

3. Newly diagnosed and not considered candidate for high-dose chemotherapy with SCT due to:

   - Being age ≥65 years, Or
   - In subjects <65 years: presence of important comorbid condition(s) likely to have a negative impact on tolerability of high dose chemotherapy with stem cell transplantation. Sponsor review of these comorbid conditions and approval is required before randomization.

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

5. Criterion modified per Amendment 1

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

   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 (G-CSF 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, then direct bilirubin ≤1.5 x ULN;

   f) creatinine clearance ≥40 mL/min, may be calculated or measured according to local practice (if calculated, MDRD or CKD-EPI formulae preferred, see Section 9.1.2)

   g) corrected serum calcium ≤14 mg/dL (≤3.5 mmol/L); or free ionized calcium ≤6.5 mg/dL (≤1.6 mmol/L) (Attachment 3);

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

6. Women of childbearing potential must commit to either abstain continuously from heterosexual sexual intercourse or to use 2 methods of reliable birth control simultaneously. This includes one highly effective form of contraception (tubal ligation, intrauterine device, hormonal [birth control pills, injections, hormonal patches, vaginal rings or implants] or partner's vasectomy) and one additional effective contraceptive method (male latex or synthetic condom, diaphragm, or cervical cap). Contraception must begin prior to dosing. Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy or bilateral oophorectomy

7. Criterion modified per Amendment 1

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

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, as referenced in the ICF.

4.2. Exclusion Criteria

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

1. Subject has a diagnosis of primary amyloidosis, monoclonal gammopathy of undetermined significance, or smoldering multiple myeloma. 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).[18] Smoldering multiple myeloma is defined as asymptomatic multiple myeloma with absence of related organ or tissue impairment or end-organ damage (Kyle 2003, Kyle 2007).[18,20]

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

3. Subject has prior or current systemic therapy or SCT for multiple myeloma, 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.

4. 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.

5. Subject has a history of malignancy (other than multiple myeloma) within 3 years before the date of randomization (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or malignancy that in the opinion of the investigator, with concurrence with the sponsor's medical monitor, is considered cured with minimal risk of recurrence within 3 years).

6. Subject has had radiation therapy within 14 days of randomization.

7. Subject has had plasmapheresis within 28 days of randomization.

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

9. Criterion modified per Amendment 1

   9.1a) Subject has known chronic obstructive pulmonary disease (COPD) with a Forced Expiratory Volume in 1 second (FEV1) < 50% of predicted normal. Note that FEV1 testing is required for subjects suspected of having COPD and subjects must be excluded if FEV1 <50% of predicted normal

   9.1b) Subject has had known moderate or severe persistent asthma within the last 2 years (see Attachment 4), 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).

10. Criterion modified per Amendment 1

    10.1 Subject is known to be seropositive for human immunodeficiency virus (HIV), known to have hepatitis B surface antigen positivity, or known to have a history of hepatitis C.

11. 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.

12. Criterion modified per Amendment 1

    12.1 Criterion modified per Amendment 2

    12.2 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 or clinically significant ECG abnormalities
    - screening 12-lead ECG showing a baseline corrected QT interval (QTc) >470 msec

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

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

15. Subject is known or suspected of not being able to comply with the study protocol (eg, because of alcoholism, drug dependency, or psychological disorder). Subject has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments. Subject is taking any prohibited medications as per Section 8.3.

16. Criterion Modified per Amendment 2

    16.1 Subject is a woman who is pregnant, or breast-feeding, or planning to become pregnant while enrolled in this study or within 3 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 3 months after the last dose of any component of the treatment regimen.

17. Criterion modified per Amendment 1

    17.1 Subject has had major surgery within 2 weeks before randomization or has not 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. Note: subjects with planned surgical procedures to be conducted under local anesthesia may participate.

18. 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.

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

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's status changes (including laboratory results or receipt of additional medical records) after screening but before the first dose of study treatment is given such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study. Section 17.4 describes the required documentation to support meeting the enrollment criteria. Subjects who fail to meet the inclusion and exclusion criteria (ie, screen failures) may be rescreened once if their condition changes. Rescreening must be discussed with and approved by the sponsor on a case-by-case basis. Subjects who are determined to be eligible for rescreening must sign a new ICF and will then be assigned a new screening number.

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. For restrictions related to concomitant medications, please refer to Section 8.3.

1. For women of childbearing potential, adequate contraception as specified in Section 4.1 must continue during the Treatment Phase, during any dose interruptions, and for 3 months after the last dose of daratumumab. In addition, women must not donate ova during the study and for 3 months after the last dose of daratumumab.

2. A man who is sexually active with a woman of childbearing potential must always use a latex or synthetic condom during the study and for 3 months after discontinuing daratumumab. All men must not donate sperm during the study and for 3 months after the last dose of daratumumab.

3. Typically, IV contrast is NOT used in computed tomography (CT) scanning of 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.

5. TREATMENT ALLOCATION AND BLINDING

Treatment Allocation

Eligible subjects will be stratified by International Staging System (I vs II vs III based on central laboratory results at Screening, see Attachment 9), region (Europe vs Other), and age (<75 vs ≥75) and then randomized to treatment in a 1:1 ratio to either Treatment Arm A (VMP alone) or Treatment Arm B (daratumumab+VMP [D-VMP]). The method of randomization is randomly permuted blocks. An interactive web based randomization system (IWRS) will be used. Each subject will be assigned a unique subject number.

Blinding

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

6. DOSAGE AND ADMINISTRATION

In this protocol, the term "study drug" refers to daratumumab only, and "study treatment" refers to daratumumab, VELCADE, melphalan, and prednisone. Daratumumab is to be administered as described in the Time and Events Schedule. On dosing days where the combination products are given with daratumumab (ie, Arm B only), the study drug and chemotherapy should be administered in the following order:

- prednisone, daratumumab, VELCADE, and melphalan

Detailed information on the composition of the study treatments can be found in the Site Investigational Product Procedures Manual (SIPPM) or equivalent document. The administration schedule is provided in the Time and Events schedule. Cycles are based on the administration of VELCADE and will be approximately 42 days (6 weeks) in duration.

In Cycles 2-9, before initiating a new cycle of therapy, subjects should meet the following criteria:

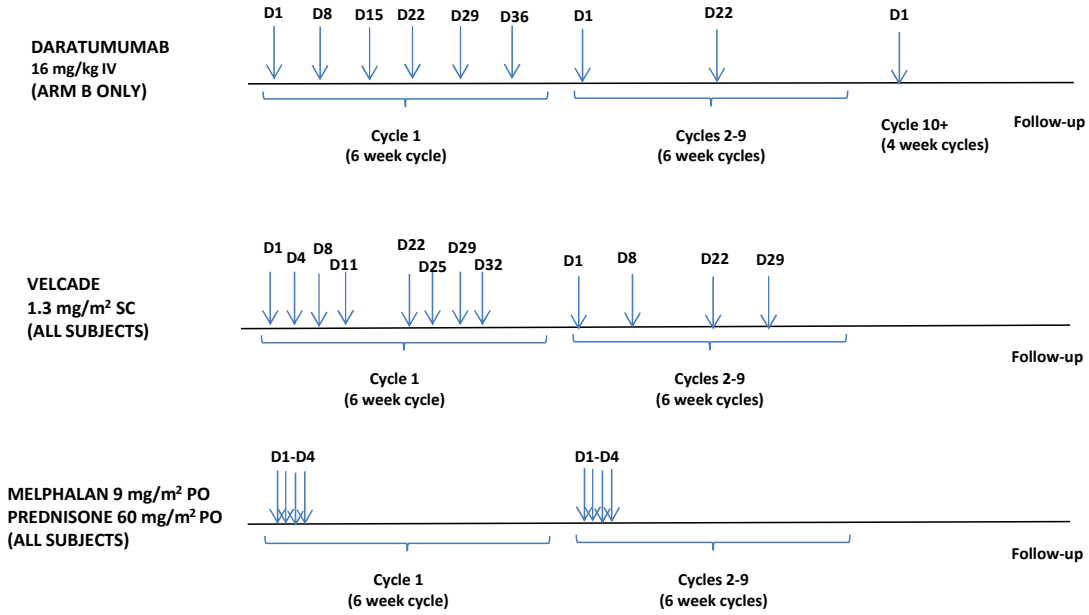
- Platelet count $\geq 70 \times 10^9$/L
- ANC $\geq 1.0 \times 10^9$/L
- Non-hematological toxicities resolved to Grade 1 or baseline

The start of each cycle may occur within ±3 days of the scheduled day in order to accommodate the schedule of the site or subject. If the start of a cycle is delayed, Day 1 of subsequent cycles should be adjusted accordingly to maintain the 42-day cycle duration. In Cycles 1 through 9, weekly or every-three-week daratumumab infusions may be given within ±1 day of the scheduled day in order to accommodate the schedule of the site or subject. Additionally, weekly or twice weekly VELCADE doses may be given within ±1 day of the scheduled day in order to accommodate the schedule of the site or subject. Changes to within-cycle dosing should not impact Day 1 of the next cycle.

Subjects are to receive VMP for a maximum of 9 cycles. For subjects randomized into Treatment Arm B, daratumumab will be given according to the Time and Events Schedule until disease progression, unacceptable toxicity, or other reasons as listed in the Section 10.2.

A schematic of study treatment administration is provided in Figure 5.

Figure 5: Study Treatment Administration



6.1. Daratumumab (Arm B Only)

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 Site Investigational Product Procedures Manual (SIPPM) or equivalent document.

6.1.2. Daratumumab Administration

Daratumumab (16 mg/kg) will be administered to subjects in Arm B by IV infusion initially once every week for 6 weeks (Cycle 1; 1 VELCADE cycle); then once every 3 weeks for an additional 16 doses (Cycles 2-9); then once every 4 weeks thereafter (post-VMP Treatment Phase), until documented progression, unacceptable toxicity, or study end. After the end of the study, the sponsor will ensure that subjects benefiting from treatment with daratumumab will be able to continue treatment.

A daratumumab infusion will be skipped if it cannot be administered within the prescribed time window as outlined in Table 4. Each subject's dose will be calculated based on the subject's weight rounded to the nearest kilogram. There is no cap on the absolute dose allowed, as long as the dose does not exceed 16 mg/kg. If a subject's weight changes by more than 10% from baseline, the dose of daratumumab will be re-calculated. For recommendations on daratumumab infusion rate, please refer to the SIPPM or equivalent document.

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

6.1.3. Guidelines for Prevention of Infusion Reactions

6.1.3.1. Pre-infusion Medication

Pre-infusion medications for subjects receiving daratumumab 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 PO approximately 1 hour or less prior to daratumumab infusion
- An antihistamine (diphenhydramine 25-50 mg IV or PO, or equivalent H1 blocker; see Attachment 5) approximately 1 hour prior to daratumumab infusion.
- Dexamethasone 20 mg IV or PO, approximately 1 hour or less prior to daratumumab infusion. Substitutions for dexamethasone are allowed, please refer to Attachment 6. On days when subjects receive this dose of dexamethasone in the clinic, prednisone will not be self-administered at home.
- Leukotriene Inhibitor (optional) on Cycle 1 Day 1: montelukast 10 mg PO, or equivalent, approximately 1 hour or less before the daratumumab infusion

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

6.1.3.2. Post-Infusion Medication

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

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

In addition, these at-risk subjects may be hospitalized for monitoring for up to 2 nights after an infusion. If subjects are hospitalized, then their FEV1 should be measured before discharge. If these subjects are not hospitalized, then a follow up telephone call should be made to monitor their condition within 48 hours after all infusions. If the subject has not experienced a significant medical event but is hospitalized overnight only for observation, then the hospitalization should not be reported as 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 an at-risk subject experiences no major infusion-related reactions, then these post-infusion medications may be discontinued after 4 full doses at the investigator's discretion.

6.1.4. Management of Infusion-related Reactions

Subjects in Arm B should be carefully observed during daratumumab infusions. Trained study staff at the clinic should be prepared to intervene in case of any infusion-related 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 temporarily interrupted. 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 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.

6.2. VELCADE, Melphalan, and Prednisone (Arm A and Arm B)

The sponsor will provide VELCADE to the sites, if required. Sites will use commercially available melphalan and prednisone for administration in this study unless otherwise communicated to the site. Before administering, refer to the currently approved package inserts for complete prescribing information.

6.2.1. Dose Calculation of VELCADE, Melphalan, and Prednisone

The amount (in mg) of VELCADE, melphalan, and prednisone to be administered will be determined by body surface area (BSA), which will be calculated according to a standard nomogram (Attachment 7). The total calculated dose may be rounded to the nearest decimal point (eg, a calculated dose of 2.47 mg can be rounded to 2.5 mg). There is no cap on the absolute dose allowed, as long as the dose is based on the subject's BSA. If a subject's weight changes by more than 10% from baseline, the dose of VELCADE, melphalan, and prednisone will be re-calculated.

6.2.2. VELCADE Administration

Subjects will receive 1.3 mg/m^2 VELCADE as a SC injection twice weekly (Weeks 1, 2, 4, and 5) for one 6-week cycle (Cycle 1; 8 doses per cycle) followed by once weekly (Weeks 1, 2, 4, and 5) administrations for eight 6-week cycles (Cycles 2 to 9; 4 doses per cycle).

On treatment days when both VELCADE and daratumumab are administered, VELCADE must be administered after the daratumumab infusion. VELCADE will be supplied in sterile, single-use vials containing 3.5 mg of VELCADE. Each vial is for single-use administration. VELCADE dosing may be delayed up to 48 hours, however subsequent doses must be adjusted to account for the delay. Note that there should be at least 72 hours between doses of VELCADE. Skipped doses of VELCADE will not be made up later in the cycle. Individual doses within a cycle have a ±1 day window.

For subjects with unacceptable toxicity at the local injection site despite dose modifications or change in injection concentration, VELCADE can be administered intravenously as a 3 to 5 sec bolus injection. Please refer to local prescribing information for further details on either SC or IV administration.

6.2.3. Melphalan and Prednisone Administration

Melphalan will be administered at 9 mg/m^2 and prednisone will be administered at 60 mg/m^2 on Day 1 to 4 of each VELCADE cycle. Both melphalan and prednisone will be administered orally. For subjects randomized to the Treatment Arm B, 20 mg dexamethasone will substitute for the planned dose of prednisone on Day 1 of each cycle. In this setting, dexamethasone will be utilized as the treatment dose of steroid for that particular day, as well as the required pre-medication prior to daratumumab infusion. Prednisolone may be substituted for prednisone in countries where prednisone is not available. Melphalan and prednisone doses may be reduced, or the treatment schedule may be modified for the management of the study treatment-related toxicities.

In exceptional circumstances, a subject may not tolerate sudden corticosteroid withdrawal at the end of 4 days of prednisone treatment. In such an instance, a tapering regimen of prednisone (30 mg/m^2 on Day 5, 20 mg/m^2 on Day 6, 10 mg/m^2 on Day 7, then stop) can be prescribed to the subject after sponsor review. Under no circumstances will melphalan administration be prolonged beyond 4 days.

Breaking or dividing melphalan or prednisone tablets is strongly discouraged; the total calculated dose should be rounded to the closest dose that can be administered using the tablets available. Prednisone tablets are to be taken with or immediately after a meal or snack, preferably in the morning.

If subjects develop renal and/or hepatic impairment, please follow recommendations given in Table 8.

6.3. Dose Delays and Dose Modification

Subjects who need to discontinue treatment with any one component of study treatment (VELCADE, melphalan, prednisone, or daratumumab) may continue to receive treatment with the other components of study treatment, as assigned.

6.3.1. Daratumumab Dose Modification

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

6.3.1.1. Daratumumab-Related Toxicity Management

Refer to Section 6.1.3 for details on management of infusion-related reactions. **Only if any of the following criteria are met and the event cannot be ascribed to other components of the chemotherapy regimen, 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
- Neutropenia with infection, of any grade
- Grade 3 or higher non-hematologic toxicities with the following exceptions:
  - Grade 3 nausea that responds to antiemetic treatment within 7 days
  - Grade 3 vomiting that responds to antiemetic treatment within 7 days
  - Grade 3 diarrhea that responds to antidiarrheal treatment within 7 days
  - Grade 3 fatigue that was present at baseline or that lasts for <7 days after the last administration of daratumumab
  - Grade 3 asthenia that was present at baseline or that lasts for <7 days after the last administration of daratumumab

Other than on Day 1 of a cycle, if a daratumumab infusion does not commence within the pre-specified window (Table 4) of the scheduled administration date, then the dose will be considered a missed dose. Administration may resume at the next planned dosing date. A missed dose will not be made up.

Table 4: Daratumumab-Related Toxicity Management

	Frequency	Dose Miss	Dosing Re-start
Cycle 1	Weekly (q1wk)	>3 days	next planned weekly dosing date
Cycle 2-9	Every 3 weeks (q3wks)	>1 week	next planned every-third-week dosing date
Post VMP	Every 4 weeks (q4wks)	>2 weeks	next planned every-fourth-week dosing date

If the daratumumab infusion cannot be given on Day 1 of a cycle, the start of the cycle should be delayed. Day 1 of a cycle should not be skipped. If a dose is delayed, then subsequent pharmacokinetic and pharmacodynamic assessments should be performed based on the actual administration days of daratumumab, not on the original scheduled administration day. A maximum delay of 4 weeks is allowed in Cycle 1 to Cycle 9. Any adverse event deemed to be related to daratumumab that requires a dose hold of more than 4 weeks will result in permanent discontinuation of daratumumab. After Cycle 9, any adverse event deemed to be related to daratumumab that requires a dose hold of 2 consecutive planned doses will result in permanent discontinuation of daratumumab.

6.3.1.2. Daratumumab Interruption or Missed Doses

A daratumumab dose that is held for more than the permitted time (Table 4) from the per-protocol administration date for any reason other than toxicities suspected to be related to daratumumab should be brought to the attention of the Sponsor at the earliest possible time. Subjects whose dose was delayed for more than 4 weeks (Cycle 1 to Cycle 9) or 2 consecutive planned doses (after Cycle 9) should have study drug discontinued, unless, upon consultation with the sponsor and the review of safety and efficacy, continuation is agreed upon.

6.3.2. Dose Reductions (VELCADE, Melphalan, and Prednisone)

VELCADE will be reduced or discontinued according to the guidelines presented in Table 5. In addition to the VELCADE dose modification guidelines presented in Section 6.3.3, Table 8, if several VELCADE doses in a cycle are withheld due to VELCADE-related toxicity (≥3 doses during twice weekly administration or ≥2 doses during weekly administration), VELCADE dose should be reduced by 1 dose level. Once reduced due to toxicity, doses of VELCADE, melphalan, or prednisone should not be re-escalated, with the exception of melphalan re-escalation following recovery of renal function (Table 8).

Table 5: Dose Reduction for VELCADE

Starting Dose	First Dose Reduction	Second Dose Reduction	Third Dose Reduction
VELCADE 1.3 mg/m^2	VELCADE 1.0 mg/m^2	VELCADE 0.7 mg/m^2	Discontinue VELCADE

Melphalan will be reduced or discontinued according to the guidelines presented in Table 6.

Table 6: Dose Reduction for Melphalan

Starting Dose	First Dose Reduction	Second Dose Reduction	Third Dose Reduction
9 mg/m^2 QD on Days 1-4	6.75 mg/m^2 QD on Days 1-4	4.5 mg/m^2 QD on Days 1-4	Discontinue melphalan
QD=every day			

Prednisone will be reduced or discontinued according to the guidelines presented in Table 7.

Table 7: Dose Reduction for Prednisone

Starting Dose	First Dose Reduction	Second Dose Reduction	Third Dose Reduction
60 mg/m^2 QD on Days 1-4	45 mg/m^2 QD on Days 1-4	30 mg/m^2 QD on Days 1-4	Discontinue prednisone
QD=every day			

6.3.3. Dose Modification Guidelines for VELCADE, Melphalan, and Prednisone Related Toxicities

Dose modification guidelines for VELCADE, melphalan, and prednisone are provided in Table 8.

Table 8: Dose modification Guidelines for VELCADE, Melphalan, and Prednisone

Body System	NCI-CTC Adverse Event and or Symptom and Category	VELCADE	Melphalan	Prednisone
Allergic reactions	Allergic reaction or hypersensitivity Grade 2 OR 3	Hold all therapy. If the toxicity resolves to ≤ Grade 1, restart VMP. 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 VMP. NOTE: If the reaction was cutaneous in nature, refer to the cutaneous category below.		
	Allergic reaction or hypersensitivity Grade 4	Discontinue VMP.		
Constitutional	Fluid Retention (ie, 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 prednisone and do not resume if symptoms persist despite second reduction.
	Fatigue[a] ≥ Grade 3 (ie, severe fatigue interfering with activities of daily living)	Reduce VELCADE by 1 dose-level.		

Table 8: Dose modification Guidelines for VELCADE, Melphalan, and Prednisone

Body System	NCI-CTC Adverse Event and or Symptom and Category	VELCADE	Melphalan	Prednisone
Cutaneous	Non-blistering rash Grade 2	Hold VELCADE therapies. Begin treatment with antihistamines and/or low-dose steroids as per institutional practice. If the toxicity resolves to ≤ Grade 1, restart at 1 dose reduced level of VELCADE		
	Non-blistering rash ≥ Grade 3 or 4	Hold VELCADE therapies. Begin treatment with antihistamines and/or low-dose steroids as per institutional practice. If the toxicity resolves to ≤ Grade 1, restart VELCADE (only) at 1 dose reduced level and continue antihistamines and/or low-dose steroids as per institutional practice. If toxicity recurs despite above measure, discontinue VELCADE permanently, as appropriate.		
	Desquamating (blistering) rash-any grade or erythema multiform ≥ Grade 3	Discontinue VELCADE 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.		
Gastrointestinal	Constipation[b] ≥ Grade 3	Hold. Upon recovery to ≤ Grade 1, restart VELCADE at 1 dose-reduced level.		
	Diarrhea[c] ≥ Grade 3	Hold VELCADE and consider loperamide therapy. Upon recovery to ≤ Grade 1, restart VELCADE at 1 dose-reduced 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 prednisone dose by 1 dose-level.

Table 8: Dose modification Guidelines for VELCADE, Melphalan, and Prednisone

Body System	NCI-CTC Adverse Event and or Symptom and Category	VELCADE	Melphalan	Prednisone
	Dyspepsia, gastric or duodenal ulcer, gastritis ≥ Grade 3 (requiring hospitalization or surgery)			Hold prednisone and consider treatment with histamine-2 blockers, sucralfate, or omeprazole. Restart prednisone 1 dose reduction level if symptoms are adequately controlled. If symptoms persist despite above measures, discontinue prednisone and do not resume.
Hematological	Neutropenia Grade 3 (without complications)	No dose reduction required of VELCADE. Consider treatment with G-CSF.	Continue melphalan dosing and add G-CSF support.	
	Grade 3 neutropenia associated with fever (≥38.5°C) or any Grade 4 neutropenia	Hold therapy with all drugs until recovery to baseline OR ≤ Grade 2. Upon recovery, restart melphalan at 1 dose reduced level. Maintain VELCADE at current dose and consider G-CSF support. If recurrence is seen, reduce VELCADE by 1 dose-level.		
	Thrombocytopenia Grade 3 (without complications)	No dose reduction required for VELCADE.	Reduce melphalan by 1 dose-level	
	Platelet count ≤ 30 x 10^9/L or ANC ≤ 0.75 x 10^9/L on a VELCADE dosing day (See Section 6 for minimum criteria for dosing on Day 1 of a cycle)	Withhold VELCADE therapy.		
	Platelet count <25,000/µL (ie, Grade 4) or Grade 3 thrombocytopenia with bleeding	Hold therapy with all drugs until recovery to baseline OR ≤ Grade 2. Upon recovery, restart melphalan and VELCADE at 1 dose reduced level. If recurrence is seen, reduce melphalan by 1 *further* dose-level.		
Infection	Herpes Zoster[d] 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.		

Table 8: Dose modification Guidelines for VELCADE, Melphalan, and Prednisone

Body System	NCI-CTC Adverse Event and or Symptom and Category		VELCADE	Melphalan	Prednisone
Musculoskeletal	Muscle weakness >Grade 2 (symptomatic and interfering with function +/- interfering with activities of daily living)				Decrease prednisone 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.
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[e]	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)	Reduce VELCADE by 1 dose-level or change schedule to once weekly		
		Grade 2 with pain or Grade 3 (interfering with activities of daily living)	Hold VELCADE until toxicity resolves to <Grade 2. When toxicity resolves, reinitiate with a reduction by 1 dose-level and change VELCADE treatment schedule to once per week[f]		
		Grade 4 (permanent sensory loss that interferes with function) and/or severe autonomic neuropathy	Discontinue VELCADE permanently.		

Table 8: Dose modification Guidelines for VELCADE, Melphalan, and Prednisone

Body System	NCI-CTC Adverse Event and or Symptom and Category	VELCADE	Melphalan	Prednisone
Neuro-psychological	Confusion or mood alteration >Grade 2 (interfering with function +/- interfering with activities of daily living)			Hold prednisone until symptoms resolve. Restart with 1 dose-level reduction. If symptoms persist despite above measures, discontinue prednisone 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 until toxicity resolves and, if not already given, start anticoagulation therapy. Restart prednisone at full dose after adequate anticoagulation,
Renal Impairment			If a subject develops renal function impairment with a serum creatinine >2 mg/dL (>176.8 mcmol/L) but less than Grade 3, the melphalan dose must be reduced to 4.5 mg/m^2, while VELCADE and prednisone can be continued at the current dose. On recovery of renal function, melphalan can be re escalated to the previous dose.	
Other toxicities	Any reported ≥ Grade 3	Determine drug attribution of the toxicity and hold the therapy(ies) as appropriate. If toxicity resolves to ≤ Grade 1, resume therapy with 1 level of dose reduction for suspect drug.		

[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.
[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 (ie, bacterial or viral infections) of diarrhea.
[d] 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.
[e] 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.
[f] If therapy is continued as twice weekly, VELCADE treatment should be continued at once weekly dosing.

7. TREATMENT COMPLIANCE

Study drug (daratumumab) and VELCADE 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 treatment diary which will be used to assess compliance with melphalan and prednisone treatment. Additional details are provided in the SIPPM or equivalent document.

8. CONCOMITANT THERAPY

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 8.3. 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 anti-myeloma treatment, if earlier: growth factors, transfusions, anti-infectives (antibacterials, antivirals, and antimycotics), steroids, anti-arrhythmics and other cardiac supportive therapy, anti-epileptics, centrally acting psychiatric medication, anti-histamines and other medications targeting post-infusion systemic reactions, bisphosphonates, and any anti-myeloma therapy (including radiation). Concomitant medications to manage AEs and SAEs will be recorded as per Section 12.3.1.

8.1. Recommended Therapies

8.1.1. Bisphosphonate Therapy

Bisphosphonate therapy is recommended to be continued per treatment guidelines (NCCN 2013).[30] 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 should not prescribe bisphosphonates to subjects who have not received them before, unless approved by the sponsor after confirming that the subject does not have disease progression at the time of bisphosphonate initiation.

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, are highly recommended. It is also recommended that high-risk subjects, ie, those with a high tumor burden, be treated

prophylactically in accordance with local standards (eg, rehydration; diuretics; allopurinol 300 mg daily and medication to increase urate excretion).

8.1.3. Prophylaxis for Pneumocystis carinii

Pneumocystis carinii pneumonia 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, as per institutional guidelines.

8.1.5. Prevention of Hemorrhagic Cystitis

Melphalan may cause hemorrhagic cystitis, especially in patients who have marginal renal function and/or dehydration. Measures to prevent hemorrhagic cystitis include IV hydration and the administration of Mesna. These measures are permitted therapies during the course of the study and may be used per institutional policy. Urine alkalinization is not recommended.

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
- 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

8.3. Prohibited Therapies

Concomitant administration of any other antineoplastic therapy for the intention of treating multiple myeloma is prohibited prior to confirmation of disease progression, including medications that target CD38, as well as medications used for other indications that have anti-myeloma properties (for example, interferon and clarithromycin [Ghosh 2013][13]).

Continuation of the study drug and components of the VMP regimen during or after emergency orthopedic surgery or radiotherapy for conditions related to multiple myeloma may occur only in the absence of disease progression and after review 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 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 used with caution in order 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.

Concomitant administration of strong CYP3A4 inducers is prohibited with the use of VELCADE. Administration of strong CYP3A4 inhibitors (eg, ketoconazole, ritonavir) should be avoided and is not recommended in patients receiving VELCADE. If a strong CYP3A4 inhibitor must be given in combination with VELCADE, monitor patients for signs of VELCADE toxicity and consider a VELCADE dose reduction. For an ongoing list of CYP3A inhibitors and inducers, see http://medicine.iupui.edu/flockhart/.

8.4. Subsequent Therapies

After completion or discontinuation of study therapy subjects should continue efficacy evaluations per the Time and Events Schedule until PD. Subsequent anti-myeloma therapy cannot be started before disease progression is established per the IMWG criteria (Section 9.2.1.1, Response Categories) or prior to sponsor confirmation of PD.

After sponsor confirmation of PD, choice of subsequent therapy is at the discretion of the investigator. Subjects randomized to Arm A (VMP) may have the option to receive daratumumab provided by the sponsor (in any subsequent line of therapy) if recommended by the investigator. Eligibility for and administration of daratumumab must be in accordance with local prescribing information and local regulations. Subjects in Arm A (VMP) who receive daratumumab post progressive disease through the sponsor will remain in the Follow-up phase of study. SAEs (including second primary malignancies) must be reported for these subjects until 30 days after daratumumab is discontinued. The option for sponsor provision of daratumumab will not be implemented in Japan or in countries where daratumumab is not approved.

All subsequent therapy for multiple myeloma (including start and end date, best response, and date of progression to the subsequent therapy) should be documented in the appropriate section of the eCRF.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedule summarizes the frequency and timing of efficacy, pharmacokinetic, immunogenicity, biomarker, patient-reported outcomes, and safety measurements applicable to this study.

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 9.6 for details.

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

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

The total blood volume for the study is estimated at approximately 45 mL during screening and 480 mL during VMP treatment in the first year. In the post-VMP treatment phase, blood sampling for subjects in Arm B will be approximately 305 mL per year on treatment. In the Follow-up Phase, subjects prior to PD will have approximately 120 mL blood drawn per year for serum disease evaluations. 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 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 (that was not performed as part of the subject’s standard of care). During the Screening Phase, eligibility criteria will be reviewed and a complete clinical evaluation will be performed as specified in Time and Events Schedule. Screening procedures will be performed within 21 days before randomization; 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 full chest CT scan); 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. If collection of blood and urine specimens for disease evaluation (SPEP, UPEP, calcium, and albumin) is performed within 14 days of Cycle 1 Day 1, it does not need to be repeated on Cycle 1 Day 1.

Prior to randomization, the Sponsor will review key eligibility criteria for all subjects. Relevant eCRF forms will be completed by site staff for review prior to approval for randomization being

granted by the Sponsor (further details provided as a separate document). Subjects <65 years must have known presence of important comorbid condition(s) likely to have a negative effect on the tolerability of high dose chemotherapy with SCT. Documentation of the condition, for example diagnosis of concomitant infectious disease, should be provided.

At screening, creatinine clearance may be measured or calculated according to local practice. If calculated, formulae according to the modification of diet in renal disease [MDRD, Levey 2006][22] or chronic kidney disease epidemiology collaboration [CKD-EPI, Levey 2009][23] are preferred. For online calculators, please go to https://www.kidney.org/professionals/KDOQI/gfr_calculator. Creatinine clearance will be analyzed locally.

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

All attempts should be made to determine eligibility of the subject based on the central laboratory results of Screening blood and urine M-protein measurements. In exceptional circumstances, the local laboratory results of blood and urine M-protein measurements may be used to determine eligibility, but only if the results are clearly (eg, 25% or more) above the thresholds for measurability.

9.1.3. Treatment Phase

Details of the procedures performed during the Treatment Phase are outlined in the Time and Events Schedule. Subjects should start study treatment within 72 hours after randomization. The start of each cycle may occur within ±3 days of the scheduled day in order to accommodate the schedule of the site or subject. If the start of a cycle is delayed, Day 1 of subsequent cycles should be adjusted accordingly to maintain the 42-day cycle duration. In Cycles 1 through 9, weekly or every-three-week daratumumab infusions may be given within ±1 day of the scheduled day in order to accommodate the schedule of the site or subject. Additionally, weekly or twice weekly VELCADE doses may be given within ±1 day of the scheduled day in order to accommodate the schedule of the site or subject. Changes to within-cycle dosing should not impact Day 1 of the next cycle.

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 study treatment, complete the End-of-Treatment Visit, and enter the Follow-up Phase.

End of Treatment Visits

Unless a subject withdraws consent for study participation or is lost to follow up, an End-of-Treatment Visit is to occur within 30 days after the last dose all study treatments. Every effort should be made to conduct the End-of-Treatment Visit before the subject starts subsequent treatment. If a subject is unable to return to the site for the End-of-Treatment Visit, then the subject should be contacted to collect information on adverse events that occur up to 30 days

after the last dose of study treatment. Additional information on reporting of adverse events is presented in Section 12.

9.1.4. Follow-up Phase

The Follow-up Phase will begin once a subject completes the VMP regimen (Treatment Arm A) or completes the daratumumab-VMP regimen (Treatment Arm B), or discontinues treatment in either arm for any reason. Subjects who discontinue treatment before disease progression must continue to have disease evaluations according to the Time and Events Schedule (ie, every 3 weeks in Year 1, every 4 weeks in Year 2, and every 8 weeks thereafter) until confirmed PD (see Section 8.4, Subsequent Therapies), subsequent anti-myeloma treatment, death, withdrawal of consent, lost to follow-up, or the end of the study. After disease progression is documented, follow-up information will be obtained every 16 weeks (±2 weeks). Every 16-week follow-up contacts, as well as Week 8 post-PD and Week 16 post-PD ECOG and ePRO assessments, should be scheduled from the date of confirmed progression (ie, the date of the confirmatory laboratory assessment, not the date of confirmation by the sponsor). In subjects for whom disease progression cannot be documented (eg, received subsequent anti-myeloma treatment or refused disease evaluations, but agreed to follow-up contacts), the every-16-week follow-up should be scheduled from the date of the End of Treatment Visit. Subsequent anti-myeloma treatment, PFS2 (per investigator judgment), second primary malignancies, and survival will also be recorded.

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

The end of the study occurs after 330 subjects have died, or for a maximum of 5 years after the last subject is randomized, whichever occurs first. The sponsor will ensure that subjects benefiting from treatment with daratumumab will be able to continue treatment after the end of the study.

9.1.5. Assessments Following the Positive Second Interim Analysis of PFS

Following the positive second interim analysis of PFS, subjects remaining in the study will continue to be monitored as follows until the next interim analysis of OS (ie, when 200 deaths have occurred):

Subjects who have had disease progression

For subjects whose disease has already progressed, every-16-week follow-up contacts should be performed to capture:

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

These data may be collected by telephone. Beyond the end of the serious adverse event reporting period (30 days after the last dose of study drug or the start of any subsequent anti-myeloma treatment, whichever comes first), only those serious adverse events that are considered to be possibly, probably, or definitely related to the study drug need to be reported.

Subjects who have not had disease progression

For subjects in the randomized portion of the study who have not experienced disease progression, disease assessments will continue to occur every 3 weeks in Year 1, every 4 weeks in Year 2, and every 8 weeks thereafter until disease progression is confirmed by central laboratory examination per the Time and Event Schedules.

9.1.6. Assessments Following the OS Interim Analysis

Following the OS interim analysis (ie, when 200 deaths have occurred), subjects remaining in the study will continue to be monitored as follows until the study end (ie, when 330 deaths have occurred, or 5 years after the last subject is randomized, whichever comes first):

- For subjects whose disease has already progressed at the time of the OS interim analysis, only survival, subsequent anti-myeloma therapy, and all new second primary malignancy information will be collected, which may be obtained by telephone contact.
- For subjects without disease progression at the time of the OS interim analysis, disease assessments will continue but will be performed locally per the standard of care. Sponsor confirmation of disease progression will no longer be required prior to initiation of subsequent anti-myeloma therapy.
- For subjects in Arm B who are continuing to receive study medication at the time of the OS interim analysis, dosing data and safety information will be collected. Safety information will include adverse events during treatment and within 30 days after last dose, concomitant medications associated with a serious adverse event, and information on all second primary malignancies.

9.2. Efficacy

9.2.1. Evaluations

9.2.1.1. Response Categories

Disease evaluations must be performed every 3 weeks during the first year, every 4 weeks during the second year, and every 8 weeks thereafter until disease progression (or other reasons as per Section 10). A window of ±7 days is allowed. If treatment has been delayed for any reason, the disease evaluations must be performed according to the original schedule, regardless of any changes to the dosing regimen.

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 2006, Kumar 2016, Rajkumar 2011).[8,17,37] For quantitative immunoglobulin, M-protein, and immunofixation measurements in serum and 24-hour urine, the investigator will use results provided by the central laboratory. Disease progression must be consistently

documented across clinical study sites using the criteria in Table 9. Per Table 9, for patients with measurable disease by SPEP and/or UPEP at baseline, increases in serum free light chains or the FLC ratio alone do not meet criteria for progressive disease.

Table 9: 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

EBMT = European Group for Blood and Marrow Transplantation; 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.

Table 9: International Uniform Response Criteria Consensus Recommendations

Clinical Relapse Clinical relapse is defined using the definition of clinical relapse in the IMWG criteria (Durie 2006, Rajkumar 2011).[8,37] 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.

For continuation of treatment, the IMWG response will be determined on an ongoing basis by the investigator. For data analysis and reporting, however, the sponsor 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 2006).[8] For subjects who discontinue study treatment before disease progression, disease evaluations should continue to be performed per the Time and Events Schedule until confirmed disease progression (see Section 8.4, Subsequent Therapies), death, the start of a new treatment for multiple myeloma, withdrawal of consent for study participation, lost to follow-up, or the end of study, whichever occurs first. Disease evaluations scheduled for treatment days should be collected before study treatment is administered.

9.2.1.2. 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.

- All subjects will be evaluated for IgG, IgA, IgM, IgE, and IgD at Screening. During the study, subjects with IgD or IgE disease will be evaluated for IgG, IgA, IgM, IgE, and IgD and subjects with IgG, IgA, or IgM disease will be evaluated for IgG, IgA, and IgM.
- Serum M-protein quantitation by electrophoresis (SPEP)
- Serum immunofixation at Screening and thereafter when a CR is suspected. If daratumumab interference is suspected based on SPEP and immunofixation (IFE) results, additional reflex IFE testing may be performed.
- Serum free light chain assay will be done at screening, and to confirm CR. In addition, FLC will be used to monitor subjects who have light chain only disease
- 24-hour urine M-protein quantitation by electrophoresis (UPEP)
- Urine immunofixation at Screening and thereafter when a CR is suspected

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 a repeat investigation performed at least 1 day later. Disease evaluations will continue beyond relapse from CR until disease progression is confirmed. Serum and urine IFE and serum free light chain assay will be performed at Screening and thereafter when a CR is suspected (when SPEP or UPEP are 0 or nonquantifiable). For subjects with light chain multiple myeloma, serum FLC assay will be performed routinely per the Time and Events Schedule. Previous studies have demonstrated potential interference of therapeutic monoclonal antibodies with detection of endogenous myeloma M-protein on serum IFE (McCudden 2010).[28] For subjects with suspected daratumumab interference on SPEP and/or serum IFE, a follow-up test will be run utilizing anti-idiotype antibodies against daratumumab to remove antibody interference. Subjects who meet all other IMWG criteria for CR or sCR, and whose positive IFE is confirmed to be daratumumab, will be considered complete responders or stringent complete responders.

9.2.1.3. Serum Calcium Corrected for Albumin

Blood samples for calculating serum calcium corrected for albumin will be collected and analyzed centrally (as specified in the Time and Events Schedules) until the development of confirmed disease progression. During the Treatment Phase, 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). 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"). 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.

9.2.1.4. 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. The central laboratory values will be used to calculate International Staging System (ISS) stage.

9.2.1.5. Bone Marrow Examination

Bone marrow assessments to be performed locally and centrally are summarized in Table 10.

Table 10: Bone Marrow Testing

	Local Testing	Central Testing
Screening	Disease characterization (morphology and either immunohistochemistry or immunofluorescence or flow cytometry). Cytogenetics by conventional karyotype or FISH.	MRD and molecular subtyping: a portion of bone marrow aspirates collected at screening will be sent to a central laboratory. If a fresh bone marrow aspirate will not be performed at screening because a sample is available within 42 days prior to randomization, obtain non-decalcified slides (bone marrow aspirate, touch preparation or clot selection) or FFPE block (clot section only, no bone marrow biopsy).
CR, sCR	For response confirmation, additional bone marrow aspirates or biopsies (or both) will be performed locally to confirm sCR or CR. Response characterization (morphology by immunohistochemistry or immunofluorescence or flow cytometry). For sCR: Detection of kappa/lambda ratio by 2-4 color flow cytometry is strongly preferred. If flow cytometry is not available at site, either immunohistochemistry or immunofluorescence can be done, however, kappa/lambda ratio from analysis of ≥100 plasma cells is required to confirm sCR. If sCR is not met, repeat local testing for sCR with subsequent bone marrow examinations will be done at the time of the next protocol-required bone marrow examination.	MRD Assessment: A portion of bone marrow aspirate collected for confirmation of CR/sCR will be sent to the central laboratory for MRD assessment. For subjects with CR/sCR, an additional bone marrow aspirate will be obtained at 12, 18, 24, and 30 months after first dose and sent to the central laboratory to monitor for MRD. For the 12, 18, 24, and 30-month bone marrow aspirate, subjects can have a window of 2 months after each time point to complete the bone marrow aspiration (ie, range of 12-14, 18-20, 24-26 and 30-32 months after C1D1).
Disease Progression	Not applicable.	If feasible, a bone marrow aspirate is requested to be collected from subjects in both treatment arms at disease progression to evaluate mechanisms of resistance.

CR=complete response; FFPE=formalin-fixed paraffin embedded; FISH=fluorescence in situ hybridization; MRD=minimal residual disease; sCR=stringent complete response

9.2.1.6. Minimal Residual Disease Assessment

Minimal Residual Disease (MRD) assessment by next-generation sequencing (NGS) is a relatively new and effective tool in the assessment of patients with multiple myeloma (Ladetto, 2014).[21] Several studies have demonstrated that MRD status is correlated with PFS and OS (Martinez-Lopez, 2014).[24] In the present study, bone marrow aspirate will be collected for MRD analysis when bone marrow samples are obtained at Screening, confirmation of CR/sCR, and subsequent time points after the first dose (see Table 10).

9.2.1.7. 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) is an acceptable method for evaluation of bone disease, and may be included as an additional assessment at the discretion of the investigator (see the disease response criteria in Table 9).

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

9.2.1.8. Documentation of Extramedullary Plasmacytomas

Sites of known extramedullary plasmacytomas must be documented during the Screening Phase. Clinical examination or MRI may be used to document extramedullary sites of disease. Computed tomography scan evaluations are an acceptable alternative if there is no contraindication to the use of intravenous contrast. Positron emission tomography scan or ultrasound tests are not acceptable to document the size of extramedullary plasmacytomas.

Extramedullary plasmacytomas should be assessed for all subjects with a history of plasmacytomas or if clinically indicated at Screening, by clinical examination or radiologic imaging. For subjects with a history of plasmacytomas assessed by physical examination, physical examination should be repeated on Cycle 1 Day 1 if not done within 14 days prior to randomization. Assessment of measurable sites of extramedullary disease will be performed and evaluated locally every 6 weeks (by physical examination) or every 12 weeks by imaging (if required) for subjects with a history of plasmacytomas or as clinically indicated during treatment for other subjects, until confirmed disease progression. For every subject, the methodology used for evaluation of each disease site should be consistent across all visits.

Irradiated or excised lesions will be considered not measurable, and will be monitored only for disease progression.

To qualify for PR, the sum of products of the perpendicular diameters of the existing extramedullary plasmacytomas must have decreased by at least 50%, and new plasmacytomas must not have developed (see the disease response criteria in Table 9). 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.

9.2.2. Endpoints

Primary Endpoints

The primary endpoint is PFS, which is defined as the duration from the date of randomization to either progressive disease or death, whichever comes first. Disease progression will be determined according to the IMWG criteria (Durie 2006, Rajkumar 2011).[8,37] For subjects who have not progressed and are alive, data will be censored at the last disease evaluation before the start of any subsequent anti-myeloma therapy. Relapse from CR by positive immunofixation or trace amount of M-protein is not considered to be progressive disease and is not included in the PFS calculation.

As the superiority of daratumumab combined with VMP over VMP alone with respect to PFS was established at the second interim analysis, the interim PFS analysis will serve as the primary PFS analysis, which otherwise was to occur when approximately 360 PFS events had been observed.

Secondary Endpoints

The secondary efficacy endpoints include:

- Time to disease progression (TTP) is defined as the time from the date of randomization to the date of first documented evidence of PD, as defined in the IMWG criteria. For subjects who have not progressed, data will be censored at the date of the disease evaluation before the start of any subsequent anti-myeloma therapy.
- CR rate, defined as the percentage of subjects achieving CR, as defined by:
  - Negative immunofixation of serum and urine, and
  - Disappearance of any soft tissue plasmacytomas, and
  - <5% PCs in bone marrow
  - For those subjects with negative or low SPEP (≤0.2 g/L) and suspected daratumumab interference on immunofixation, a reflex assay using anti-idiotype antibody will be utilized to confirm daratumumab interference and rule out false positive

immunofixation. Subjects who have confirmed daratumumab interference, but meet all other clinical criteria for CR or sCR, will be considered CR/sCR.

- MRD negativity rate, defined as the proportion of subjects who have negative MRD at any time point after the date of randomization.
- Progression-free Survival on Next line of Therapy (PFS2), defined as the time from randomization to progression on the next line of treatment or death, whichever comes first. Disease progression will be based on investigator judgment. Subjects who are still alive and not yet progressed on the next line of treatment will be censored on the last date of follow-up.
- Time to next treatment, defined as the time from randomization to the start of the next-line treatment.
- Overall response rate (ORR), defined as the proportion of subjects who achieve PR or better, according to the IMWG criteria, during or after the study treatment.
- sCR rate, defined as the percentage of subjects achieving CR in addition to having a normal FLC ratio and an absence of clonal cells in bone marrow by immunohistochemistry, immunofluorescence, 2-4 color flow cytometry.
- Proportion of subjects who achieve VGPR or better, defined as the proportion of subjects achieving VGPR and CR (including sCR) according to the IMWG criteria during or after the study treatment at the time of data cutoff.
- Time to response, defined as the time between randomization and the first efficacy evaluation that the subject has met all criteria for PR or better. For subjects without response, data will be censored either at the date of progressive disease or, in the absence of progressive disease, at the last disease evaluation before the start of subsequent anti-myeloma therapy.
- Duration of response, calculated from the date of initial documentation of a response (PR or better) to the date of first documented evidence of progressive disease, as defined in the IMWG criteria. For subjects who have not progressed, data will be censored at the last disease evaluation before the start of any subsequent anti-myeloma therapy.
- OS, measured from the date of 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.
- Impact of D-VMP compared to VMP on patient-reported perception of global health.
- Clinical efficacy of D-VMP in high risk molecular subgroups compared to VMP alone.

Exploratory Endpoints

- Biomarkers predictive of response or resistance to daratumumab.
- Durability of MRD negativity.

9.3. Pharmacokinetics and Immunogenicity

9.3.1. Evaluations

Samples to assess both the serum concentration (pharmacokinetics) of daratumumab and the generation of antibodies to daratumumab (immunogenicity) will be obtained from all subjects in the D-VMP group according to the Time and Events Schedule. In the Follow-up Phase, for all subjects in Arm B (D-VMP), samples are to be collected 8 weeks after the last dose of daratumumab, regardless of whether there has been confirmed disease progression. At specified time points, venous blood samples (5 mL per sample) will be collected and the serum will be divided into 3 aliquots (1 aliquot for pharmacokinetic analysis, 1 aliquot for immunogenicity assessment [when appropriate], and 1 aliquot as a back-up).

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

Samples collected for determining serum concentrations of daratumumab in this study may be retained to address questions about drug characteristics that may arise at a later time point.

9.3.2. Analytical Procedures

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

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

9.3.3. Pharmacokinetic Parameters

The pharmacokinetic parameters are defined as:

Cmax	Maximum observed concentration
Cmin	Minimum observed concentration

For daratumumab, the pharmacokinetic evaluations include Cmin and Cmax. If sufficient data are available, then other pharmacokinetic parameters may be calculated. If sufficient data are available, population pharmacokinetic analysis of serum concentration-time data of daratumumab may be performed and may include data from other clinical studies; details will be provided in a population pharmacokinetic analysis plan and results will be presented in a separate report.

9.3.4. Immunogenicity Assessments (Antibodies to daratumumab)

Serum from venous blood samples collected from D-VMP subjects will be assessed for the generation of antibodies to daratumumab (immunogenicity) according to the Time and Events Schedule. In the Follow-up Phase, for all subjects in Arm B (D-VMP), samples are to be collected for immunogenicity assessments 8 weeks after the last dose of daratumumab, regardless of whether there has been confirmed disease progression. Daratumumab concentration is also evaluated at all immunogenicity time points to ensure appropriate interpretation of immunogenicity data. When both serum concentration and immunogenicity analyses are specified, they are performed on aliquots from the same blood draw and no additional sampling is required. Procedures for sample collection, preparation, identification, storage, and shipment will be provided in the Laboratory Manual or equivalent document.

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

9.4. Pharmacokinetic/Pharmacodynamic Evaluations

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

9.5. Biomarkers

Biomarker assessments will focus on two main objectives including evaluating the ability of daratumumab + VMP to reduce minimal residual disease (MRD) in subjects that achieve a complete response (compared to VMP alone), and to determine the clinical benefit (ORR, PFS, and OS) of daratumumab + VMP in high-risk molecular subtypes (del17p, t(4;14), t(14;16), specific gene signatures, specific mutations). Bone marrow aspirates will be collected at screening and following treatment as outlined in the Time and Events Schedule. Baseline bone marrow aspirate samples will be subjected to DNA and RNA sequencing in order to classify subjects into high-risk molecular subgroups and to establish the myeloma clone for MRD monitoring. A fresh bone marrow aspirate or biopsy at Screening is required if at all possible; by exception non-decalcified diagnostic tissue (bone marrow aspirate slides or FFPE tissue) may be supplied for MRD assessment instead. For subjects who achieve a CR or sCR, bone marrow aspirates will be utilized for assessment of MRD by next-generation sequencing (NGS) of immunoglobulin heavy and light chains (Vij 2013).[43] If this methodology is unavailable, or determined to be scientifically inferior, then alternative methods for MRD assessment may be

utilized. In cases where daratumumab is suspected of interfering with serum IFE and preventing clinical CR response calls, subjects with VGPR will also be evaluated for MRD by NGS.

In addition to planned bone marrow aspirate assessments, a whole blood sample will be collected from subjects as outlined in the Time and Events Schedule for processing to plasma and PBMCs. These samples may be used to evaluate specific subsets of immune cells such as cytotoxic T cells, regulatory T cells, MDSCs, and activated NK cells. Cells may also be used for additional phenotypic and functional profiling. Proteomic analysis may also be used to evaluate changes in cytokines, complement proteins, soluble CD38, soluble CD59, IFNγ, granzyme, perforin, and other proteins associated with ADCC/CDC/ADCP to evaluate potential biomarkers of response and resistance.

Potential mechanisms of tumor resistance, such as changes in antigen (CD38) expression or increased expression in complement inhibitory proteins (CD46, CD55, and CD59) in multiple myeloma cells, may be monitored in subjects if a bone marrow aspirate sample is deemed feasible for collection at progressive disease. In addition, changes in expression patterns of genes associated with ADCC, CDC, or other mechanisms of action of daratumumab may be evaluated.

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

9.6. 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 time points outlined in the Time and Events Schedule before any other study procedures scheduled for the same day. All PRO measures will be completed using an electronic device (ePRO). For more details, refer to the ePRO user manual.

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, Wisloff 1997).[44,45] 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).[15] The scores for the 5 separate questions are categorical and cannot be analyzed as cardinal numbers. However, the scores for the 5 dimensions are used to compute a single utility score ranging from zero (0.0) to 1 (1.0) representing the general health status of the individual.

9.7. Medical Resource Utilization

Medical resource utilization (MRU) data, principally number of hospitalizations, will be derived from data collected in the eCRF for all subjects throughout the study.

9.8. Safety Evaluations

Safety will be measured by adverse events, laboratory test results, ECGs, vital sign measurements, physical examination findings, and assessment of ECOG performance status score. Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the eCRF. Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached.

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.

Details regarding the Independent Data Monitoring Committee are provided in Section 11.11.

The study will include the following evaluations of safety and tolerability according to the time points provided in the Time and Events Schedule:

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 study treatment. Adverse events will be followed by the investigator as specified in Section 12, Adverse Event Reporting.

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 section of the eCRF. The laboratory reports must be filed with the source documents.

The following tests will be performed by the local laboratory:

- Hematology Panel

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

- Serum Chemistry Panel

  Screening, Cycles 1-9 and End-of-Treatment:
  -blood urea nitrogen (BUN) or urea
  -creatinine
  -glucose
  -aspartate aminotransferase (AST)
  -alanine aminotransferase (ALT)
  -total bilirubin (direct bilirubin if total bilirubin >1.5xULN)
  -alkaline phosphatase
  -lactic acid dehydrogenase (LDH)
  -uric acid
  -total protein
  -sodium*
  -potassium*

  *Sodium and potassium assessments were added in Protocol Amendment 2, however, entry of sodium and potassium results in the eCRF will be done retrospectively from the date of subject consent for the duration of the study, if collected as part of routine care.

  Cycle 10+:
  -creatinine
  -sodium
  -blood urea nitrogen (BUN) or urea
  -potassium

  Cycle 10+, every third cycle:
  -aspartate aminotransferase (AST)
  -alanine aminotransferase (ALT)

- Pregnancy testing: Serum or urine pregnancy test for women of childbearing potential only
- Calcium and albumin adjusted calcium: These parameters will be part of the efficacy evaluations as specified in Section 9.2.1.3, and will be analyzed by the central laboratory. 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, Chapuy 2016).[5,4]

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

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

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

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

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

Pulmonary Function Test

Subjects with known or suspected COPD must have a FEV1 test during screening. Refer to Section 6.1.3.2 for details on subjects with higher risk of respiratory complications.

Electrocardiogram (ECG)

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, the procedures should be performed in the following order: ECG(s), vital signs, blood draw.

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

Physical Examination

A complete physical examination (including neurological examination) should be performed during the Screening Phase. Height will be measured at screening only; weight will be measured regularly as specified in the Time and Events Schedule. Thereafter, only a symptom and disease directed physical examination is required. Abnormalities will be recorded in the appropriate sections of the eCRF.

Eastern Cooperative Oncology Group (ECOG) Performance Status

When scheduled, ECOG assessments along with PRO questionnaires should be obtained prior to any other study procedures planned for the same day.

9.9. Sample Collection and Handling

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

Refer to the Time and Events Schedule for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual.

10. SUBJECT COMPLETION/WITHDRAWAL

10.1. Completion

A subject will be considered to have completed the study if he or she has finished all protocol-specified procedures before the end of the study, has not been lost to follow up, or has not withdrawn consent for study participation before the end of the study. The study end is defined as when 330 deaths have occurred, or 5 years after the last subject is randomized, whichever comes first.

Completion of Study Treatment

Subjects in Arm A (VMP) will be considered to have completed the study treatment if they have received at least 1 dose of study treatment in Cycle 9 and have not discontinued study treatment in Cycle 9 due to any of the reasons in Section 10.2 (Discontinuation of Study Treatment).

Subjects in Arm B (D-VMP) will continue daratumumab monotherapy until PD or until discontinuation due to an AE. As there is no protocol-defined study treatment period for this arm, no subjects in Arm B will be considered to complete study treatment at any time.

10.2. Discontinuation of Study Treatment

If a subject's study treatment must be discontinued before the end of the treatment regimen, **this will not result in automatic withdrawal of the subject from the study**. After treatment discontinuation, the subject will move into the Follow-up Phase. The End-of-Treatment Visit and 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.

Subjects who need to discontinue treatment with any one component of study treatment (VELCADE, melphalan, prednisone, or daratumumab) may continue to receive treatment with the other components of study treatment, as assigned.

A subject's study treatment should be discontinued if:

- The investigator believes that for safety reasons (eg, adverse event) it is in the best interest of the subject to discontinue study treatment
- The subject becomes pregnant
- The subject (or the subject's legally acceptable representative) withdraws consent for administration of study treatment
- The subject initiates treatment with a prohibited medication
- The subject received concurrent (non-protocol) treatment for multiple myeloma
- The subject experiences unacceptable toxicity, including infusion-related reactions as described in Section 6.1.4
- The subject's dose of daratumumab is held for more than 4 weeks (Cycle 1 to Cycle 9), after Cycle 9 if the subject misses 2 consecutive planned doses (unless Sponsor approves continuation)
- 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.

If any component of VMP requires dose reduction for a third time, only the component requiring dose reduction for a third time should be discontinued (ie, other components of the VMP regimen may continue to be administered).

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

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

10.3. 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
- The study investigator or Sponsor, for any reason, stops the study or stops the subject's participation in the study

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

When a subject withdraws from the study, the reason for withdrawal is to be documented in the eCRF and in the source document. Study treatment assigned to the withdrawn subject may not be assigned to another subject. If a subject withdraws from the study before the end of treatment, assessments outlined in the End-of-Treatment Visit should be completed. If the reason for withdrawal from the study is withdrawal of consent then no additional assessments are allowed.

Withdrawal From the Use of Samples in Future Research

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

11. STATISTICAL METHODS

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

11.1. Subject Information

The primary analysis population will be the intent-to-treat (ITT) population, which will include all randomized subjects. Safety will be evaluated for the population of all treated subjects. The pharmacokinetic analyses will be performed on the pharmacokinetic evaluable population. Continuous variables will be summarized using descriptive statistics such as mean, standard deviation, and range. Categorical variables will be summarized using frequency tables. For time-to-event variables, the Kaplan-Meier method will be used for descriptive summaries.

11.2. Sample Size Determination

In the VISTA study, the median PFS (as calculated by algorithm), was 18.3 months. The sample size calculation is performed based on the assumption that the median PFS for the VMP group in this study is estimated to be 21 months. Assuming that the addition of daratumumab can reduce the risk of the disease progression or death by 27.6%, ie, assuming the hazard ratio (VMP vs. D-VMP) of 0.724, which translates into a median PFS of 29 months for the D-VMP group, a total of 360 PFS events is needed to achieve a power of 85% to detect this hazard ratio with a log-rank test (two-sided alpha = 0.05). With a 20-month accrual period and an additional 21-month follow-up, the total sample size needed for the study is approximately 700 (350/treatment group) subjects. The sample size calculation has taken into consideration an annual dropout rate of 5%.

Long-term survival follow-up will continue until 330 deaths have been observed. Therefore, this study will achieve more than 80% power to detect a 27% reduction in the risk of death (hazard ratio=0.73) with a log-rank test (two-sided alpha=0.05).

11.3. Efficacy Analyses

Response to study treatment and progressive disease will be evaluated by a validated computer algorithm.

Primary Endpoint

For the primary endpoint of PFS, the primary analysis will consist of a stratified log-rank test for the comparison of the PFS distribution between the 2 treatment groups. The Kaplan-Meier method will be used to estimate the distribution of overall PFS for each treatment. The treatment effect (hazard ratio) and its two-sided 95% confidence intervals are to be estimated using a stratified Cox regression model with treatment as the sole explanatory variable.

Secondary Endpoints

Other time-to-event efficacy endpoints, including TTP, PFS2, OS, and time to next treatment, will be analyzed using the same method as for PFS. For overall survival, the final analysis will occur after 330 deaths have been observed. Earlier analyses, in which overall survival is analyzed, will be considered as interim analyses. Even though the significance of PFS has already been established at the second interim analysis, testing of OS will continue as planned until a definitive conclusion on OS is reached. The details about testing of OS over time are specified in Section 11.10. The analysis of OS may be confounded by subjects from Arm A receiving daratumumab after their study treatment was stopped. Exploratory analysis may be performed to adjust for the effect daratumumab exposure may have on OS for the subjects who were randomized to Arm A (VMP).

Comparison between the 2 treatment groups of overall response rates, rate of VGPR or better, rate of CR or better, and other binary endpoints will be conducted using the stratified Cochran Mantel Haenszel test. The Mantel-Haenszel odds ratio will be provided along with its two-sided 95% confidence interval, and will be provided as the measure of treatment effect. Duration of response will be provided descriptively without formal statistical comparison.

Strong control of familywise Type I error rate will be controlled at a two-sided significance level of 0.05 for the major secondary endpoints, including ORR, rate of VGPR or better, rate of CR or better, MRD negativity rate, and OS. A sequential hierarchical testing procedure will be used. The details of the testing procedure will be pre-specified in a statistical analysis plan that will be finalized prior to any unblinded efficacy analysis.

11.4. Pharmacokinetic Analyses

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

Descriptive statistics will be used to summarize daratumumab serum concentrations at each sampling time point and pharmacokinetic parameters of daratumumab such as Cmin and Cmax. If sufficient data are available, then other pharmacokinetic parameters may be calculated, including but not limited to CL and V.

11.5. Immunogenicity Analyses

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

11.6. Pharmacokinetic/Pharmacodynamic Analyses

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

11.7. Biomarker Analyses

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 + VELCADE based chemotherapy regimen compared with the VELCADE 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-analysis 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, MMY3008) may also be performed.

11.8. Patient-reported Outcomes

EORTC-QLQ-C30 scores will be evaluated for all domains except “financial problems” among patients with at least one post-baseline assessment and 50% completion of the relevant items for a domain. Descriptive analyses followed by mixed model repeated measures will be used to analyze each domain score. No adjustment for multiple comparisons will be made.

EQ-5D-5L scores will be summarized at each time point.

11.9. Safety Analyses

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). The severity assessment for an adverse event or serious adverse event should be completed using the NCI CTCAE Version 4. All reported adverse events with onset during the treatment phase (ie, treatment-emergent adverse events, and adverse events that have worsened since baseline) will be included in the analysis. For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group.

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

Clinical Laboratory Tests

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

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

Electrocardiogram (ECG)

Electrocardiogram data will be summarized by ECG parameter and listed.

Vital Signs

Descriptive statistics of baseline temperature, pulse/heart rate, and blood pressure (systolic and diastolic) values will be summarized.

11.10. Interim Analysis

Two interim analyses are planned for this study. The first interim analysis will be performed after a total of approximately 100 subjects have been treated for at least 2 cycles or discontinued the study treatment. Its purpose is to evaluate safety. The second interim analysis will be performed when approximately 216 PFS events, which is 60% of the total planned PFS events, have been accumulated. The purpose of this interim analysis is to evaluate cumulative interim safety and efficacy data. The significance level at this interim analysis to establish the superiority of D-VMP over VMP with regard to PFS will be determined based on the observed number of PFS events at the interim analysis, using the O'Brien-Fleming boundaries as implemented by the Lan-DeMets alpha spending method. Assuming 216 PFS events are observed, the alpha to be spent in this interim analysis will be 0.00762 (2-sided). If the experimental group (D-VMP) is numerically worse than the control group in terms of PFS (observed hazard ratio >1 favoring the control group), then the study may be terminated for futility.

As planned in the original protocol, two interim OS analyses will be performed at the time of the interim PFS (216 events) and the primary PFS (360 events) prior to the final OS analysis at 330 deaths. As the superiority of daratumumab combined with VMP over VMP alone with respect to PFS was established at the interim PFS analysis, the second interim OS will occur when 200 deaths (60% of all planned deaths) have been accumulated which is about the same

time of the primary PFS analysis as if it would have occurred. The stopping boundary for OS will be determined using an alpha-spending approach. At the interim PFS analysis, an alpha of 0.0001 will be spent. For the second OS interim and final analyses, the alpha to be spent will be determined by a linear alpha spending function based on the observed number of deaths at that time, ie, the cumulative alpha to be spent will be the total alpha (0.05) multiplied by the proportion of the observed number of deaths out of the total planned number of deaths (330).

11.11. Data Monitoring Committee

An IDMC, consisting of 2 clinicians and 1 statistician who are independent experts not otherwise participating in the study, will be established to review efficacy and safety results at the 2 planned interim analyses. After the interim review, they will make recommendations regarding the continuation of the study. In addition, the IDMC may also review cumulative safety data every 6 months besides the two interim analyses. The IDMC will no longer review study data after the database lock for the primary analysis has been completed. The details will be provided in a separate IDMC charter.

12. ADVERSE EVENT REPORTING

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

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

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

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

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

Serious Adverse Event

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

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

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

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

Unlisted (Unexpected) Adverse Event/Reference Safety Information

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

Adverse Event Associated With the Use of the Drug

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

12.1.2. Attribution Definitions

Not Related

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

Doubtful

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

Possible

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

Probable

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

Very Likely

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

12.1.3. Severity Criteria

The severity assessment for an adverse event or serious adverse event should be completed using the NCI CTCAE Version 4. 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 on a sponsor study drug that may require expedited reporting and/or safety evaluation include, but are not limited to:

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

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

12.3. Procedures

12.3.1. All Adverse Events

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

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

Only clinically relevant laboratory abnormalities (ie, those causing a treatment intervention or need for concomitant therapy) should be recorded on the adverse event eCRF. All other laboratory abnormalities need not be recorded as adverse events.

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. Anticipated events will be recorded and reported as described in Attachment 10.

All adverse events, regardless of seriousness, severity, or presumed relationship to study treatment, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as

"upper respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). For anticipated events reported as individual serious adverse events the sponsor will make a determination of relatedness in addition to and independent of the investigator's assessment. The sponsor will periodically evaluate the accumulating data and, when there is sufficient evidence and the sponsor has determined there is a reasonable possibility that the drug caused a serious anticipated event, they will submit a safety report in narrative format to the investigators (and the head of the investigational institute where required). The sponsor assumes responsibility for appropriate reporting of anticipated events to the regulatory authorities per requirements of the countries in which the studies are conducted. 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.

For all studies with an outpatient phase, including open-label studies, the subject must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study treatment phase (Arm A) and for at least 6 months after the study treatment is discontinued (Arm B) indicating the following:

- Study number
- Statement, in the local language(s), that the subject is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical staff only)
- Site number
- Subject number
- Blood type and indirect antiglobulin test results (as described in Section 9.8 for subjects in Treatment Arm B)

12.3.2. Serious Adverse Events

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

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

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

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

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

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

12.3.3. Pregnancy

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

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

12.4. Reporting, Monitoring, and Review of Safety Events in Japanese Subjects in Arm B (Japanese Sites Only)

There will be enhanced reporting, monitoring, and review of pre-specified safety events that occur during Cycle 1 at Japanese sites, for Japanese subjects in Arm B until a minimum of

3 Japanese subjects in Arm B have completed Cycle 1. A list of these pre-specified safety events and details regarding the reporting requirements are available in Attachment 8.

12.5. Contacting Sponsor Regarding Safety

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

13. PRODUCT QUALITY COMPLAINT HANDLING

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

13.1. Procedures

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

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

13.2. Contacting Sponsor Regarding Product Quality

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

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drug

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

14.2. Packaging

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

14.3. Labeling

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

14.4. Preparation, Handling, and Storage

All study drug vials must be stored in the original carton at controlled temperatures 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 Investigational Product Preparation Instructions or Site Investigational Product Procedures Manual for details regarding dose preparation, storage, and handling of diluted solutions.

14.5. Drug Accountability

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

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

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

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

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Investigator Brochure for daratumumab

- Site Investigational Product Procedures Manual
- Laboratory manual
- PRO questionnaires on a TrialSlate and user guidelines
- eCRF completion guidelines
- Sample ICF
- Subject diaries
- Subject wallet card indicating blood type and indirect antiglobulin test results
- Other manuals and guidance documents as needed

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

The primary safety profile of daratumumab is consistent with infusion-related reactions; see Section 6.1.3 for prevention details. Based on the mode of action of daratumumab, a potential risk could be infection; therefore, the protocol requires the review of hematological laboratory results prior to daratumumab 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. Anemia was also reported in Study GEN501. Free hemoglobin was mildly elevated, but other parameters did not support hemolysis. No bleeding events were observed. Routine safety laboratory measurement of RBCs and platelets will be closely monitored in this study.

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

The total blood volume for the study is estimated at approximately 45 mL during screening and 480 mL during VMP treatment in the first year. In the post-VMP treatment phase, blood sampling for subjects in Arm B will be approximately 305 mL per year on treatment. In the Follow-up Phase, subjects prior to PD will have approximately 120 mL blood drawn per year for serum disease evaluations. This is considered to be within the normal range of a single blood donation.

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

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

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

16.2.2. Independent Ethics Committee or Institutional Review Board

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

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the subjects)
- Investigator's Brochure (or equivalent information) and amendments/addenda
- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries 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.

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.

When prior consent of the subject is not possible and the subject's legally acceptable representative is not available, enrollment procedures should be described in the protocol with documented approval/favorable opinion by the IEC/IRB to protect the rights, safety, and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or legally acceptable representative must be informed about the study as soon as possible and give consent to continue.

16.2.4. Privacy of Personal Data

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

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

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

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

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

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

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

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand daratumumab, to understand 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, Withdrawal From the Study (Withdrawal From the Use of Samples in Future Research).

16.2.6. Country Selection

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

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

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

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

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

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

17.2.2. Required Pre-Study Documentation

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

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

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

- Completed investigator financial disclosure forms from all sub-investigators
- Documentation of sub-investigator 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 (as allowed by local regulations). In cases where the subject is not randomized into the study, the date seen and date of birth (as allowed by local regulations) will be used.

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

17.4. Source Documentation

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

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

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

Subject- and investigator-completed scales and assessments designated by the sponsor (EORTC QLQ-C30 and EQ-5D-5L) will be recorded directly into an electronic device or other tool and will be considered source data.

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

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

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

17.5. Case Report Form Completion

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

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

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

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

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

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

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

17.6. Data Quality Assurance/Quality Control

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

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

17.7. Record Retention

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

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

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

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

17.8. Monitoring

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

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

17.9. Study Completion/Termination

17.9.1. Study Completion

The study is considered completed after 330 deaths have occurred or 5 years after the last subject is randomized, whichever is first. The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject at that study site, in the time frame specified in the Clinical Trial Agreement.

17.9.2. Study Termination

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

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

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

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

17.10. On-Site Audits

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

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

17.11. Use of Information and Publication

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

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

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain eCRF data from all study sites that participated in the study, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's database. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator for the study. 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 (ICMJE) 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 18 months after study end date, 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 ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

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

REFERENCES

1. American Cancer Society (ACS). Cancer Facts & Figures 2012. Atlanta: American Cancer Society; 2012. Available from: http://www.cancer.org/Cancer/MultipleMyeloma/DetailedGuide/multiple-myeloma-key-statistics. Accessed on 25 March 2013.
2. Bringhen S, Larocca A, Rossi D, et al. Efficacy and safety of once-weekly bortezomib in multiple myeloma patients. Blood. 2010;116:4745-4753.
3. Burtis CA, Ashwood ER. Tietz textbook of clinical chemistry, 3rd ed. Philadelphia; WB Saunders, 1999.
4. Chapuy C, Aguad MD, Nicholson RT, et al. International validation of dithiothreitol (DTT)-based method to resolve the daratumumab interference with blood compatibility testing. Transfusion. 2016;00:1-9.
5. Chapuy, C, Nicholson R, Aguad MD, et al. Resolving the daratumumab interference with blood compatibility testing. Transfusion. 2015; 55:1545-1554.
6. de Weers M, Tai YT, van der Veer MS, et al. Daratumumab, a novel therapeutic human CD38 monoclonal antibody, induces killing of multiple myeloma and other hematological tumors. J Immunol. 2011;186:1840-1848.
7. 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 Onco. 2009;27:6086-6093.
8. Durie BG, Harousseau JL, Miguel JS, et al. International uniform response criteria for multiple myeloma. Leukemia. 2006;20:1467–1473. Corrigenda/Erratum in: Leukemia. 2007;21:1134-1135.
9. Facon T, Dimopoulos MA, Dispenzieri A, et al. Initial Phase 3 Results Of The First (Frontline Investigation Of Lenalidomide + Dexamethasone Versus Standard Thalidomide) Trial (MM-020/IFM 07 01) In Newly Diagnosed Multiple Myeloma (NDMM) Patients (Pts) Ineligible For Stem Cell Transplantation (SCT). Blood 2013;122:21. ASH Annual Meeting Abstract. http://bloodjournal.hematologylibrary.org/content/122/21/2.abstract?sid=06133b3d-094e-452b-aeb2-f12d2a83ce53. Accessed on 16 January 2014.
10. Fayers PM, Palumbo A, Hulin C, et al. Thalidomide for previously untreated elderly patients with multiple myeloma: meta-analysis of 1685 individual patient data from 6 randomized clinical trials. Blood 2011:118;1239-1247.
11. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, and Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer. 2010;127:2893-2917.
12. Gay F and Palumbo A. Management of older patients with multiple myeloma. Blood Reviews 2011;25:65-73.
13. Ghosh N, Tucker N, Zahurak M, et al. Addition of clarithromycin to lenalidomide and dexamethasone (BiRd) is effective in MM after progression on lenalidomide and dexamethasone. Session 653. Myeloma: Therapy, excluding Transplantation. American Society of Hematology (ASH) 2013 meeting. Abstract 1960.
14. Harousseau JL, 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. 2010;116:3743-3750.
15. 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.
16. Investigator's Brochure: JNJ-54767414 (daratumumab) Edition 10. Janssen Research & Development, LLC (16 December 2013).
17. Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol. 2016;17:e328-346.
18. Kyle RA, Gertz MA, Witzig TE, et al. Review of 1027 patients with newly diagnosed multiple myeloma. Mayo Clin Proc. 2003;78:21-33.
19. Kyle RA, Rajkumar SV. Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma. Leukemia. 2009;23:3-9.

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

21. Ladetto M, Bruggemann M, Monitello L, et al. Next-generation sequencing and real-time quantitative PCR for minimal residual disease detection in B-cell disorders. Leukemia. 2014;1-9.doi:10.1038/leu.2013.375.

22. Levey AS, Coresh J, Greene T, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med. 2006;145(4):247-254.

23. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-612.

24. Martinez-Lopez J, Lahuerta JJ, Pepin F, et al. Prognostic value of deep sequencing method for minimal residual disease detection in multiple myeloma. Blood, prepublished online March 19, 2014: 10.1182/blood-2014-01-55020.

25. Mateos MV, Bringhen S, Richardson PG, et al. Bortezomib cumulative dose, efficacy, and tolerability with three different bortezomib-melphalan-prednisone regimens in previously untreated myeloma patients ineligible for high-dose therapy. Haematologica. 2014:Apr 24 [Epub ahead of print].

26. Mateos MV, Oriol A, Martinez-Lopez J, et al. Bortezomib, melphalan, and prednisone versus bortezomib, thalidomide, and prednisone as induction therapy followed by maintenance treatment with bortezomib and thalidomide versus bortezomib and prednisone in elderly patients with untreated multiple myeloma: a randomised trial. Lancet Oncol. 2010;11:934-941.

27. Mateos MV, Oriol A, Martínez-López J, et al. Maintenance therapy with bortezomib plus thalidomide or bortezomib plus prednisone in elderly multiple myeloma patients included in the GEM2005MAS65 trial. Blood. 2012;120:2581-2588.

28. McCudden, CR, Voorhees PM, Hainsworth SA, et al. Interference of monoclonal antibody therapies with serm protein electrophoresis tests. Clin Chem. 2010;56:1897-1904.

29. Moreau P, Pylypenko H, Grosicki S, et al. Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: a randomised, phase 3, non-inferiority study. Lancet Oncol. 2011;12:431-440.

30. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Multiple Myeloma, version 2.2013.

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

32. 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.

33. Palumbo A, Anderson K. Multiple myeloma. N Engl J Med. 2011;364:1046-1060.

34. Palumbo A, Brighen S, Rossi D, et al. A Prospective, Randomized, Phase III Study of Bortezomib, Melphalan, Prednisone and Thalidomide (VMPT) Versus Bortezomib, Melphalan and Prednisone (VMP) in Elderly Newly Diagnosed Myeloma Patients. Blood. 2008;112:652. ASH Annual Meeting Abstract.

35. Palumbo A, Bringhen S, Rossi D, et al. Bortezomib-Melphalan-Prednisone-Thalidomide Followed by Maintenance With Bortezomib-Thalidomide Compared With Bortezomib-Melphalan-Prednisone for Initial Treatment of Multiple Myeloma: A Randomized Controlled Trial. J Clin Oncol. 2010;28:5101-5109.

36. 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.

37. 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;117:4691-4695.

38. 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.

39. San Miguel JF, Schlag R, Khuageva NK, et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. N Engl J Med. 2008;359:906-917.

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

41. Sonneveld P, Goldschmidt H, Rosinol L, et al. Bortezomib-Based Versus Nonbortezomib-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. 2013:31;3279-3287.

42. van der Veer M, de Weers M, van Kessel B. The therapeutic human CD38 antibody daratumumab improves the anti-myeloma effect of newly emerging multi-drug therapies. Blood Cancer Journal. 2011a; 1 e41. Doi:10.1038/bcj.2011.42.

43. Vij R, Mazumder A, Klinger M, et al. Deep sequencing reveals myeloma cells in peripheral blood in majority of multiple myeloma patients, Clinical Lymphoma, Myeloma and Leukemia (2013), doi: 10.1016/j.clml.2013.09.013.

44. 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.

45. 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: Modified IMWG Diagnostic Criteria for Multiple Myeloma

Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma[a] 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[b] <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[c]

Footnotes:

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

b) Measured or estimated by validated equations.

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

Reference: Rajkumar 2014[38]

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 self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Reference: Oken 1982[31]

Attachment 3: Serum Calcium Corrected for Albumin

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

If calcium is expressed in 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 1999[3]

Attachment 4: Guideline for Asthma Eligibility Criteria

Components of Severity		Classification of Asthma Severity											
		Intermittent			Persistent								
					Mild			Moderate			Severe		
		0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs
Impairment	Symptoms	≤2 days/week			≤2 days/week but not daily			Daily			Throughout the day		
	Nighttime awakenings	0	≤ 2x/month		1-2x/ month	3-4x/month		3-4x/ month	> 1x/week but not nightly		> 1x/ month	Often 7x/week	
Normal FEV1/FVC : 8-19 yr 85% 20-39 yr 80% 40-59 yr 75% 60-80 yr 70%	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		
	Lung function FEV1 FEV1/FVC	N/A	Normal FEV1 between exacerbations > 80% > 85%	Normal FEV1 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 FEV1.	≥ 2/year Relative annual risk may be related to FEV1.	≥ 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 FEV1.	≥ 2/year Relative annual risk may be related to FEV1.	≥ 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 FEV1.	≥ 2/year Relative annual risk may be related to FEV1.
		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.							

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.	

American Lung Association of Minnesota

Attachment 5: Antihistamine Medications

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

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

* The IV use of promethazine should be avoided.

Attachment 6: Conversion Table for Glucocorticosteroid Dose

Generic Name	Oral or Intravenous Dose (mg)
Dexamethasone	0.75
Methylprednisolone	4
Prednisolone	5
Prednisone	5
Betamethasone	0.6

Attachment 7: Body Surface Area Nomogram

Body surface area should be calculated according to the following formula:

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

or

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

Attachment 8: Reporting, Monitoring, and Evaluating Safety Events in Japanese Subjects in Arm B (Japanese Sites Only)

Enhanced reporting of specific events (as described below) will be required until a minimum of 3 Japanese subjects in Arm B have completed Cycle 1 of treatment. If these specific events (as described below) occur in Cycle 1 in ≥2 subjects from the first 3 treated subjects in Arm B, an additional 3 subjects in Arm B will be monitored (for a total of 6 subjects). The events (as described below) that occur during Cycle 1 of treatment in Japanese subjects in Arm B will be reported to the sponsor by the investigator or study personnel within 24 hours of awareness.

Definitions of Adverse Events in Japanese Subjects in Arm B that are Subject to Evaluation by External Safety Monitor (ESM)

Any of the following events considered by the investigator to be related to study treatment (VELCADE, melphalan, prednisone, or daratumumab):

Infusion-related reactions

- Any Grade 4 infusion-related reactions occurring within 48 hours of the infusion of daratumumab
- Any Grade 3 infusion-related reactions occurring within 48 hours of the infusion of daratumumab that do not resolve with a reduced infusion rate or temporarily stopping (maximum 2 hours) the infusion, supportive care, and symptomatic therapy such as administration of steroid and antihistamine

Non-hematologic toxicity of Grade 3 or higher with the exception of:

- Grade 3 nausea or Grade 3 vomiting that responds to antiemetic treatment
- Grade 3 diarrhea that responds to antidiarrheal treatment
- Grade 3 fatigue or asthenia present at baseline or lasting for less than 7 days after the last administration of daratumumab

Hematologic toxicity, defined as:

- Grade 4 thrombocytopenia (platelet count <25,000/mm^3) lasting for more than 7 days, or Grade 3 or 4 thrombocytopenia with bleeding
- Grade 4 neutropenia (ANC <500 cells/mm^3) lasting for more than 7 days
- Grade 3 febrile neutropenia (ANC <1000 cells/mm^3 and a single temperature >38.3°C or a sustained temperature >38°C for >1 hour), or sepsis
- Grade 4 anemia

These events should follow the same reporting process as serious adverse events (see Section 12.3.2). Receipt of a report of a serious adverse event or any of the events listed above during Cycle 1 of treatment will, in turn, trigger enhanced reporting and review as described below.

An External Safety Monitor (ESM) who is a hematologist will evaluate these events in Japan and will review the reported safety data and may request additional information from the sites. If the ESM identifies a critical safety signal, he/she may, at his/her discretion, suspend enrollment in Japan until Independent Data Monitoring Committee (IDMC) review is completed. The IDMC chair will be notified of the signal and will review the data. After the review is complete, the IDMC chair will communicate the final recommendation to the sponsor.

Japanese sites will be notified when the first 3 subjects in Arm B have completed Cycle 1 of treatment. However, if the above events occur in Cycle 1 in ≥2 subjects from the first 3 treated subjects in Arm B, an additional 3 subjects in Arm B will be monitored (for a total of 6 subjects) as described above. After enrollment of a minimum of 3 subjects (and up to 6 subjects, as described above) is complete, enhanced reporting, monitoring, and evaluation of the above safety events in Japanese subjects will no longer be required. However, serious adverse events and adverse events of special interest must continue to be reported to the sites within 24 hours of awareness, as described in Section 12.3.2.

Attachment 9: International Staging System (ISS) Staging

International Staging System		
Stage	**Criteria**	**Median Survival (months)**
I	Serum ß^2 microglobulin <3.5 mg/L, serum albumin ≥3.5 g/dL	62
II	Not I or III[a]	44
III	Serum ß^2 microglobulin ≥5.5 mg/L	29

[a] There are 2 possibilities for Stage II:
1) Serum ß^2 microglobulin <3.5 mg/L but serum albumin <3.5 g/dL, or
2) Serum ß^2 microglobulin 3.5 to <5.5 mg/L irrespective of the serum albumin

Attachment 10: Anticipated Adverse Events

Anticipated Event

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

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

- Anemia
- Bleeding
- Bone diseases
- Hypercalcemia
- Hyperuricemia
- Hyperviscosity syndrome
- Infection
- Neutropenia
- Renal failure or insufficiency
- Thrombocytopenia

Reporting of Anticipated Events

All adverse events will be recorded in the CRF regardless of whether considered to be anticipated events and will be reported to the sponsor as described in Section 12.3.1, All Adverse Events. Any anticipated event that meets serious adverse event criteria will be reported to the sponsor as described in Section 12.3.2 Serious Adverse Events. These anticipated events are exempt from expedited reporting as individual single cases to Health Authorities. However, if based on an aggregate review, it is determined that an anticipated event is possibly related to study drug, the sponsor will report these events in an expedited manner.

Anticipated Event Review Committee (ARC)

An Anticipated Event Review Committee (ARC) will be established to perform reviews of pre-specified anticipated events at an aggregate level. The ARC is a safety committee within the sponsor's organization that is independent of the sponsor's study team. The ARC will meet to aid in the recommendation to the sponsor's study team as to whether there is a reasonable possibility that an anticipated event is related to the study drug.

Statistical Analysis

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

INVESTIGATOR AGREEMENT

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

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

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Ming Qi, MD, PhD

Institution: Janssen Research & Development

Signature: electronic signature appended at the end of the protocol 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.

SIGNATURES

Signed by	Date	Justification
Ming Qi	15Feb2018, 05:12:59 AM, UTC	Document Approval