Janssen Research & Development*

Clinical Protocol

A Phase 3 Randomized, Multicenter Study of Subcutaneous Daratumumab Versus Active Monitoring in Subjects with High-risk Smoldering Multiple Myeloma

Protocol 54767414SMM3001; Phase 3
Amendment 6/EEA-1

JNJ-54767414 (daratumumab)

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This study will be conducted at sites in the United States (US) under US Food & Drug Administration IND regulations (21 CFR Part 312) and at sites in the European Economic Area (EEA) under Regulation EU No. 2023-507143-11.

EU TRIAL NUMBER: 2023-507143-11

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

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Country/Territory Affected**	**Date**
Amendment 6/EEA-1	All	9 September 2024
Amendment 5/EEA-1	All	14 August 2023
Amendment 5/FRA-2	France	14 January 2021
Amendment 5	All	14 January 2021
Amendment 4/FRA-2	France	22 June 2020
Amendment 4	All	22 June 2020
Amendment 3/FRA-2	France	12 June 2019
Amendment 3/FRA-1	France	31 January 2019
Amendment 3	All	25 January 2019
Amendment 2/FRA-1	France	14 November 2018
Amendment 2	All	19 September 2018
Amendment 1	All	30 January 2018
Original Protocol	All	19 July 2017

In the description of change column, modified text is presented as follows: text in strikethrough has been deleted, text in bold has been added.

Amendment 6/EEA-1: the primary analysis concluded when the planned number of PFS events were achieved and the study was subsequently unblinded. The overall reason for this amendment is to discontinue the use of central laboratory assessments and IRC evaluation of progressive disease. Disease evaluations and confirmation of disease progression will continue, according to the Time and Events Schedule, by local assessment only.

The changes made to the clinical protocol as part of Protocol Amendment 6 are listed below, including the rationale of each change and a list of all applicable sections. Changes made in previous protocol amendments are listed in Section 19: Protocol Amendment History.

Section Number and Name	**Description of Change**	**Brief Rationale**
Table 1: Time and Events Schedule **3.1** Overview of Study Design **9.2** Efficacy Evaluations **9.2.1** Assessment of Response	Evaluation of disease progression by IRC and validated computerized algorithm will be discontinued. Disease evaluations will be conducted locally, according to the Time and Events Schedule, and disease progression will be assessed according to IMWG criteria and reported when confirmed.	The primary analysis concluded when the planned number of PFS events were achieved, hence evaluation of disease progression by IRC criteria and validated computerized algorithm is no longer required.

Table 1: Time and Events Schedule 9.2 Efficacy Evaluations 9.2.3 CRAB Criteria-related Laboratory Assessments 9.2.4 Myeloma Protein Measurements in Serum and Urine 9.2.5 β2-microglobulin and Lactate Dehydrogenase 9.2.6 Bone Marrow Examination **Assessment** of Bone Disease 9.7 Safety Evaluations 9.5 Patient-reported outcomes 9.6 Medical Resource Utilization	Central laboratory testing will be discontinued. Pre-PD follow up and PD assessments: • Disease evaluations should continue according to Time & Events Schedule, by local assessment • Only disease progression by investigator via local assessment will be reported to the Sponsor. • Assessment of response for disease evaluations and local laboratory and imaging results will not be reported to the Sponsor. Post-PD follow-up: PRO and MRU collection at Months 12 and 18 in the have been discontinued.	Post primary analysis, central laboratory testing and central imaging are no longer required. Post primary analysis, PRO and MRU collection at Months 3 and 6 are considered sufficient.
Table 1: Time and Events Schedule 9.4 Biomarkers Table 10	Central Laboratory Biomarker assessments will be discontinued.	Post primary analysis, biomarker analyses are no longer required.
9.3 Pharmacokinetics and Immunogenicity	Immunogenicity and PK assessments will no longer be collected.	

SYNOPSIS Table 1: Time and Events Schedule Table 2: Daratumumab Administration (Arm B Only) 9.1.1 Overview 9.2 Efficacy Evaluations 9.3.2 Analytical Procedures 9.4 Biomarkers 9.5 Patient-reported Outcomes 9.6 Medical Resource Utilization	Home health care visits have been removed throughout the protocol.	Home health care visits are no longer available. NOTE: Tele health visits (conducted via phone or video conference) may continue as deemed necessary.
11.12 Data Monitoring Committee	The IDMC will be discontinued once the primary analysis endpoint has been achieved.	IDMC will no longer be required.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

SYNOPSIS

A Phase 3 Randomized, Multicenter Study of Subcutaneous Daratumumab Versus Active Monitoring in Subjects with High-risk Smoldering Multiple Myeloma

EU TRIAL NUMBER: 2023-507143-11

BENEFIT-RISK ASSESSMENT

Currently, the standard of care for patients with high-risk smoldering multiple myeloma (SMM) is active monitoring, and most patients with SMM are not treated until end organ damage and evolution to an incurable disease occur. Preliminary data show that daratumumab has single agent activity in intermediate- and high-risk SMM.

Based on the results of nonclinical studies, the mechanism of action, the route of administration, and results from participants treated in daratumumab studies, the potential safety risks for daratumumab are systemic administration-related reactions, cytopenia, and infections. Considering the measures taken to minimize risk to participants of this study, the potential risks associated with daratumumab are justified by the anticipated benefits that may be afforded to participants with SMM.

OBJECTIVES AND HYPOTHESIS

Primary Objective

To determine whether treatment with daratumumab administered subcutaneously (SC) prolongs progression-free survival (PFS) compared to active monitoring in subjects with high-risk smoldering multiple myeloma (SMM)

Secondary Objectives

- To demonstrate additional clinical benefit (overall response rate, duration of response, overall survival, etc) for subjects with high-risk SMM treated with daratumumab compared with active monitoring
- To assess the safety profile of daratumumab in subjects with high-risk SMM
- To assess the clinical characteristics of symptomatic multiple myeloma (MM) following progression of disease after therapy with daratumumab
- To evaluate the pharmacokinetics and immunogenicity of daratumumab administered SC in subjects with high-risk SMM
- To evaluate the immunogenicity of recombinant human hyaluronidase (rHuPH20) when administered in combination with daratumumab SC in subjects with high-risk SMM
- To evaluate the effect of treatment with daratumumab on health-related quality of life

Exploratory Objectives

- To investigate clinical efficacy of daratumumab in high-risk subjects with genetic modifications (del17p, t(4:14), 1q gain, or other high-risk molecular subtypes)
- To explore biomarkers of response or resistance to daratumumab, including immunophenotypes and expression of MM markers (ie, CD38)

Hypothesis: Daratumumab administered as monotherapy will prolong PFS compared with active monitoring in subjects with high-risk SMM.

OVERVIEW OF STUDY DESIGN: This is a Phase 3, randomized, open-label, 2-arm, multicenter study to evaluate the efficacy and safety of daratumumab SC administration versus active monitoring in subjects with high-risk SMM. Approximately 360 subjects will be assigned randomly to active monitoring (Arm A) or daratumumab (Arm B) in a 1:1 ratio. Key inclusion criteria include the following: subjects who are ≥18 years of age, have a confirmed diagnosis of high-risk SMM, and an Eastern Cooperative Oncology Group performance status score of 0 or 1.

For subjects in both study arms for whom there are no safety concerns, tele-health (conducted via phone or video conference) visits are permitted per the clinical judgement of the investigator, and where feasible and permissible by local policy and regulations. All assessments should be followed with in person examination, if clinically indicated. Refer to the Time and Events Schedule (Tables 1 and 2) for guidance.

DOSAGE AND ADMINISTRATION

Subjects randomized to active monitoring will receive no study medication but will undergo the same disease evaluations and at the same frequency as subjects randomized to daratumumab. Subjects randomized to daratumumab will receive daratumumab SC (daratumumab 1800 mg + rHuPH20 [2000 U/mL]) once weekly in Cycle 1 and 2, then every 2 weeks for Cycle 3 to Cycle 6, and thereafter every 4 weeks for up to 39 cycles or 36 months, whichever occurs first. Each cycle will be 28 days. All doses should be administered at outpatient visits.

EFFICACY EVALUATIONS

Assessment of disease will be conducted in accordance with the International Myeloma Working Group (IMWG) response criteria. Disease evaluations will include the following: measurements of myeloma proteins; bone marrow examinations; other imaging studies; and measurements of β2-microglobulin, lactate dehydrogenase, albumin, hemoglobin, creatinine clearance, and serum calcium corrected for albumin.

OTHER EVALUATIONS

In the daratumumab group, blood samples will be drawn from subjects to characterize the pharmacokinetics of daratumumab and to assess for the generation of antibodies to daratumumab; additional blood samples will be assessed for the generation of antibodies to rHuPH20. Blood, bone marrow aspirate, and stool samples will be used to better understand the mechanism of action of daratumumab and to obtain information about potential markers of clinical response and resistance.

Safety will be measured by adverse events, physical examination findings, electrocardiogram monitoring, SC injection site evaluation, clinical laboratory test results (hematology and chemistry), and assessment of Eastern Cooperative Oncology Group performance status.

STATISTICAL METHODS

Assuming a median PFS for Arm A (active monitoring) of 30 months and that daratumumab treatment will reduce the risk of the disease progression or death by 37.5% (ie, a hazard ratio of 0.625; median PFS of 48 months for daratumumab), 165 PFS events are needed to achieve a power of 85% to detect this hazard ratio with a log-rank test (one sided alpha=0.025). With a 24-month accrual period and an additional 24 months of follow-up, the sample size needed for the study is approximately 360 (180 in active monitoring, 180 in daratumumab) subjects. There will be one interim analysis for futility. This analysis will occur when approximately 60% of the PFS events (99) have occurred. This is expected to occur approximately 8 months after the last subject has been randomized. The purpose of this interim analysis is to evaluate cumulative interim safety and efficacy data. The non-binding futility boundary at this interim analysis will be determined using the Kim-Demets power spending function with parameter p=4.0. The beta spent at this futility analysis will be 0.0194.

TIME AND EVENTS SCHEDULE

Table 1: Active Monitoring (Arm A) and Daratumumab (Arm B): Active Monitoring/Treatment Phase, End-of-Active Monitoring/End-of-Treatment, Pre-PD Follow-up, and Post-PD Follow-up

With implementation of Amendment 6, Central laboratory testing will be discontinued, and pre-PD, PD and post-PD disease evaluations will be conducted per protocol frequency using local laboratory testing. All biomarker assessments will be discontinued. Home health care visits are no longer available.

	Notes	Active Monitoring (Arm A; 12-week disease evaluations) / Treatment Phase (Arm B; 4-week treatment cycles after Cycle 6)[a] (up to 39 cycles or 36 months, whichever occurs first)								End of Active Monitoring/ End of Treatment	Pre-PD Follow-up	PD	Post-PD Follow-up
		Screening (within 35 days before randomization)	C1-2				C3-6		C7-39	30 (±3) days after the last Daratumumab dose[c]	every 12 weeks (±7 days)		at least every 6 months (until end of study)
			D1[b]	D8	D15	D22	D1	D15	D1				
The start of Cycles 2 to 39 may occur ±3 days of the scheduled day in order to accommodate the schedule of the site or subject, only if a minimal interval of 4 days between daratumumab doses is maintained. All subsequent days within that cycle and Day 1 of subsequent cycles should be adjusted accordingly to maintain the 28-day cycle duration. In case of dose delays affecting days other than Day 1, because of reasons other than toxicity, administration should occur within the prespecified window (Table 7). If an administration does not commence within the prespecified window 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. Every effort should be made to avoid dose delays because of reasons other than toxicity (refer to Section 6.5.3 for details on interrupted or missed doses). Unless otherwise stated, all blood and urine samples must be obtained before administration of daratumumab.													
Procedures													
Informed Consent	ICF must be signed before any study-related procedures are performed.	X											
Eligibility criteria		X											
Demography/ Medical History/benign/post-traumatic pre-existing bone lesions[d]		X											
FEV1 test	Subjects with known or suspected chronic obstructive pulmonary disease Acceptable for screening if performed as part of standard of care within 35 days before randomization	X											
ECOG performance status	As clinically indicated and additionally when PD suspected	X	Every 6 months							X		X	
12-lead electrocardiogram[l]	Acceptable for screening if performed as part of	X								X			

	Notes	Active Monitoring (Arm A; 12-week disease evaluations) / Treatment Phase (Arm B; 4-week treatment cycles after Cycle 6)[a] (up to 39 cycles or 36 months, whichever occurs first)								End of Active Monitoring/ End of Treatment	Pre-PD Follow-up	PD	Post-PD Follow-up
		Screening (within 35 days before randomization)	C1-2				C3-6		C7-39	30 (±3) days after the last Daratumumab dose[e]	every 12 weeks (±7 days)		at least every 6 months (until end of study)
			D1[b]	D8	D15	D22	D1	D15	D1				
	standard of care within 56 days before randomization												
Physical exam[l]	Symptom and disease directed exam as clinically indicated	X								X			
Height and weight		X											
Laboratory Assessments[e]													
Pregnancy test (local laboratory) for women of childbearing potential		X (within 14 days before randomization)	as clinically indicated										
HBV serology [k]	Local testing for HBsAg, Anti-HBs, and Anti-HBc.	X	X (subjects ongoing in arm B only who are within 6 months of starting study treatment when Protocol Amendment 3 is implemented will be required to have HBV serology performed locally upon signing the updated ICF.)										
HBV DNA test	For subjects with serologic evidence of resolved HBV infection (ie, positive Anti-HBs or positive Anti-HBc) at Screening, HBV DNA testing by PCR must be performed locally.	X[f]	Q12W (for arm B patients, only) [f]							X (for arm B patients only)[f]	Q12w (for arm B patients only)[f]		Q12w (for arm B patients only)[f]

	Notes	Active Monitoring (Arm A; 12-week disease evaluations) / Treatment Phase (Arm B; 4-week treatment cycles after Cycle 6)[a] (up to 39 cycles or 36 months, whichever occurs first)							End of Active Monitoring/ End of Treatment	Pre-PD Follow-up	PD	Post-PD Follow-up
		Screening (within 35 days before randomization)	C1-2			C3-6		C7-39	30 (±3) days after the last Daratumumab dose[e]	every 12 weeks (±7 days)		at least every 6 months (until end of study)
			D1[b]	D8	D15	D22	D1	D15	D1				
Hematology Serum chemistry including calcium, albumin, creatinine SPEP, SIFE UPEP, UIFE Serum free light chain	Sample to be sent to local laboratory. After Cycle 1, IFE only when endogenous M-protein is 0 or nonquantifiable. Not required on C1D1 if screening values were obtained within 14 days of C1D1. In subjects with a baseline UPEP result below the level of measurable disease (<200 mg/24 hours), UPEP analysis will be repeated only at the time of suspected CR[g]	X	Every 12 weeks (window ±7 days)						X	X	Albumin only	
Quantitative immunoglobulin		X	yearly						X	yearly		
β2-microglobulin and lactate dehydrogenase	Sample to be sent to local laboratory	X									X	
Bone marrow aspirate[l]	Per Amend 6: Bone marrow testing to be performed at local laboratory. Morphology and additional diagnostic tests (including local Cytogenetics by FISH)	X[h]	At least every 2 years and at suspected CR. See Table 10 for details.								X	

	Notes	Active Monitoring (Arm A; 12-week disease evaluations) / Treatment Phase (Arm B; 4-week treatment cycles after Cycle 6)[a] (up to 39 cycles or 36 months, whichever occurs first)							End of Active Monitoring/ End of Treatment	Pre-PD Follow-up	PD	Post-PD Follow-up
		Screening (within 35 days before randomization)	C1-2			C3-6		C7-39	30 (±3) days after the last Daratumumab dose[e]	every 12 weeks (±7 days)		at least every 6 months (until end of study)
			D1[b]	D8	D15	D22	D1	D15	D1				
Imaging and Additional Studies												
Lytic lesion assessment by low-dose whole body computed tomography (preferred), PET-CT, or CT (central read)[d,l]	Use same methodology throughout study. Per Amend 6: to be read by local radiologist.	X (within 56 days before randomization)	Every 12 months until confirmed PD								Optional, encouraged for subjects progressing based on FLC criteria	
Focal lesion assessment by magnetic resonance imaging (central read) d,l	Spine and pelvis magnetic resonance imaging. Per Amend 6: to be read by local radiologist.	X (within 56 days before randomization)	Every 12 months and at biochemical progression or at suspected PD								Optional, encouraged for subjects progressing based on FLC criteria	
Patient Reported Outcomes[i] (EORTC QLQ-C30, EORTC QLQ-MY20, and EQ-5D-5L)	To be collected after the subject signs informed consent and before any interventions scheduled for the same day as the PRO assessments are collected	X	Week 12, Week 24, and Week 60 (with disease evaluations), then every year until the end of the Treatment /Active Monitoring Phase (with disease evaluations).						X[m]	Every year until the end of the study or PD.	X	Months 3 and 6,
Medical Resource Utilization	See Section 9.6	At disease assessment visits										Months 3 and, 6,
Ongoing Subject Review												
Adverse Events		Active Monitoring (Arm A): Continuous from the time of signing of ICF until 36 months from the start of active monitoring or until start of next therapy, whichever is earlier Daratumumab (Arm B): Continuous from the time of signing of ICF until 30 days after last daratumumab dose, or until start of next therapy, whichever is earlier										
Concomitant Medications		Active Monitoring (Arm A): Continuous from the time of signing of ICF until 36 months from the start of active monitoring or until start of next therapy, whichever is earlier										

	Notes	Active Monitoring (Arm A; 12-week disease evaluations) / Treatment Phase (Arm B; 4-week treatment cycles after Cycle 6)[a] (up to 39 cycles or 36 months, whichever occurs first)							End of Active Monitoring/ End of Treatment	Pre-PD Follow-up	PD	Post-PD Follow-up
		Screening (within 35 days before randomization)	C1-2			C3-6		C7-39	30 (±3) days after the last Daratumumab dose[c]	every 12 weeks (±7 days)		at least every 6 months (until end of study)
			D1[b]	D8	D15	D22	D1	D15	D1				
		Daratumumab (Arm B): Continuous from the time of signing of ICF until 30 days after last daratumumab dose, or until start of next therapy, whichever is earlier.										
Survival, Second primary malignancies		Throughout study until the end of study, and at a frequency of at least every 12 weeks until PD.										X
Best response to first-line MM treatment, PFS2	Investigator review; no central laboratory testing											X
Biomarkers Assessments. Per Amendment 6 all biomarker assessments by central lab are discontinued. FISH testing at PD to be performed locally.												
Whole blood (biomarkers)	Cytometry by time of flight	X	Week 24, Week 48, Week 96, and at suspected CR (±1 month with disease evaluations)						X		X	
	PBMCs	X										
	Plasma	X	Every 12 months from C1D1 (±1 month with disease evaluations)								X	
Stool (biomarkers)	Microbiome	X	Week 24 and at suspected CR (±1 month with disease evaluations)								X	
Bone Marrow aspirate[m]	Cytogenetics by FISH[k]	X									X	

	Notes	Active Monitoring (Arm A; 12-week disease evaluations) / Treatment Phase (Arm B; 4-week treatment cycles after Cycle 6)[a] (up to 39 cycles or 36 months, whichever occurs first)							End of Active Monitoring/ End of Treatment	Pre-PD Follow-up	PD	Post-PD Follow-up
		Screening (within 35 days before randomization)	C1-2				C3-6		C7-39	30 (±3) days after the last Daratumumab dose[c]	every 12 weeks (±7 days)		at least every 6 months (until end of study)
			D1[b]	D8	D15	D22	D1	D15	D1				

a. Treatment Phase (Arm B): daratumumab SC administered weekly in Cycles 1 and 2, every 2 weeks for Cycles 3 to 6, and every 4 weeks thereafter until 39 cycles or 36 months (whichever occurs first) or confirmed PD.
b. C1D1 should occur within 5 days after randomization (Arm B).
c. After 36 months (±3 days) from date of randomization of active monitoring, an equivalent visit should occur for subjects on Arm A. The End-of-Active- Monitoring visit is to be performed within 30 days (±3 days) of confirmation of disease progression by investigator, or in case of discontinuation because of reasons other than disease progression, it is to be performed within 30 days (±3 days) after notification that the subject will discontinue Active Monitoring/treatment.
d. Bone lesions assessment at screening will be done by an independent reviewer after subject eligibility is confirmed by the site. This central review of screening images will be used to determine the subject's eligibility. For optimal assessment of the screening images by the independent reviewers, additional clinical data, including benign/post-traumatic pre-existing bone lesions, data of recent bone marrow procedures, and general medical history, will be included in the independent review. Details on benign/post-traumatic pre-existing bone lesions that can be seen on the screening images (eg, old fractures) and were also present on previous imaging are to be reported in the CRF (see also Section 9.1.2 and Section 9.2.7).
e. Laboratory assessments scheduled for treatment days should be collected before daratumumab is administered.
f. Subjects with serologic findings suggestive of HBV vaccination (Anti-HBs positivity as the only serologic marker) AND a known history of prior HBV vaccination do not need to be tested for HBV DNA by PCR. To be performed only for subjects with serologic evidence of resolved HBV infection. For arm B patients only, HBV DNA testing is required Q12W during treatment, at the End of Treatment Visit, and Q12W for up to 6 months after the last dose of study treatment (Refer to section 9.7 HBV DNA test). Hepatitis B virus DNA testing by PCR must be performed locally.
g. Repeat laboratory studies in cases where screening values were obtained >14 days from C1D1 only need to be obtained for Arm B subjects.
h. Within 56 days before randomization; fresh aspirate preferred. If not available, non-decalcified archival tissue is acceptable (smears or clots).
i. Telephone contact for timepoints where an in-person visit is not applicable.
j. Within 2 months of confirmed PD.
k. Includes HBsAg, Anti-HBs, and Anti-HBc. Testing to be performed locally prior to randomization. Additionally, subjects ongoing in the Treatment Phase (arm B only) who are within 6 months of starting study treatment when Protocol Amendment 3 is implemented will be required to have HBV serology performed locally upon signing the updated ICF. HBV serology is not required at Screening or for subjects ongoing in the Treatment Phase (arm B only) who are within 6 months of starting study treatment if this was performed as part of standard of care within 3 months prior to first dose (Refer to section 9.7 HBV serology). For patients on treatment > 6 months, testing is at investigator discretion. (Refer to Appendix 18.1 for specific requirements for France.)
l. Assessments should be performed at the study site or designated facilities (eg, imaging assessments are only to be performed at facilities that are specifically trained on the imaging acquisition guidelines as determined by the imaging vendor).
m. If end of active monitoring/end-of-treatment visit is performed due to PD, the PRO assessments do not need to be performed twice if the visits take place on the same day.

Abbreviations to the Time and Events Schedule:
Anti-HBc= antibodies to hepatitis B core antigen; Anti-HBs=antibodies to hepatitis B surface antigen; C=cycle; CR=complete response; CT=computed tomography; D=day; DNA=deoxyribonucleic acid; ECOG=Eastern Cooperative Oncology Group; EORTC=European Organization for Research and Treatment of Cancer; EQ-5D-5L=European Quality of Life Five Dimensions Questionnaire; FEV1=forced expiratory volume in 1 second; FFPE= formalin-fixed paraffin-embedded; FISH=fluorescence in situ hybridization; FLC=free light chain; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; ICF=informed consent form; IFE=immunofixation electrophoresis; LDCT=low-dose whole-body computed tomography; MM=multiple myeloma; PET=positron emission tomography; PFS2=progression-free survival on first-line treatment for MM; PBMC=peripheral blood mononuclear cell; PCR=polymerase chain reaction; PD=disease progression; PRO=patient-reported outcomes; QLQ=quality of life questionnaire; Q12W= every 12 weeks; SIFE=serum immunofixation electrophoresis; SPEP=serum M-protein quantification by electrophoresis; UIFE=urine immunofixation electrophoresis; UPEP=urine M-protein quantitation by electrophoresis

TIME AND EVENTS SCHEDULE

Table 2: Daratumumab Administration (Arm B Only)

	Notes	Treatment Phase (4-week treatment cycles up to 39 cycles or 36 months, whichever occurs first)									End of Treatment	8 weeks after last daratumumab dose
		C1-2					C3-6			C7-C39		
		D1[a]	D4	D8	D15	D22	D1	D4	D15	D1	30 (±3) days after the last Daratumumab dose	
Refer to Site Investigational Product Procedures Manual for recommendations on daratumumab administration.												
Daratumumab[g]	SC injection over approximately 5 minutes. See Table 7 for acceptable window of administration.	X		X	X	X	X		X	X		
Pre- and Postdose Medications, see Section 6.3												
Other Study Procedures												
Hematology[b] (CBC with differential) (Local laboratory)	For C1D1, no need to repeat tests if they have been performed within the past 7 days. Testing may be performed up to 2 days before other administration days. Perform at additional timepoints, as clinically indicated.	Prior to every daratumumab administration: hemoglobin, white blood cell count with absolute neutrophils and lymphocytes, platelet count										
Chemistry (Local laboratory)		C2D1 and C3D1 (see Section 9.7 for specific laboratory tests)										
Blood group and type assessment and indirect antiglobulin test results[c]	To be obtained before start of administration; includes ABO, Rh, and indirect antiglobulin test results.	X										
Pharmacokinetic and Immunogenicity Assessments												
Pharmacokinetics[d] (send to central laboratory)		C1 (pre)	C1[e]				C3 (pre), C5 (pre)	C3[f]		C7 (pre), C12 (pre), C24 (pre)	X	X
Immunogenicity Daratumumab[d,f] (send to central laboratory)	Use sample drawn for pharmacokinetics.	C1 (pre)					C3 (pre), C5 (pre)			C7 (pre), C12 (pre), C24 (pre)	X	X

	Notes	Treatment Phase (4-week treatment cycles up to 39 cycles or 36 months, whichever occurs first)									End of Treatment	8 weeks after last daratumumab dose
		C1-2					C3-6			C7-C39		
		D1[a]	D4	D8	D15	D22	D1	D4	D15	D1	30 (±3) days after the last Daratumumab dose	
Immunogenicity rHuPH20[d,f] (send to central laboratory)	Draw dedicated sample after daratumumab pharmacokinetic sample is drawn.	C1 (pre)					C3 (pre), C5 (pre)			C7 (pre), C12 (pre), C24 (pre)	X	X

a. C1D1 should occur within 5 days after randomization.
b. Results of hematology tests must be evaluated before each daratumumab administration.
c. A wallet card with the subject's blood type will be provided.
d. Samples intended to be collected on dosing days should be collected on the actual day of daratumumab administration. Predose sample to be collected within 4 hours before but not after the start of daratumumab administration.
e. Sample may be collected any time on Day 4 (±1 day).
f. Additional samples to be obtained in case of IRR in association with Dose 2 and beyond.
g. Administration should be performed at the study site or designated facilities.

Abbreviations to the Time and Events Schedule:
Anti-HBs=antibodies to hepatitis B surface antigen; C=cycle; CBC=complete blood count; D=day; DNA=deoxyribonucleic acid; HBV=hepatitis B virus; IRR=infusion/injection-related reaction; pre=predose; rHuPH20=recombinant human hyaluronidase; SC=subcutaneous

ABBREVIATIONS

ADCC	antibody-dependent cell-mediated cytotoxicity
ALT	alanine aminotransferase
Anti-HBc	antibodies to hepatitis B core antigen
Anti-HBs	antibodies to hepatitis B surface antigen
AST	aspartate aminotransferase
BMPCs	bone marrow plasma cells
BOD	biochemical or diagnostic
CDC	complement-dependent cytotoxicity
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	maximum observed serum concentration
C_{min}	minimum observed serum concentration
COPD	chronic obstructive pulmonary disease
CR	complete response
CRAB	calcium, renal insufficiency, anemia, or bone lesions
CT	computed tomography
C_{trough}	maximum trough concentration
Dara-CF	daratumumab and recombinant human hyaluronidase for subcutaneous injection: co-formulated (Dara-SC)
Dara-MD	daratumumab and recombinant human hyaluronidase for subcutaneous injection: mix and deliver
DNA	deoxyribonucleic acid
DTT	dithiothreitol
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
eDC	electronic data capture
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D-5L	European Quality of Life Five Dimensions Questionnaire
FEV1	forced expiratory volume in 1 second
FFPE	formalin-fixed paraffin-embedded
FISH	fluorescence in situ hybridization
FLC	free light chain
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HR	hazard ratio
HRQoL	health-related quality of life
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
IgG1κ	immunoglobulin G1 kappa
IMiD	immunomodulatory agent
IMWG	International Myeloma Working Group
IPPI	Investigational Product Preparation Instructions
IRB	Institutional Review Board
IRC	Independent Review Committee
IRR	infusion/injection-related reactions
IV	intravenous(ly)
IWRS	interactive web response system
LDCT	low-dose whole body computed tomography

mAb	monoclonal antibody
MDE	Myeloma Defining Event
MDRD	Modification of Diet in Renal Disease
MDSC	myeloid derived suppressor cells
MGUS	monoclonal gammopathy of undetermined significance
MM	multiple myeloma
MRD	minimal residual disease
MRI	magnetic resonance imaging
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NGS	next generation sequencing
NK	natural killer
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	progressive disease
PET	positron-emission tomography
PET-CT	positron-emission tomography-computed tomography
PFS	progression-free survival
PFS2	progression-free survival on first-line treatment for MM
PI	proteasome inhibitor
PK	pharmacokinetics
PO	per os (by mouth; orally)
PQC	Product Quality Complaint
PR	partial response
PRO	patient-reported outcome
QIg	quantitative immunoglobulin
QLQ	quality of life questionnaire
RBC	red blood cell
rHuPH20	recombinant human hyaluronidase
Rd	lenalidomide and dexamethasone
RNA	ribonucleic acid
SAE	serious adverse event
SAR	systemic administration-related
SC	subcutaneous(ly)
sCR	stringent complete response
SD	standard deviation
SIFE	serum immunofixation electrophoresis
SLiM-CRAB	≥60% bone marrow plasma cells, free light chain involved/uninvolved ratio ≥100, >1 focal bone lesions on MRI, calcium elevation, renal insufficiency by creatinine clearance, anemia, or bone disease due to lytic bone lesions
SMM	smoldering multiple myeloma
SPEP	serum M-protein quantification by electrophoresis
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
T_{max}	time to maximum serum concentration
UIFE	urine immunofixation electrophoresis
ULN	upper limit of normal
UPEP	urine M-protein quantitation by electrophoresis
US	United States
VGPR	very good partial response

1. INTRODUCTION

Daratumumab is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody (mAb) that binds CD38 expressing malignant cells with high affinity. In the United States, intravenously (IV) administered daratumumab is indicated for use as follows: (1) in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy; (2) in combination with pomalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor (PI); (3) as monotherapy, for the treatment of patients with multiple myeloma who have received at least 3 prior lines of therapy including a PI and an immunomodulatory agent (IMiD), or whose disease is refractory to both a PI and an IMiD. In the European Union, IV administered daratumumab is indicated for use as follows: (1) as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a PI and an IMiD and who have demonstrated disease progression on the last therapy; (2) in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy. For other countries/territories, refer to the daratumumab label for the approved indication in that country.

For the most comprehensive nonclinical and clinical information regarding daratumumab, refer to the latest version of the Investigator's Brochure daratumumab. The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

1.1. Background

Disease Background

Multiple myeloma (MM) is thought to evolve from premalignant, asymptomatic plasma cell disorders such as (non-immunoglobulin [Ig]M) monoclonal gammopathy of undetermined significance (MGUS) or smoldering multiple myeloma (SMM), which are characterized by monoclonal plasma cell proliferation in the bone marrow without end-organ damage (Kyle 2009[16], Kyle 2010[15], Landgren 2009[17], Weiss 2009[36]). Smoldering multiple myeloma accounts for approximately 15% of all myeloma patients (Rios-Tamayo 2014[33]). Several models for high-risk SMM have been proposed (Mateos 2016[24], Rajkumar 2013[30]). According to these risk models, subjects with high-risk SMM have an approximate 50% risk of progression to MM within the first 2 years. This is in contrast to the lower risk of progression in the broader SMM population where it is estimated that 50% of patients will progress to MM within the first 5 years, equivalent to 10% per year (Rajkumar 2015[32]). These models were developed prior to the update of the International Myeloma Working Group (IMWG) criteria for the diagnosis of SMM, ie, they included a population of ultra-high risk SMM patients, who are now considered to have MM. It is estimated that approximately 40% of all patients with SMM are at high-risk of progression to MM (Mateos 2013[23]). Overall, approximately 50% of all patients with SMM are at high-risk of progression to MM, and 10% to 15% of those have been reclassified as MM under the 2014 SLiM criteria (Rajkumar 2015[32]).

There is no approved treatment for patients with SMM. Outside of clinical studies, clinical management involves monitoring patients for the development of symptomatic disease (Landgren 2013[18]). Some early studies that investigated treatment for SMM with various chemotherapy regimens (melphalan-prednisone, thalidomide) or bisphosphonates did not show consistent clinical benefit (Dispenzieri 2013[6], Landgren 2013[18]). A recent study (QuiRedex) of patients with high-risk SMM compared treatment with lenalidomide and dexamethasone (Rd, n=57) with observation (n=62). Rd treatment was associated with a significant delay in the progression to symptomatic MM (Mateos 2016[24]). Median time to progression was not reached with Rd compared with 23 months for observation (hazard ratio [HR] 0.24, p<0.0001). Rd significantly improved overall survival (OS) (median not reached vs 117.6 months; HR 0.43, p=0.027) (Mateos 2016[24]). In summary, these data have provided proof of concept that treatment of patients with SMM may prolong progression-free survival (PFS) and OS.

However, critiques have been put forward. In the QuiRedex study, mandatory evaluation for bone lesions was not required at baseline. The majority of progression events were related to bone disease, which raises the question of whether a portion of the subjects met criteria of symptomatic MM at the time of enrollment. Furthermore, the QuiRedex study was conducted prior to the 2014 update of the IMWG criteria for the diagnosis of MM. The new SLiM criteria include a bone marrow plasma cell content >60% or a serum (involved:uninvolved) free light chain (FLC) ratio >100 as well as >1 focal lesion on magnetic resonance imaging (MRI) imaging. This raises concern about whether data from the QuiRedex study are applicable to a population of patients who meet the current definition of SMM (Rajkumar 2014).[29] Rd is not without toxicities, and is not currently approved for the treatment of patients with SMM. In summary, a number of limitations of the QuiRedex study leave room to establish a less toxic treatment regimen for this asymptomatic patient population.

Nonclinical Studies

Pharmacology

Daratumumab is a human IgG1κ mAb that binds with high affinity to a unique epitope on CD38, a transmembrane glycoprotein. It is a targeted immunotherapy that attacks tumor cells that overexpress CD38, a transmembrane glycoprotein, in a variety of hematological malignancies including MM. Daratumumab induces lysis of CD38-expressing tumor cells, including MM tumor cells that were freshly isolated from patients, by a wide spectrum of mechanisms including complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cellular phagocytosis, through activation of complement proteins, natural killer (NK) cells, and macrophages, respectively (de Weers 2011[5], Overdijk 2015[28]).

Clinical Studies

Daratumumab IV Monotherapy

Efficacy/Safety Studies

Daratumumab monotherapy induces deep and durable responses in subjects with heavily pretreated MM. Phase 2 Study 54767414MMY2002 (hereafter referred to as MMY2002) and Phase 1/2 Study GEN501 Part 2 (Part 1 was the dose-escalation phase of this first-in-human study) are ongoing single-arm, open-label studies in which subjects with relapsed and refractory MM are administered daratumumab IV as monotherapy weekly for 8 weeks, every 2 weeks for an additional 16 weeks, and every 4 weeks thereafter until disease progression or unacceptable toxicity. One hundred forty-eight (148) subjects treated with daratumumab 16 mg/kg administered IV were included in a combined analysis of efficacy in Study GEN501 and Study MMY2002. The overall response rate (ORR) for the combined data set was 31.1% (95% confidence interval [CI], 23.7%-39.2%). Responses included 3 subjects with stringent complete response (sCR; 2.0%), 4 subjects with complete response (CR; 2.7%), 13 subjects with very good partial response (VGPR; 8.8%), and 26 subjects with partial response (PR; 17.6%). Within the individual studies, the ORR was 35.7% (95%CI, 21.6%-52.0%) in Study GEN501 and 29.2% (95% CI, 20.8%-38.9%) in Study MMY2002. After a median duration of follow-up of 20.7 months, the Kaplan-Meier based median OS was 20.1 months (Usmani 2016[34]).

Among 156 subjects treated with daratumumab 16 mg/kg IV in Studies GEN501, MMY2002, and 54767414MMY1002 (hereafter referred to as MMY1002) (a single-arm, open-label Phase 1 study of pharmacokinetics (PK) and safety conducted in Japanese subjects), 6 subjects (4%) discontinued daratumumab treatment due to a treatment-emergent adverse event (TEAEs). Three subjects (2%) died due to TEAEs. The most frequently reported TEAEs were fatigue (40%), nausea and anemia (28% each), back pain (26%), cough (24%), neutropenia (23%), pyrexia (22%), upper respiratory tract infection (22%), and thrombocytopenia (21%). Serious adverse events were reported in 33% of subjects; the most frequently reported serious adverse events were pneumonia (6%), pyrexia, hypercalcemia, and general physical health deterioration (3% each).

In the ongoing Phase 2 study 54767414SMM2001 (hereafter referred to as SMM2001), which evaluates daratumumab in SMM, single-agent activity in this population has been established in interim analysis 1 (March 2017). The safety profile of daratumumab in SMM2001 was consistent with what was observed in Studies GEN501, MMY2002, and MMY1002. For additional details regarding Study SMM2001, see Section 3.2.

Human Pharmacokinetics and Immunogenicity

Over the dose range from 1 to 24 mg/kg as daratumumab monotherapy or in combination with other treatments, increases in area-under-the-concentration-time curve were more than dose-proportional. Clearance decreased with increasing dose and repeated dosing, indicating target-mediated clearance. The mean (SD) estimated terminal half-life associated with linear clearance was approximately 18 (±9) days.

Of the 199 subjects in Studies GEN501 and MMY2002 who were evaluable for immunogenicity, none were positive for anti-daratumumab antibodies; 2 (0.7%) of the 298 daratumumab combination therapy subjects analyzed were positive for anti-daratumumab antibodies.

For further details and the most up-to-date information about single-agent studies, please refer to the Investigator's Brochure (IB Daratumumab 2017 [11]).

Daratumumab SC Monotherapy

Study 54767414MMY1004 (hereafter referred to as MMY1004) is an ongoing, open-label, dose-escalation, Phase 1b study to assess the safety and PK of subcutaneous (SC) delivery of daratumumab. In Part 1 of this study, a mix and-deliver SC presentation (Dara-MD) of the currently approved daratumumab IV formulation was used: recombinant human hyaluronidase (rHuPH20) and daratumumab were mixed just prior to delivery. Up to 90 mL of Dara-MD was administered SC weekly for 8 weeks, every 2 weeks for 16 weeks, and then every 4 weeks thereafter. Preliminary data from this study show that SC administration results in acceptable PK, is efficacious, and has a substantially shortened administration time compared with standard IV administration. Part 2 of this study uses a new co-formulated preparation of daratumumab for SC administration (Dara-CF). Hereafter, Dara-CF will be referred to as Dara-SC. Updated information regarding daratumumab SC can be found in the Investigator's Brochure (IB Daratumumab 2017 [11]).

Efficacy

Fifty-three subjects (8 subjects in the 1200 mg cohort and 45 subjects in the 1800 mg cohort) were evaluable for efficacy. In the Dara-MD 1200-mg cohort, the ORR was 25% (95% CI: 3%-65%), both PRs; 1 was achieved at 8 weeks and the other at 20 weeks. In the Dara-MD 1800-mg cohort, 17 responses were observed for an ORR of 38% (95% CI: 24%-54%). One subject (2%) had a sCR, 3 subjects (7%) had VGPR, and 13 subjects (29%) had PRs. The median time to first response was 4 weeks (range, 4 to 8 weeks). In relapse or refractory MM, the antitumor activity of daratumumab 1800 mg SC (ORR 38%) was consistent with daratumumab 16 mg/kg IV (Usmani 2016[34]).

Pharmacokinetics

CCI -time curves following administration indicate a later time to maximum serum concentration (T_{max}) of approximately 72 hours post-dose, compared with IV administration when T_{max} occurs at or near the end of infusion. The 1800-mg SC dose achieved similar or higher maximum trough concentrations (C_{trough}) (the predose concentration on Cycle 3 Day 1) as 16 mg/kg IV and had similar variability. Preliminary analyses indicate that the bioavailability of Dara-MD is approximately 77% when administered SC.

Safety

Treatment-emergent adverse events for daratumumab administered SC appeared to be similar to those reported in single-agent studies of daratumumab administered IV, but with a lower incidence of infusion/injection-related reactions (IRRs) (Lokhorst 2015[20], Lonial 2016[21]). The incidence of all-grade IRRs was 13% and 24% in the Dara-MD 1200 mg and 1800 mg cohorts, respectively. By comparison, among subjects treated in single-agent or combination studies with IV daratumumab, IRRs were reported in 47% of subjects.

Administration of daratumumab in the abdominal SC tissue was associated with injection site erythema in 34% of subjects (1200 mg: 63%; 1800 mg: 29%) and induration 26% of subjects (1200 mg; 50%; 1800 mg: 22%).

1.2. Overall Rationale for the Study

The standard of care for premalignant stages of disease in the MM continuum, ie, MGUS and SMM, has been active monitoring. Published data show that specific criteria can identify patients with SMM who are at particularly high risk for progression (see Section 1.1). The general interest in the field in developing effective therapies for high-risk SMM is illustrated by the initiation of several studies. The regimens evaluated in these studies vary considerably from relatively low-intensity monotherapy to multi-agent therapy incorporating autologous stem cell transplantation. One shortcoming noted is that most studies are single-arm studies that will not allow a definitive evaluation of survival endpoints.

Daratumumab is a CCI candidate for use in high-risk SMM. Compelling clinical activity has been demonstrated with daratumumab treatment in subjects with pretreated MM, as monotherapy and in combination with bortezomib/dexamethasone, lenalidomide/dexamethasone or pomalidomide/dexamethasone. Importantly, daratumumab is well-tolerated as demonstrated by a low rate of treatment discontinuation across clinical studies. This favorable safety profile is especially important in the treatment of patients with an asymptomatic condition. A Phase 2 study designed to evaluate whether daratumumab IV given as a single agent is effective in delaying the transition from a high-risk SMM to MM and to find the optimal dosing is currently ongoing. Preliminary data are presented in Section 3.1.

Plasma cells from subjects with SMM and MM express high levels of CD38. In addition to direct targeting of CD38+ tumor cells, daratumumab can deplete CD38+ immune suppressive subpopulations, such as myeloid derived suppressor cells (MDSC) and regulatory T cells that express high levels of CD38. Reduction of these immune suppressive populations may promote expansion of cytotoxic CD8+ T cells that could have additional antitumor effects in these pre-symptomatic subjects with presumably higher immune competent system versus those with MM.

Subjects with high-risk SMM as defined in this study have approximately 50% risk of progression to MM within 30 months. This study is designed to evaluate whether daratumumab will be effective in delaying the transition from a high-risk premalignant condition (SMM) to MM in a safe manner. Given the potential advantages of SC administration of daratumumab (eg, small

volume; fewer IRRs), this study will use a new, co-formulated drug product administered SC. The co-formulated drug product will reduce the time for drug preparation, reduce the infusion volume to approximately 15 mL, and can be administered in approximately 5 minutes by manual SC push.

1.3. Benefit-Risk Assessment

1.3.1. Risks Associated with Daratumumab SC

Study participants with SMM will receive treatment with daratumumab.

The primary acute toxicities for daratumumab SC are systemic administration-related reactions that occur mainly within 6 hours after the first administration. Although the majority of these are predominantly Grade 1 and Grade 2, severe injection-site reactions which could be considered potential aggravating risk factors for cardiac events have occurred. Details regarding the management of injection-site reactions are presented in Section 6.4.1.

Daratumumab may increase neutropenia and thrombocytopenia induced by background therapy. Neutropenia and hypogammaglobulinemia associated with daratumumab may contribute to the risk of infection. Higher incidence of Grade 3 or 4 neutropenia has been observed in participants with lower body weight who receive daratumumab SC. Increased incidence of serious infections, most notably pneumonia, in association with daratumumab have been reported.

Daratumumab binds to CD38 found at low levels on red blood cells (RBCs); it may interfere with blood typing and result in a positive Indirect Antiglobulin Test (IAT) (see Section 9.7).

The potential risks for daratumumab detailed in Table 3 are based on: 1) results of nonclinical studies; 2) mechanism of action; 3) route of administration; and 4) results from participants treated in daratumumab studies (see Sections 1.1 and 3.2). See discussions in Section 9.2.4 and 9.7 regarding the potential for daratumumab to interfere with disease evaluations.

Please refer to the current label/IB of daratumumab for additional information.

Table 3: Mitigation Strategies for Potential Risks Associated with Daratumumab

Potential Risk	Mitigation Strategies
Systemic administration-related reactions	Required pre-treatment medications are provided in Sections 6.3.1. May require dose delay or treatment discontinuation. Follow the guidance for management of systemic administration-related reactions in Section 6.4
Injection-site reaction	Monitor for local reactions surrounding the injection-site and manage per institutional standards (see Section 6.4.1).
Cytopenia	Frequently monitor hematologic parameters and provide supportive care (eg, blood and thrombocyte concentrates, G-CSF for neutropenia) per institutional standards. Prolonged neutropenia may increase the risk of infection. Severe thrombocytopenia may increase the risk of bleeding.
Infection	Frequently monitor for the presence of infections, with the acquisition of cultures and/or implementation of empiric antibiotic therapy as appropriate, based on clinical judgment and institutional standards. Administer antimicrobial prophylaxis to reduce risk of infection as per institutional SOC. Perform screening for HBV (see Section 4.2 and 9.7), monitor as clinically indicated, and initiate treatment or supportive care (anti-infectives, transfusions) as appropriate (Section 8.4).

Abbreviations: G-CSF=granulocyte colony-stimulating factor; HBV=hepatitis B virus; SOC=standard of care.

1.3.2. Benefits for Study Participation

Currently, the standard of care for patients with high-risk SMM is active monitoring, and most patients with SMM are not treated until end organ damage and evolution to an incurable disease occur. Patients with SMM have clonal plasma cells which express high levels of CD38, making daratumumab a candidate therapeutic. Preliminary data show that daratumumab has single agent activity in intermediate- and high-risk SMM (Section 1.1).

1.3.3. Benefit-Risk Assessment for Study Participation

Considering the measures taken to minimize risk to participants of this study, the potential risks associated with daratumumab are justified by the anticipated benefits that may be afforded to participants with SMM.

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

2.1. Objectives and Endpoints

2.1.1. Objectives

Primary Objective

The primary objective is to determine whether treatment with daratumumab administered SC prolongs PFS compared with active monitoring in subjects with high-risk SMM.

Secondary Objectives

- To demonstrate additional clinical benefit (ORR, duration of response, OS, etc) for subjects with high-risk SMM treated with daratumumab compared with active monitoring
- To assess the safety profile of daratumumab in subjects with high-risk SMM

- To assess the clinical characteristics of symptomatic MM following progression of disease after therapy with daratumumab
- To evaluate the PK and immunogenicity of daratumumab administered SC in subjects with high-risk SMM
- To evaluate the immunogenicity of rHuPH20 when administered in combination with daratumumab SC in subjects with high-risk SMM
- To evaluate the effect of treatment with daratumumab on health-related quality of life (HRQoL)

Exploratory Objectives

- To investigate clinical efficacy of daratumumab in high-risk subjects with genetic modifications (del17p, t(4:14), 1q gain, or other high-risk molecular subtypes)
- To explore biomarkers of response or resistance to daratumumab, including immunophenotypes and expression of MM markers (ie, CD38)

2.1.2. Endpoints

Primary Endpoint

The primary endpoint of this study is PFS (defined as the time from the date of randomization to the date of initial documented progression to MM according to the IMWG diagnostic criteria for MM or the date of death, whichever occurs first).

Secondary Endpoints

To demonstrate additional clinical benefit, the following secondary endpoints will be evaluated:

- Time to biochemical or diagnostic (SLiM-CRAB) progression defined as the earlier of time to the earlier of biochemical progression or diagnostic (SLiM-CRAB) progression (see Section 9.2.2)
- Overall response rate (ORR), defined as, the proportion of subjects with a PR or better as defined by the IMWG response criteria
- Complete response (CR) rate, defined as, the proportion of subjects with a CR (or better) as defined by the IMWG response criteria
- Time to first-line treatment for MM, defined as, the time from the date of randomization to the date of the first-line treatment for MM
- Progression-free survival on first-line treatment for MM (PFS2), defined as, the time from the date of randomization to the date of documented progressive disease (PD) on the first-line treatment for MM or death, whichever comes first
- Overall survival (OS), defined as, the time from the date of randomization to the date of death
- Incidence of MM with adverse prognostic features, which include International Staging System Stage III (based on β2-microglobulin and albumin) and adverse cytogenetic characteristics

- Serum daratumumab PK concentrations and parameters including minimum observed concentration (C_{min}) and maximum observed concentration (C_{max})
- Incidence of anti-daratumumab antibodies and anti-rHuPH20 antibodies
- Change from baseline in global health status and emotional functioning scales of the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ)-C30, future perspective scale of the EORTC QLQ-MY20, and utility and visual analog scale of the European Quality of Life Five Dimensions Questionnaire (EQ-5D-5L)
- Duration of response, defined as date of onset of first response until date of disease progression or death
- Time to response, defined as the time from randomization until onset of first response

Exploratory Endpoints

- Identification of novel biomarkers in relation to PFS/OS

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

2.2. Hypothesis

Daratumumab SC administered as monotherapy will prolong PFS compared with active monitoring in subjects with high-risk SMM.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a Phase 3, randomized, open-label, 2-arm, multicenter study of active monitoring and daratumumab in subjects with high-risk SMM (see inclusion criteria, Section 4.1). Approximately 360 subjects will be stratified and then randomized in a 1:1 ratio to receive active monitoring (Arm A) or daratumumab (Arm B). Randomization will be stratified based on the number of factors associated with progression to MM (<3 vs ≥3). The factors are (1) involved:uninvolved FLC ratio ≥8 (yes vs no), (2) serum M-protein ≥30 g/L (yes vs no), (3) IgA SMM (yes vs no), (4) immunoparesis (reduction of 2 uninvolved immunoglobulins vs other), and (5) bone marrow plasma cells (BMPCs) (>50% to <60% vs ≤50%).

Subject participation will include a Screening Phase, an Active Monitoring Phase (Arm A) or a Treatment Phase (Arm B), and a Follow-up Phase. The Screening Phase will be within 35 days before randomization. The Active Monitoring Phase (Arm A) and Treatment Phase (Arm B) will be 36 months in duration, to balance efficacy with subject convenience and expected side effects. Cycles are 4 weeks in length. For all subjects, disease evaluations will be performed every 12 weeks until confirmed PD. Confirmation of eligibility will be based on central disease, hematology, and chemistry laboratory assessments and will also include assessment of ECG, ECOG, medical history, concomitant medications, adverse events, and screening images. Bone lesions assessment at screening will be done by an independent reviewer after subject eligibility is confirmed by the site (no lytic lesions and/or ≤ 1 focal lesion with diameter ≥5 mm present unless proven benign/post-traumatic origin) (refer to Section 9.2.7). This central review of screening

images will be used to determine the subject's eligibility. For optimal assessment of the screening images by the independent reviewers, additional clinical data, including benign/post-traumatic pre-existing bone lesions, data of recent bone marrow procedures, and general medical history, will be included in the independent review.

For subjects randomized to active monitoring (Arm A), no disease-specific treatment will be given and subjects are to be evaluated every 12 weeks. For subjects randomized to daratumumab (Arm B), daratumumab SC (daratumumab 1800 mg + rHuPH20 [2000 U/mL]) will be administered weekly in Cycles 1 and 2, then every 2 weeks for Cycle 3 to Cycle 6, and every 4 weeks thereafter until 39 cycles or up to 36 months or confirmed PD (or other reasons as outlined in Section 10), whichever occurs first. All subjects in the daratumumab group will be observed for at least 6 hours after the end of the SC injection during Cycle 1 Day 1 and, if deemed necessary by the investigator, after subsequent injections. Based on the data available as of October 2017 from Study MMY1004, no subject has had an IRR with an onset >6 hours after daratumumab SC injection (IB Daratumumab 2017 [11]). Measures to prevent IRRs include predose medication with methylprednisolone, paracetamol, and an antihistamine. Montelukast may also be added as a predose medication at the investigator's discretion. Methylprednisolone also will be administered after daratumumab administration with the intention of preventing delayed IRRs.

The Follow-up Phase will begin once a subject completes 39 cycles or 36 months (whichever occurs first) or discontinues active monitoring (Arm A) or daratumumab treatment (Arm B) and completes the End-of-Active Monitoring Visit (Arm A) or End-of-Treatment Visit (Arm B). In both groups, disease evaluation will continue every 12 weeks thereafter until disease progression, as indicated in the Time and Events Schedule (Table 1). The Follow-up Phase for each subject will continue until death, lost to follow up, consent withdrawal, or study end, whichever occurs first.

Assessment of disease response will be conducted in accordance with the IMWG response criteria (Table 8) using a validated computer algorithm. Disease progression will be assessed using the IMWG diagnostic criteria for MM using a computer algorithm. Cases for which progression is based on FLC criteria only, progression will be determined based on modified FLC criteria combining IMWG progression criteria with IMWG FLC ratio criteria (Section 9.2.2). Progression evaluations for the primary endpoint/final analysis will be based on IRC review, in a blinded fashion, to objectively and consistently implement the IMWG diagnostic criteria for MM (Section 9.2.2). Evaluation of disease progression by IRC and validated computerized algorithm will be discontinued once the number of planned PFS events for the primary analysis is achieved. Per protocol Amendment 6, following the primary analysis, disease evaluations will be conducted locally and disease progression will be assessed by the study investigator according to IMWG criteria.

Safety evaluations will include adverse event monitoring, physical examinations, SC injection site evaluations, clinical laboratory parameters (hematology and chemistry), and Eastern Cooperative Oncology Group (ECOG) performance status. Blood samples will be drawn for assessment of PK and biomarker parameters. All study evaluations will be conducted according to the Time and

Events Schedules (Table 1 and Table 2). An Independent Data Monitoring Committee (IDMC) will review safety data at regular intervals during the study.

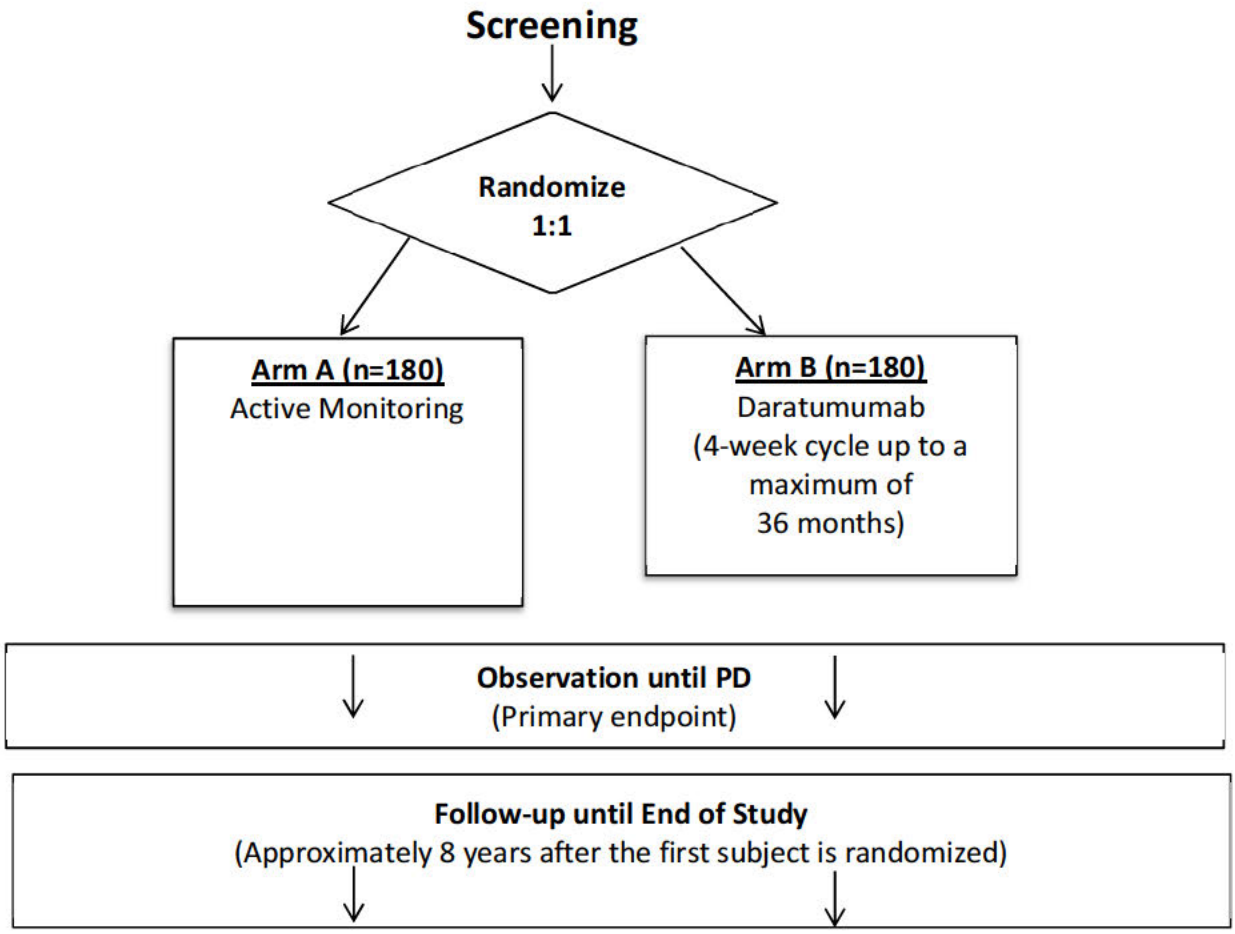
Three data cutoff time points are planned:

- The first is for an interim analysis for futility when approximately 60% of the planned PFS events (99) have occurred. This is expected to occur approximately 8 months after the last subject has been randomized. All available data at the time of this data cutoff will be included in the interim analysis.
- The second is for the primary analysis and will occur when approximately 165 PFS events have occurred. This analysis is expected to occur approximately 2 years after the last subject is randomized. All available data at the time of this data cutoff will be included in the Clinical Study Report.
- A third will occur at the end of the study. The data collected will be reported as an addendum to the Clinical Study Report.
- Additionally, the IDMC will meet after the first 60 subjects have been randomized and treated or observed for 8 weeks to assess safety, 6 months later, and thereafter every 12 months until the primary analysis.

The end of the study will occur approximately 8 years after the first subject is randomized, or when the sponsor decides to stop the study. At this time, approximately 107 OS events are expected in both arms (64 at the time of the primary analysis of PFS). This will provide approximately 65% probability to show that the upper 95% CI of the HR is below 1.25, assuming the true HR is 0.80 (median OS: 100 vs. 125 months). Note, that in the hierarchical testing procedure, only superiority will be tested for this endpoint. Furthermore, approximately 134 PFS2 events are expected in both arms (81 at the time of the primary analysis of PFS). This will provide approximately 80% probability to show that the upper 95% CI of the HR is below 1.25, assuming the true HR is 0.75 (median PFS2: 72 vs. 96 months). Note that in the hierarchical testing procedure, only superiority will be tested for this endpoint.

A diagram of the study design is provided in Figure 1.

Figure 1: Schematic Overview of the Study



3.2. Study Design Rationale

Blinding, Control, Study Phase/Periods, Treatment Groups

Randomization will be used to minimize bias in the assignment of subjects to treatment groups, to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. To minimize further imbalance across treatment arms and to allow for balanced enrollment in important subgroup analyses, subjects will be stratified based on the number of factors associated with progression to MM (<3 vs ≥3), as described in Section 3.1.

Rationale for Daratumumab Dose Selection

The approved dose of daratumumab for the treatment of relapse or refractory MM is 16 mg/kg (weekly for 8 weeks, then every 2 weeks for 16 weeks, then every 4 weeks thereafter) administered IV until disease progression or unacceptable toxicity. The dose selection was based on an acceptable safety profile, maximal clinical activity, and PK consistent with saturation of the target (CD38).

Preliminary data from an ongoing Phase 2 study in subjects with SMM (SMM2001) suggest that long and intense treatment with daratumumab IV (as used in MM) yields better results than less intense administration. The approved dose regimen used in MM is being used in the current study in SMM.

Study SMM2001 is an ongoing, randomized, open-label, 3-arm, multicenter study of daratumumab IV in subjects at least 18 years old with intermediate- or high-risk SMM. The study is designed to evaluate whether daratumumab as a single agent is effective in delaying the transition from a high-risk premalignant condition (SMM) to MM, and to find the optimal schedule of treatment administration. Approximately 120 subjects were planned to be enrolled in this study, 40 subjects per treatment arm. It was originally hypothesized that in a pre-symptomatic patient population, a less intensive dosing schedule may be preferred by patients and healthcare providers. Therefore, 3 dose schedules are being evaluated in the Phase 2 study. Subjects were assigned randomly to treatment in a 1:1:1 ratio to 1 of the following 3 treatment arms:

- Arm A (long intense): daratumumab IV is administered weekly in Cycle 1, every other week in Cycle 2 and Cycle 3, every 4 weeks in Cycle 4 to Cycle 7, and every 8 weeks from Cycle 8 to Cycle 20.
- Arm B (intermediate): daratumumab IV is administered weekly in Cycle 1 and then every 8 weeks from Cycle 2 to Cycle 20.
- Arm C (short intense): daratumumab is administered weekly for 8 weeks in Cycle 1.

Each cycle is 8 weeks. Disease progression to MM is evaluated using the IMWG criteria (Rajkumar 2014[29]). The key efficacy data from the interim analysis (6 months after the last subject was randomized) and the Kaplan-Meier (biochemical or diagnostic [BOD] PFS) curves are displayed in Table 4 and Figure 2, respectively. The long-intense arm had numerically better VGPR-or-better rate and ORR. The only deep response (sCR) observed in this study to date was also observed in the long-intense arm. The PD/death rate was also numerically lower in the long-intense arm compared with the intermediate- and short-intense arms. Furthermore, the 12-month BOD PFS rate was higher in the long-intense arm (97.5%) compared with the intermediate-intense arm (76.8%) and short-intense arm (71.1%). These data suggest that the long-intense arm demonstrates better efficacy than the other 2 treatment arms.

Table 4: Summary of Key Efficacy Endpoints; Response-evaluable Analysis Set (Study 54767414SMM2001)

	Long Intense	Intermediate	Short Intense
Complete response (sCR+CR) rate	1 (2.4%)	0	0
90% confidence interval[a]	(0.1%, 11.1%)		
VGPR or better (sCR+CR+VGPR) rate	9 (22.0%)	7 (17.1%)	6 (15.0%)
90% confidence interval[a]	(12.0%, 35.2%)	(8.3%, 29.7%)	(6.7%, 27.5%)
Overall response (sCR+CR+VGPR+PR) rate	23 (56.1%)	21 (51.2%)	15 (37.5%)
90% confidence interval[a]	(42.1%, 69.4%)	(37.4%, 64.9%)	(24.7%, 51.7%)
PD/Death rate[b] 80% confidence interval[c]	0.028 (-0.0078,0.0629)	0.093 (0.0241,0.1611)	0.159 (0.0680,0.2505)
BOD PFS			
12-month BOD PFS rate % (90% CI)	97.5 (87.7, 99.5)	76.8 (61.1, 86.8)	71.1 (56.8, 81.3)

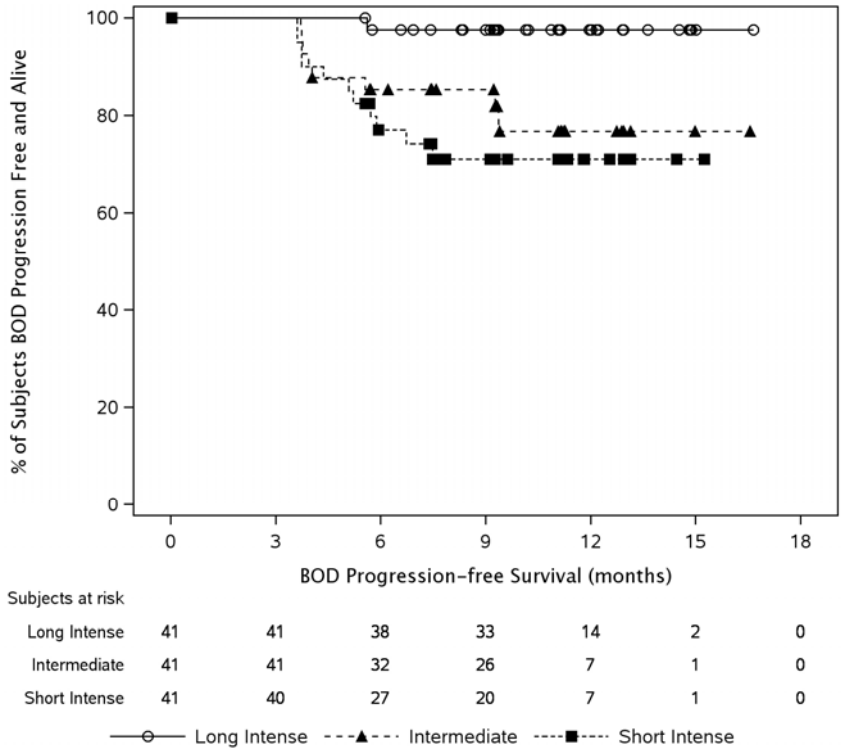
BOD=biochemical or diagnostic; CI=confidence interval; CR=complete response; PD=progressive disease; PFS=progression-free survival; PR=partial response; sCR=stringent complete response; VGPR=very good partial response

[a] Exact 90% CI.

[b] PD/Death rate is the ratio of the patients who progressed or died divided by the total progression-free survival for all subjects.

[c] Normal approximation.

Figure 2: Biochemical or Diagnostic Progression-free Survival; Intent-to-Treat Analysis Set (Study 54767414SMM2001)



BOD=biochemical or diagnostic

Safety analyses are consistent with previous experience using daratumumab for the treatment of MM. No new safety signals were identified in the SMM population (Table 5). No subjects died due to a TEAE). Although the percentages of Grade 3 or 4 TEAEs and SAEs were higher in the long-intense treatment arm, the percentages of daratumumab discontinuations due to TEAEs were low (5% or less in each arm) and similar in the 3 treatment arms.

Table 5: Overview of Treatment-emergent Adverse Events; Safety Analysis Set (Study 54767414SMM2001)

	Long Intense	Intermediate	Short Intense
Analysis set: safety	41	41	40
Any treatment-emergent adverse event	39 (95.1%)	40 (97.6%)	37 (92.5%)
At least one reasonably related to daratumumab	33 (80.5%)	30 (73.2%)	28 (70.0%)
Maximum toxicity grade			
Grade 1	7 (17.1%)	8 (19.5%)	9 (22.5%)
Grade 2	18 (43.9%)	28 (68.3%)	22 (55.0%)
Grade 3	11 (26.8%)	4 (9.8%)	4 (10.0%)
Grade 4	3 (7.3%)	0	2 (5.0%)
Grade 5	0	0	0
Any serious treatment-emergent adverse event	10 (24.4%)	1 (2.4%)	4 (10.0%)
Treatment-emergent adverse events leading to dose delay	4 (9.8%)	0	1 (2.5%)
Treatment-emergent adverse events leading to discontinuation of daratumumab	2 (4.9%)	1 (2.4%)	2 (5.0%)

Note: Adverse events are reported using Medical Dictionary for Regulatory Activities, version 19.0.
Note: Percentages are calculated with the number of subjects in each group as denominator.

Preliminary PK data from Study SMM2001 were analyzed. In this study, which used a dose of 16 mg/kg IV, the data indicate that the long-intense schedule maintains trough concentrations above the 99% CD38 target saturation concentration (defined in MM subjects) throughout dosing. However, for subjects treated on the intermediate-intense schedule, trough concentrations fall below the target saturation concentration by Cycle 3 Day 1 (the end of the first cycle of every-8-week dosing), and for subjects treated in the short-intense schedule, concentrations fall below the target saturation concentration by 8 weeks after the last dose. Data are not available after every-8-week dosing starts in the long-intense schedule; however, it is expected that as the dosing frequency decreases to every 8 weeks, the trough concentrations will begin to fall below the target saturation concentration. In addition, an increase in BOD progression events was observed in intermediate and short-intense schedules after weekly dosing ended (Table 4), indicating that daratumumab treatment needs to continue longer than 8 weeks of weekly dosing, but continuing to dose daratumumab only every 8 weeks may not be sufficient to maintain response.

In summary, these data suggest that more intense treatment with daratumumab may be required for optimal efficacy in high-risk SMM. Therefore, the long-intense schedule will be used in SMM3001 with the modification that dosing every 4 weeks will continue until treatment discontinuation.

Treatment with daratumumab IV in SMM has led to a low number of subjects who discontinued treatment due to a TEAE and there were no deaths due to a TEAE. The most common side effect

associated with daratumumab is infusion-related reactions, which were experienced by approximately half of the subjects receiving daratumumab. The vast majority (>90% of infusion-related reactions) occurred during the first infusion. Due to the risk of infusion-related reactions, the IV infusion requires a large volume (500 mL to 1000 mL), and the median infusion time for the first infusion is 7 hours; subsequent infusions are approximately 3 to 4 hours.

A new SC formulation of daratumumab co-formulation with rHuPH20 (Dara-SC) offers several key benefits, such as:

- Potential to reduce IRRs (compared with IV administration), due to slower absorption of daratumumab into systemic circulation
- Shorter preparation and administration time
- Reduced administration volume (SC administration of approximately 15 mL instead of 500 mL to 1000 mL IV infusion), which may be clinically meaningful for elderly patients with comorbid cardiac or renal insufficiency

An ongoing Phase 1b study of SC daratumumab (MMY1004) has provided preliminary evidence of local tolerance for SC administration of daratumumab (Section 1.1). The study aims to identify a dose which can be safely administered SC and achieves a maximum C_{trough} at Cycle 3 Day 1 similar to or higher than that achieved following 16 mg/kg IV administration. The maximum C_{trough} has been shown in population PK and exposure-response analyses to be related to ORR in MM.

Preliminary PK data from the 1800-mg SC cohort indicate that the serum maximum trough concentrations at Cycle 3 Day 1 were similar to or higher than those achieved with 16 mg/kg of IV daratumumab. Furthermore, to date, the rate of IRRs reported with SC administration of daratumumab has been substantially lower than the rate reported with IV administration of daratumumab. Preliminary efficacy data suggest that, in this patient population, SC administration of 1800 mg daratumumab may enable comparable response rates compared with IV daratumumab. Based on these preliminary PK, safety, and efficacy data, the 1800-mg SC dose is selected for this study. For further details and the most up-to-date information about single-agent studies, please refer to the Investigator's Brochure (IB Daratumumab 2017 [11]).

Rationale for Pharmacokinetics and Immunogenicity Assessments

Preliminary PK data from a planned interim analysis in Study SMM2001 indicate PK in SMM subjects using IV daratumumab appears similar to MM subjects based on similar predose and end-of-infusion concentrations. To obtain additional data for daratumumab in SMM, especially regarding PK of daratumumab following SC administration of the co-formulated product, samples will be obtained from all subjects for assessment of C_{min} and C_{max}. Data may also be used for a population-PK analysis to estimate additional PK parameters and provide information about the determinants of intersubject variability in this population. Pharmacokinetic data may also be used in an exposure-response analysis incorporating safety, efficacy or other endpoints.

Immunogenicity to daratumumab or rHuPH20 is possible. The incidence of anti-drug antibody generation in subjects with SMM may be different from previously studied. Therefore, the

presence of antibodies to daratumumab and antibodies to rHuPH20 (immunogenicity) will be determined from serum samples collected from subjects who receive daratumumab.

Rationale for Biomarker Evaluations

The biomarker hypotheses are that administration of daratumumab will result in better responses in high-risk subjects and greater anti-tumor immune modulation versus active monitoring. Biomarker samples will be collected to evaluate factors that may contribute to daratumumab response including but not limited to CD38 expression, resistance markers, immune repertoire changes, and depth of response by minimal residual disease (MRD).

Certain high-risk cytogenetic modifications are known to be present in the plasma cells of the premalignant phases of MM (Rajkumar 2013[30]). Progression to MM has been associated with several cytogenetic modifications, such as deletion 17p, amp(1q21), t(4;14), and t(14;16) that confer different levels of risk or poor prognosis. Though there has been debate about their frequencies and effect on plasma cells (Agarwal 2012[1]), significantly shorter time to progression and OS was observed in t(4;14) SMM patients (28 months, time to progression; 105 months, OS) compared to t(11;14) SMM patients (55 months, 147 months OS) (Rajkumar 2013[30]). These data suggest there maybe value in understanding the contribution these abnormalities have on disease progression. Therefore, response rates in specific molecular subgroups may be determined by deoxyribonucleic acid (DNA)/ribonucleic acid (RNA) sequencing of myeloma cells. Additionally, plasma from subjects will be collected to explore a less invasive technique for identification of prognostic biomarkers.

In previous daratumumab studies of subjects with MM, NK cell counts were reduced significantly following the first dose of daratumumab and maintained at low levels on therapy while other immune cell populations were not susceptible to decreases. Furthermore, it is hypothesized that SMM patients have a higher level of immune competency than MM patients, and this may allow for other daratumumab mechanism of actions to contribute to response (Krejcik 2016[13]). Recent data have demonstrated a potential role of the gut microbiome in influencing clinical outcomes by modulating inflammatory regulators (Goodman 2018[9], Meisel 2018[26]). Therefore, immune cell populations and gut immune microenvironment may be examined to determine whether similar changes play a role in daratumumab response for this premalignant condition.

Minimal residual disease assessment allows evaluation of the depth of clinical response beyond the standard IMWG CR/sCR response category. Several studies have demonstrated that MRD status is correlated with PFS and OS in MM (Martinez-Lopez 2014[22]) and achievable in SMM (Korde 2015[12]). In the present study, standardized methodology will be used for MRD in bone marrow aspirate when samples are obtained at screening, at confirmation of CR, and 12 months after the date of the initial CR for those subjects who maintain CR.

Rationale for Patient-Reported Outcomes

Patient-reported outcome (PRO) data complement data collected by other methods to support the clinical data and cost-effectiveness modeling as well as contributing to enhanced communication of value to patients, clinicians, regulators, and payers. Based on the clinical presentation of patients

with SMM and prior PRO research in myeloma clinical trials, the PRO endpoints of interest include scales from the EORTC QLQ-C30 (global health status, emotional functioning), EORTC QLQ-MY20 (future perspective), and the EQ-5D-5L (utility value and visual analog scale). These PRO measures will be administered to support the hypothesis that treatment with daratumumab maintains HRQoL by delaying the onset of disease symptoms. PRO data will be collected as outlined in the Time and Events Schedule to understand how the endpoints change over time, with treatment, and with the clinical state of the subject.

Summary of Benefits and Risks

The primary objective of study SMM3001 is to determine whether treatment with daratumumab SC prolongs PFS compared with active monitoring in subjects with high risk SMM. Subjects with SMM have clonal plasma cell which express high levels of CD38, making daratumumab a candidate therapeutic. Preliminary data from study SMM2001 show that daratumumab has efficacy in a high-risk SMM population.

The preliminary safety and PK data from Study MMY1004 supports the 1800 mg daratumumab SC dose selection for the proposed Phase 3 study. The PK data indicate that an 1800 mg dose of daratumumab administered subcutaneously would be anticipated to result in a similar or greater Cycle 3 Day 1 trough concentration (C3D1 C_{trough}) compared to 16 mg/kg IV administration. Study MMY1004 also showed that daratumumab SC can be administered subcutaneously by manual injection with a median of 5 minutes (ranging from 2 to 11 minutes) and it is associated with a relatively low incidence of IRRs. The overall safety profile for the daratumumab SC cohort is similar to prior experience with daratumumab IV administration and subcutaneous administration with Dara-MD. There are no new safety signals with the daratumumab SC administration. The potential risks will be mitigated by comprehensive and careful medical monitoring during the conduct of the study, as described in the protocol and summarized in this section. All subjects should comply with the described inclusion and exclusion criteria and will be closely monitored for possible toxicity. This includes adverse event monitoring, physical examinations, SC injection-site evaluations, electrocardiogram (ECG) monitoring, clinical laboratory parameter (hematology and chemistry) monitoring, pulmonary function testing, and ECOG performance status score evaluation. An ongoing review of the safety data will be performed by the Study Responsible Physician and Scientist to identify any safety signal. Furthermore, an IDMC will also review the safety and efficacy in preplanned analyses, per Section 11.12, of the protocol. In addition, a Steering Committee, including 3 independent expert physicians together with the Company Clinical Team Leader and Study Responsible Physician, will meet regularly (at least yearly) or as needed (if a safety signal is identified). Lastly, a review of cumulative safety data from all daratumumab studies will be performed by an internal safety management team at regular intervals. Therefore, the Company believes the benefit/risk profile is favorable to support further evaluation of efficacy, safety, and PK of daratumumab SC in Phase 3 of Study SMM3001.

4. SUBJECT POPULATION

Screening of subjects will be performed within 35 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, then 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 the purpose of this study, a subject that is randomized is considered enrolled.

4.1. Inclusion Criteria

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

1. At least 18 years of age or at least the legal age of consent in the jurisdiction in which the study is taking place, whichever is the older age.

2. Criterion amended per Amendment 1:

2.1 Diagnosis of SMM (per IMWG criteria) for ≤5 years with measurable disease at the time of randomization, defined as serum M protein ≥10 g/L or urine M protein ≥200 mg/24 hours or involved serum FLC ≥100 mg/L and abnormal serum FLC ratio.

3. Criterion amended per Amendment 1:

3.1 Clonal BMPCs ≥10%; and

At least 1 of the following risk factors;

a. Serum M protein ≥30 g/L,

b. IgA SMM,

c. Immunoparesis with reduction of 2 uninvolved immunoglobulin isotypes (only IgA, IgM, and IgG should be considered in determination for immunoparesis; IgD and IgE are not considered in this assessment),

d. Serum involved: uninvolved FLC ratio ≥8 and <100, or

e. Clonal BMPCs >50% to <60% with measurable disease.

4. ECOG performance status score of 0 or 1 (Attachment 1).

5. Pretreatment clinical laboratory values meet the following criteria during the Screening Phase:

a. Absolute neutrophil count ≥1.0 x 10^9/L (ie, ≥1000/μL)

b. Platelet count ≥50 x 10^9/L (not permissible to transfuse a subject within 2 weeks prior to the Screening platelet count to reach this level)

c. Aspartate aminotransferase (AST) ≤2.5 x upper limit of normal (ULN)

d. Alanine aminotransferase (ALT) ⩽2.5 x ULN

e. Total bilirubin ≤2.0 x ULN, except in subjects with congenital bilirubinemia, such as Gilbert syndrome (in which case direct bilirubin ≤2.0 x ULN is required)

6. Must sign an informed consent form (ICF) or their legally designated representative must sign indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study.

7. Criterion amended per Amendment 1:

7.1 Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies.

Women of childbearing potential must commit to either abstain continuously from heterosexual sexual intercourse or to use 1 method highly effective form of contraception (tubal ligation, intrauterine device, hormonal [birth control pills, injections, hormonal patches, vaginal rings or implants], or partner's vasectomy). Contraception must begin 4 weeks prior to dosing. Highly effective contraception is indicated even where there has been a history of infertility, unless due to hysterectomy. See Attachment 11 for definitions of Women of Childbearing Potential

8. A woman of childbearing potential must have a negative serum or urine pregnancy test at screening within 14 days prior to randomization. For requirements during the Treatment Phase, see Section 4.3

9. During the study and for 3 months after receiving the last dose of daratumumab, a woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction.

10. Willing and able to adhere to the prohibitions and restrictions specified in this protocol.

4.2. Exclusion Criteria

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

1. Criterion amended per Amendment 2:

1.1 Multiple myeloma, requiring treatment, defined by any of the following:

a. Bone lesions (one or more osteolytic lesions on low-dose whole body computed tomography [LDCT], positron-emission tomography with computed tomography [PET-CT] or CT). Subjects who have benign/post-traumatic bone lesions visible on screening images as well as previous imaging, may be considered for inclusion. Details (diagnosis, location, duration) on benign/post-traumatic pre-existing bone lesions that can be seen on the screening images (eg, old fractures) and were also present on previous imaging are to be reported in the CRF (see Section 9.1.2 and Section 9.2.7).

b. Hypercalcemia (serum calcium >0.25 mmol/L [>1 mg/dL] higher than ULN or >2.75 mmol/L [>11 mg/dL]). Subjects who have clinically stable hypercalcemia attributable to a disease other than multiple myeloma (eg, hyperparathyroidism) may be considered for inclusion after a case by case review by the medical monitor (see Section 9.2.3).

c. Renal insufficiency, preferably determined by creatinine clearance <40 mL/min measured or estimated using the MDRD (Attachment 2), or serum creatinine >177 µmol/L. Subjects who have clinically stable renal insufficiency attributable to a disease other than multiple myeloma (eg, glomerulonephritis) may be considered for inclusion after a case by case review by the medical monitor (see Section 9.2.3).

d. Anemia, defined as hemoglobin <10 g/dL or >2 g/dL below lower limit of normal or both; transfusion support or concurrent treatment with erythropoietin stimulating agents is not permitted. Subjects who have clinically stable anemia attributable to a disease other than multiple myeloma (eg, thalassemia, vitamin B12 deficiency, iron deficiency) may be considered for inclusion after a case by case review by the medical monitor (see Section 9.2.3). (Refer to Appendix 18.1 for specific requirements for France.)

e. Clonal BMPC percentage ≥60%

f. Serum FLC ratio (involved:uninvolved) ≥100 (The involved FLC must be ≥100 mg/L)

g. More than 1 focal lesion ≥5 mm in diameter by MRI

2. Primary systemic AL (immunoglobulin light chain) amyloidosis.

3. Criterion amended per Amendment 2:

3.1 Exposure to any of the following

a. Prior exposure to daratumumab or prior exposure to other anti-CD38 therapies

b. Prior exposure to approved or investigational treatments for SMM or MM (including but not limited to conventional chemotherapies, IMiDs, or PIs). Stable standard dosing of bisphosphonate and denosumab as indicated for osteoporosis is acceptable.

c. Exposure to investigational drug (including investigational vaccines) or invasive investigational medical device for any indication within 4 weeks or 5 half-lives, whichever is longer, before Cycle 1, Day 1

d. Ongoing treatment with corticosteroids with a dose >10 mg prednisone or equivalent per day at the time of randomization; or >280 mg cumulative prednisone dose or equivalent for any 4-week period in the year prior to randomization

e. Ongoing treatment with other monoclonal antibodies (eg, infliximab, rituximab), immunomodulators (eg, abatacept, methotrexate, azathioprine, cyclosporine) or other treatments that are likely to interfere with the study procedures or results

4. Received treatment (chemotherapy, surgery, etc) for a malignancy (other than SMM) within 3 years before the date of randomization (exceptions are squamous and basal cell carcinomas of the skin, carcinoma in situ of the cervix or breast, or other non-invasive lesion), which is considered cured with minimal risk of recurrence within 3 years.

5. Either of the following:

a. Known or suspected chronic obstructive pulmonary disease (COPD) with a forced expiratory volume in 1 second (FEV1) <50% of predicted normal

b. Moderate or severe persistent asthma within the past 2 years (see Attachment 3), or currently has uncontrolled asthma of any classification. (Note that subjects who currently have controlled intermittent asthma or controlled mild persistent asthma are allowed in the study).

The LDCT/PET-CT/CT performed for screening should be taken into consideration to determine if additional pulmonary workup is required.

6. Criterion amended per Amendment 1:

6.1 Criterion modified per Amendment 3:

6.2 Any of the following:

a. Known to be seropositive for human immunodeficiency virus (HIV)

b. Seropositive for hepatitis B (defined by a positive test for hepatitis B surface antigen [HBsAg]). Local testing and results of hepatitis B serology (Includes

HBsAg, anti-HBs, and anti-HBc) is required for all patients prior to randomization when this amendment 3 is implemented. Subjects with resolved infection (ie, subjects who are HBsAg negative but positive for antibodies to hepatitis B core antigen [Anti-HBc] and/or antibodies to hepatitis B surface antigen [Anti-HBs]) must be screened using real-time polymerase chain reaction (PCR) measurement of hepatitis B virus (HBV) DNA levels. Those who are PCR positive will be excluded. EXCEPTION: Subjects with serologic findings suggestive of HBV vaccination (Anti-HBs positivity as the only serologic marker) AND a known history of prior HBV vaccination, do not need to be tested for HBV DNA by PCR

c. Known to be seropositive for hepatitis C (except in the setting of a sustained virologic response [SVR], defined as aviremia at least 12 weeks after completion of antiviral therapy)

7. Medical or psychiatric condition or disease (eg, active systemic disease [including presence of auto-antibodies], uncontrolled diabetes) 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.

8. Clinically significant cardiac disease, including:

a. myocardial infarction within 6 months with left ventricular dysfunction or uncontrolled ischemic cardiac disease before Cycle 1 Day 1, or unstable or uncontrolled disease/condition related to or affecting cardiac function (eg, unstable angina, congestive heart failure, New York Heart Association Class III-IV)

b. Uncontrolled cardiac arrhythmia (Grade 2 or higher by National Cancer Institute-Common Terminology Criteria for Adverse Events [NCI-CTCAE] Version 4.03) or clinically significant ECG abnormalities

c. Screening 12-lead ECG showing a baseline QT interval as corrected QT interval corrected for heart rate >470 msec.

The LDCT/PET-CT/CT performed for screening should be taken into consideration to determine if additional cardiac workup is required.

9. Criterion amended per Amendment 1:

9.1 Known allergies, hypersensitivity, or intolerance to corticosteroids, monoclonal antibodies, hyaluronidase, or other human proteins, or their excipients (refer to Daratumumab Investigator Brochure[11]), or known sensitivity to mammalian-derived products (including dairy allergy).

10. Vaccination with live attenuated vaccines within 4 weeks of first study agent administration

11. Pregnant, breast-feeding, or planning to become pregnant while receiving study treatment or within 3 months after the last dose of daratumumab

12. Plans to father a child while receiving study treatment or within 3 months after the last dose of daratumumab

13. Major surgery (requiring general anesthesia or presence of other factors that determines surgery to be considered major) within 2 weeks before randomization or who have not fully recovered from surgery, or has surgery planned during the time the subject is expected to participate in the study or within 2 weeks after the last dose of daratumumab. Note: subjects with planned surgical procedures to be conducted under local anesthesia may participate. If there is a question whether a procedure is considered a major surgery, then the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a subject in the study.

14. 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.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the start of the Active Monitoring Phase (Arm A) or the first dose of daratumumab (Arm B) is given, such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study. Section 17.4, Source Documentation, describes the required documentation to support meeting the enrollment criteria. Subjects who fail to meet the inclusion and exclusion criteria (ie, screen failures) may be rescreened if their condition changes. Rescreening must be discussed with and approved by the sponsor on a case-by-case basis. Subjects who are determined to be eligible for the study after rescreening must sign a new ICF and then will be assigned a new Subject 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 subjects randomized to the daratumumab arm, the prohibitions and restrictions listed below will apply. 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 treatment and for 3 months after the last dose of daratumumab. A woman randomized to active monitoring is not required to adhere to this prohibition/restriction.

2. A man who is sexually active with a woman of childbearing potential must always use a latex or synthetic condom during the study treatment and for 3 months after discontinuing daratumumab. All men must not donate sperm during the study treatment and for 3 months after the last dose of daratumumab. A man randomized to active monitoring is not required to adhere to this prohibition/restriction.

5. TREATMENT ALLOCATION

The study medicinal products and their designations are listed in Table 6

Table 6: Designations of Medicinal Products Used in the Study

Designation	Product
Investigational Medicinal Product (IMP)	daratumumab Authorized: Daratumumab Unauthorized:
Non-investigational Medicinal Product (NIMP)/ auxiliary medicinal product (AxMP)	Not applicable for this study.

Central randomization using an Interactive Web Response System (IWRS) will be implemented in this study. Subjects will be stratified and then randomly assigned to 1 of 2 treatment groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor.

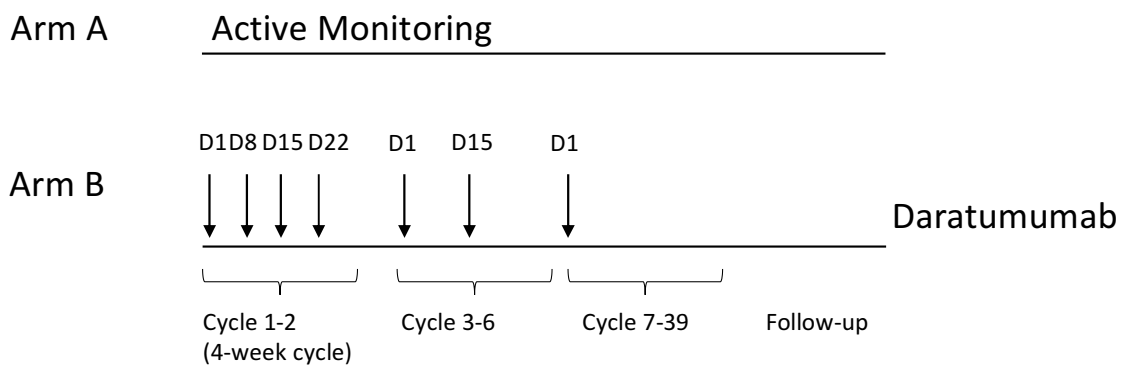
Eligible subjects will be stratified according to the number of factors associated with progression to MM (<3 vs ≥3) and then randomly assigned to a treatment. The assignment will be balanced using randomly permuted blocks. The factors, as defined in Section 3.1, will be based on central laboratory analyses with the exception of BMPCs, which will be based on data from the local laboratory. The IWRS will assign a unique treatment code, which will dictate the treatment assignment and matching study drug kit for the subject. The requestor must use his or her own user identification and personal identification number when contacting the IWRS and will then give the relevant subject details to uniquely identify the subject.

6. DOSAGE AND ADMINISTRATION

Subjects randomized to active monitoring will receive no study medication but will undergo the same disease evaluations and at the same frequency as subjects randomized to daratumumab. Daratumumab SC (daratumumab 1800 mg + rHuPH20 [2000 U/mL]) will be administered as described in the Time and Events Schedule (Table 2). Each cycle is 28 days. All doses should be administered at outpatient visits. The first visit of a cycle should be 4 weeks after the start of the previous cycle. The start of Cycles 2 to 39 may occur ±3 days of the scheduled day in order to accommodate the schedule of the site or subject, only if a minimal interval of 4 days between daratumumab doses is maintained. All subsequent days within that cycle and Day 1 of subsequent cycles should be adjusted accordingly to maintain the 28-day cycle duration. In case of dose delays affecting days other than Day 1, because of reasons other than toxicity, administration should occur within the prespecified window (Table 7). If an administration does not commence within the prespecified window 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. Every effort should be made to avoid dose delays because of reasons other than toxicity (refer to Section 6.5.3, for details on interrupted or missed doses). Changes to within-cycle daratumumab dosing should not affect Day 1 of the next cycle. Subjects will continue to receive daratumumab according to the Time and Events Schedule until disease progression, unacceptable toxicity, or other reasons as listed in Section 10.1.

A schematic of study treatment administration is provided in Figure 3.

Figure 3: Schematic Overview of Active Monitoring and Study Treatment Administration



6.1. Daratumumab

Detailed description for preparation and administration of daratumumab will be supplied in the Investigational Product Preparation Instructions (IPPI).

6.2. Treatment Schedule and Administration

Daratumumab SC (daratumumab 1800 mg + rHuPH20 [2000 U/mL]) will be administered by SC injection through a syringe by a manual push over approximately 5 minutes. For subjects randomized to daratumumab, daratumumab will be administered weekly in Cycle 1 and 2, then every 2 weeks for Cycle 3 to Cycle 6, and thereafter every 4 weeks until 39 cycles or up to 36 months or until confirmed PD, or one of the reasons outlined in Section 10, whichever occurs first. Doses will be administered at alternating locations on the abdomen. Subjects will receive predose and postdose medications as detailed in Section 8. All subjects in the daratumumab arm will be observed for at least 6 hours after the end of the SC injection during Cycle 1 Day 1 and, if deemed necessary by the investigator, after subsequent injections.

If a subject experiences a significant medical event, then the investigator should assess whether the subject should be hospitalized overnight for observation.

6.3. Guidelines for Prevention and Management of Infusion Reactions

For the purpose of this protocol, infusion-related reactions are defined as systemic reactions related to the SC administration of daratumumab.

6.3.1. Predose Medication

In an effort to prevent IRRs, subjects in the daratumumab arm will receive all of the following medications 1 to 3 hours prior to each daratumumab administration (1 hour prior to daratumumab administration is preferred):

- An antipyretic: paracetamol (acetaminophen) 650-1000 mg orally (PO) or IV
- An antihistamine: diphenhydramine 25-50 mg PO or IV, or equivalent. Avoid the use of IV promethazine. After Cycle 6, if a subject has not developed an IRR and is intolerant to antihistamines, then modifications are acceptable as per investigator discretion. (See Attachment 4 for a list of antihistamines that may be used)
- A corticosteroid: methylprednisolone 100 mg PO or IV or equivalent for the first 2 doses and 60 mg for all subsequent doses. This reduction in steroid dose can only be done in the absence of IRR adverse events in both of the first 2 doses. Substitutions for methylprednisolone are allowed, but conversion rules have to be taken into account (refer to Attachment 5).

Predose administration of a leukotriene inhibitor (montelukast 10 mg PO, or equivalent) is recommended on Cycle 1 Day 1. If necessary, all PO predose medications may be administered outside of the clinic on the day of daratumumab administration, provided they are taken within 1 to 3 hours prior to the administration.

6.3.2. Postdose Medication

In an effort to prevent delayed IRRs, subjects in the daratumumab arm will receive a long- or intermediate-acting corticosteroid (20 mg methylprednisolone PO or equivalent [refer to Attachment 5 for conversion rules], in accordance with local standards) on the 2 days following each daratumumab administration (beginning the day after daratumumab administration). Only when no IRR adverse events occurred during the first 3 doses, postdose corticosteroids should be administered per investigator discretion.

For subjects with higher risk of respiratory complications (eg, subjects with COPD who have a FEV1 <80% and subjects with asthma), the following postdose medications should be considered, as per investigator discretion:

- antihistamine (diphenhydramine or equivalent) on the first and second days after each dose,
- Short-acting β2 adrenergic receptor agonist such as salbutamol aerosol, and
- 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 daratumumab administration. If subjects are hospitalized, then an improvement in FEV1 should be documented prior to discharge. If these subjects are not hospitalized, then a follow-up telephone call should be made to monitor their condition within 48 hours. 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 IRRs, then these postdose medications may be waived after 4 doses at the investigator's discretion.

6.4. Management of Injection-site and Infusion-related Reactions

6.4.1. Local Injection-site Reactions

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

6.4.2. Infusion-related Reactions

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

If an IRR develops, then daratumumab administration should be temporarily interrupted. Please see the IPPI for further details. Subjects who experience adverse events during daratumumab

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

Infusion-related Reactions of Grade 1 or Grade 2

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

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

Infusion-related Reactions of Grade 3 or Higher

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

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

Recurrent Infusion-related Reactions

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

6.5. Dose Delays and Dose Modification

6.5.1. Dose Modification

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

6.5.2. Toxicity Management

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

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

Daratumumab administration should be resumed when the toxicity has resolved to Grade 2.

Dose delays affecting Day 1: If Day 1 of a cycle is delayed, the entire cycle will be delayed until either the dose can be given or daratumumab is to be discontinued (see below). If the start of a cycle is delayed, the starting day of subsequent cycles is adjusted accordingly.

Dose delays affecting days other than Day 1: If an administration does not commence within the prespecified window (Table 7) 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 7: Daratumumab Administration Schedule for Within Cycle Doses

Cycles	Frequency	Dose Held	Dosing Restart
1 and 2	Weekly	>3 days	Next planned weekly dosing date
3 to 6	Every 2 weeks	>1 week	Next planned biweekly dosing date

Any adverse event deemed to be related to daratumumab that requires a dose hold of >28 days due will result in permanent discontinuation of daratumumab. If a dose delay occurs, then PK and pharmacodynamic assessments should be performed on the actual day of study drug administration, not on the original scheduled administration day.

In case the dose is to be delayed because of reasons other than toxicity, the aforementioned rules should be applied as well (refer to Section 6). However, every effort should be made to avoid dose

delays because of reasons other than toxicity (refer to Section 6.5.3 for details on interrupted or missed doses).

6.5.3. Interruption or Missed Doses

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

7. TREATMENT COMPLIANCE

Daratumumab will be administered by qualified study-site personnel, 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 the use of predose and postdose medications at home. Additional details are provided in the Site Investigational Product Procedures Manual.

8. PRESTUDY AND CONCOMITANT THERAPY

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 8.3. Routine systemic use of the following concomitant medications will be collected in the eCRF and recorded in the source documents as specified in the Time and Events Schedule (Table 1):

- Growth factors
- Transfusions
- Anti-infectives (antibacterials, antivirals, and antimycotics)
- Corticosteroids
- Anti-arrhythmics and other cardiac supportive therapy
- Anti-epileptics
- Centrally acting psychiatric medication
- Antihistamines, and other medications targeting postdose systemic reactions
- Bisphosphonates, denosumab
- Any anticancer therapy (including radiation)

The use of concomitant medications used to treat adverse events will be collected as specified in the Time and Events Schedule (Table 1).

8.1. Recommended Therapies

Prophylaxis for herpes zoster reactivation, as per institutional guidelines, is recommended during the Treatment Phase for subjects in the daratumumab arm (Arm B). Prophylaxis for pneumocystis carini/jirovecci pneumonia, according to institutional guidelines, should be considered for subjects in Arm B (daratumumab).

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:

- Constipation prophylaxis (eg, adequate hydration, high-fiber diet, and stool softeners, if needed)
- Prophylactic antiemetics, with the exception of corticosteroids, in subjects with history of nausea or vomiting
- Stable standard dosing of a bisphosphonate or denosumab as indicated for osteoporosis unrelated to MM is allowed.

Other symptoms may be managed according to institutional guidelines provided prohibited therapies are not administered (see Section 8.3).

8.3. Prohibited Therapies

Use of the treatments listed below is prohibited during the study:

- Other agents that target CD38
- Medications used for other indications that have anti-myeloma properties (eg, interferon and clarithromycin; Ghosh 2013[8])
- Administration of approved or investigational treatments for SMM or MM or both (including but not limited to conventional chemotherapies, IMiDs, or PIs)
- Therapeutic use of systemic corticosteroids for MM (>280 mg cumulative dose of prednisone or equivalent for 4 weeks) (other than those given for IRRs as described in Section 6.3)
- Ongoing treatment with other monoclonal antibodies (eg, infliximab, rituximab), immunomodulators (eg, abatacept, methotrexate, azathioprine, cyclosporine), or other treatments that are likely to interfere with the study procedures or results

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

8.4. Management of Hepatitis B Virus Reactivation

Primary antiviral prophylaxis is permitted as per local standard of care. Per protocol, HBV DNA testing by PCR is mandatory for subjects at risk for HBV reactivation (see Section 9.7).

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

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedules (Table 1 and Table 2) summarize the frequency and timing of efficacy, PK, immunogenicity, pharmacodynamics, biomarker, PRO, and safety measurements applicable to this study. Every effort should be made to keep subjects on the planned study schedule. For subjects in both study arms for whom there are no safety concerns, tele-health (conducted via phone or video conference) visits are permitted per the clinical judgement of the investigator, and where feasible and permissible by local policy and regulations. All assessments should be followed with in person examination, if clinically indicated. Refer to the Time and Events Schedule (Table 1 and Table 2) for guidance.

Patient reported outcome assessments should be completed after informed consent forms are signed, but before any tests, procedures, or other consultations that may influence subject perception scheduled for the same day as the PRO assessments are collected. If the subject is unable to complete the PRO assessments, the reason for not completing the questionnaires will be documented (ie, too ill, subject refused, etc). Refer to Section 9.5 for details.

The maximum blood volume for the study is estimated at approximately 55 mL during screening, 115 mL during the first year for Arm A (active monitoring), and 302 mL for Arm B (daratumumab). In the Follow-up Phase, subjects prior to PD will continue to have approximately 20 mL blood drawn every 3 months for disease evaluations. The maximum total blood volume for a subject completing the projected study duration of approximately 8 years is estimated at 546 mL for Arm A (active monitoring) and 895 mL for Arm B (daratumumab). This includes laboratory assessments associated with safety, efficacy, and PK 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 ICF is signed. During the Screening Phase, eligibility criteria will be reviewed and a complete clinical evaluation will be performed as specified in the Time and Events Schedule. Screening procedures will be performed within 35 days before randomization;

however, 12-lead ECGs, imaging (LDCT, PET-CT, CT, or MRI), and bone marrow aspirate/biopsy performed up to 56 days before randomization as routine standard of care for the subject's disease can be used. Imaging from routine standard of care assessments can be used only if these meet the minimum requirements as set by the current version of the Image Acquisition Guidelines.

Eligibility of the subject disease status is based on central screening laboratory results and on an independent review of screening images after confirmation of eligibility by the site. For optimal assessment of the screening images by the independent reviewers, additional clinical data, including benign/post-traumatic pre-existing bone lesions, data of recent bone marrow procedures, and general medical history, will be included in the independent review. Details (diagnosis, location, duration) on benign/post-traumatic pre-existing bone lesions that can be seen on the screening images (eg, old fractures) and were also present on previous imaging are to be reported in the CRF (see Section 9.2.7).

If a subject does not meet all inclusion and exclusion criteria (is a screen failure) but at some point in the future is expected to meet the subject eligibility criteria, then the subject may be rescreened. Subjects who are rescreened will be assigned a new subject number, undergo the informed consent process, and then restart a new Screening Phase.

9.1.3. Active Monitoring Phase or Treatment Phase

Details of the procedures performed during the Active Monitoring Phase (Arm A) and the Treatment Phase (Arm B) are outlined in the Time and Events Schedule (Table 1). Subjects in the daratumumab arm (Arm B) should start study treatment within 5 days after randomization. Active monitoring of subjects in Arm A will start immediately after randomization. All 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 confirmed in a subject during the Active Monitoring Phase, then the subject will discontinue active monitoring, complete the End-of-Active Monitoring Visit, and enter the Follow-up Phase. For subjects in the Active Monitoring (Arm A), the End-of- Active-Monitoring visit is to be performed within 30 days (±3 days) of confirmation of disease progression by investigator. If disease progression is confirmed in a subject in the daratumumab arm, then the subject will discontinue study treatment, complete the End-of-Treatment Visit (30 days ±3 days after the last dose of daratumumab, or before starting subsequent therapy, if earlier), and enter the Follow-up Phase. Biochemical progression without meeting diagnostic criteria for MM (Table 9) does not constitute a reason to discontinue study treatment.

End-of-Active Monitoring Visit (Arm A)/End-of-Treatment Visit (Arm B)

Unless a subject withdraws consent for study participation or is lost to follow-up, an End-of-Active Monitoring Visit (Arm A)/End-of-Treatment (Arm B) Visit is to occur. For subjects in Arm A, the End-of Active Monitoring Visit is to occur after 36 months (±3 days) (from the date of randomization) of active monitoring if disease progression was not yet confirmed earlier, or if the subject did not meet other criteria for discontinuation prior to 36 months (refer to Section 10.2).

In case of discontinuation because of reasons other than disease progression, the End-of-Active Monitoring/End-of-Treatment Visit is to be performed within 30 days (±3 days) after notification that the subject will discontinue Active monitoring/treatment. For subjects in the Arm B, the End-of-Treatment Visit is to occur 30 (±3) days after the last dose of daratumumab. Every effort should be made to conduct the End-of-Active Monitoring Visit (Arm A)/ End-of-Treatment Visit (Arm B) before the subject starts subsequent therapy. If a subject is unable to return to the site for the End-of-Active Monitoring (Arm A)/End-of-Treatment Visit (Arm B), then the subject should be contacted to collect information on adverse events and concomitant medications used to treat adverse events as specified in Section 12.3.1. If the End-of-Treatment Visit (Arm B) occurs earlier than 30 days after the last dose of daratumumab SC, then the subject should be contacted after 30 days have passed from the last dose of daratumumab SC, so that all adverse events that occurred within the 30-day period from the last dose of daratumumab SC are recorded. 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 the subject completes 39 cycles or 36 months (whichever occurs first) of active monitoring (Arm A) or daratumumab treatment (Arm B). Reasons for premature discontinuation of active monitoring or daratumumab treatment are listed in Section 10.2. Subjects who discontinue before PD must continue to have disease evaluations as described in Section 9.2, until study completion or confirmed PD (or other reasons as outlined in Section 10). If subjects have not progressed to MM, then no other treatment for SMM or MM is allowed during the study. Follow-up for first-line MM treatment (including the response to first-line MM treatment), second primary malignancies, and survival status will be obtained as specified in the Time and Events Schedule (Table 1). Survival will be followed until the end of the study and at a frequency of at least every 12 weeks until PD. After PD, survival is to be followed at least every 6 months, until the end of the study.

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

9.2. Efficacy Evaluations

Disease assessments will be performed every 12 weeks until PD. A window of ±7 days around the scheduled assessment date is allowed. For subjects with treatment delays, disease assessments should be performed at the scheduled disease assessment dates. They do not need to be repeated at the time of delayed daratumumab administration. Disease progression, if based on laboratory results only, must be confirmed by a consecutive assessment. A repeated investigation for confirmation of disease progression does not need to occur within a specified timeframe and could potentially occur on the same date (at a later timepoint). However, the original value meeting disease progression and the confirmation value must be consecutive (ie, no intermediate values that do not meet the definition of disease progression). It is not a requirement to have a repeat investigation if disease progression is based on at least 2 of the laboratory tests of Hb, calcium,

renal function and FLC at the same assessment date (eg, when Hb <10 g/dL and creatinine clearance <40 mL/min are present on the same day).

Disease assessments will be performed according to the Time and Events Schedule (Table 1). Disease evaluations scheduled for treatment days should be collected before study drug is administered. Disease progression to MM will be evaluated using the IMWG diagnostic criteria for MM (Table 9) (Rajkumar 2014[29]). For subjects who discontinue active monitoring (Arm A) or daratumumab (Arm B) before PD, disease assessments should be performed according the Time and Events Schedule (Table 1) until study completion or confirmed PD (or other reasons as outlined in Section 10).

Per protocol Amendment 6, disease assessments will only be performed locally and locally diagnosed disease progression will be reported based upon study investigator review per IMWG criteria.

9.2.1. Assessment of Response

Per protocol Amendment 6, assessment of response will no longer be collected.

This study will use the IMWG consensus recommendations for MM treatment response criteria (Durie 2007[7], Rajkumar 2011[31], Kumar 2016[14]) presented in Table 8. For quantitative immunoglobulin (QIg) at baseline, M-protein, and immunofixation measurements in serum and 24-hour urine, the investigator will use results provided by the central laboratory.

Table 8: International Uniform Response Criteria Consensus Recommendations

Response[a]	Response Criteria
Stringent complete Response (sCR)	• CR as defined below, *plus* • Normal FLC ratio, *and* • Absence of clonal PCs by immunohistochemistry, immunofluorescence[b] or 2- to 4-color flow cytometry.
Complete response (CR)[c]	• Negative immunofixation on the serum and urine, and • <5% PCs in bone marrow.
Very good partial Response (VGPR)[c]	• 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, then 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, then a ≥50% reduction in bone marrow PCs is required in place of M-protein, provided baseline bone marrow PC percentage was ≥30%.
Stable disease	• Not meeting criteria for CR, VGPR, PR, or symptomatic MM.

IMWG=International Myeloma Working Group; FLC=free light chain; MM=multiple myeloma; PC=plasma cell.
All response categories (CR, sCR, VGPR, PR) require 2 consecutive assessments made at any time before the institution of any new therapy and 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.
[a] Subjects will continue in the last confirmed response category until there is confirmation of progression or improvement to a higher response status; subjects cannot move to a lower response category.
[b] 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.
[c] 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.

9.2.2. Assessment of Disease Progression to Multiple Myeloma

Assessment of Progression to Multiple Myeloma (diagnostic progression)

During the study, disease progression will be measured according to the published international uniform diagnostic criteria for MM established by the IMWG (Rajkumar 2014[29]) presented in Table 9. Progression evaluations for the primary endpoint/final analysis will be based on IRC review, in a blinded fashion, to objectively and consistently implement the IMWG diagnostic criteria for MM. The IRC responsibilities and procedures will be documented in a separate IRC charter.

Per protocol Amendment 6, disease progression will be evaluated locally by the study investigator using the IMWG criteria in Table 9. Disease progression will no longer be centrally evaluated by IRC. Local determination of disease progression should be reported in the eCRF.

Table 9: **Diagnostic Criteria for Progression to Multiple Myeloma[f]**

Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma[a] PLUS 1 or more of the following: • Calcium elevation (>0.25 mmol/L [>1 mg/dL] higher than ULN or >2.75 mmol/L [>11 mg/dL]) • Renal insufficiency (creatinine clearance[b] <40 mL/min or serum creatinine >177 µmol/L [>2 mg/dL]) • Anemia (hemoglobin <10 g/dL [<6.5 mmol/L] or >2 g/dL [>1.25 mmol/L] lower than the lower limit of normal • Bone disease (one or more osteolytic lesions on LDCT, PET-CT, or CT)[c] • Clonal bone marrow plasma cell percentage[a] ≥60% • Involved: uninvolved serum free light chain ratio[d] ≥100 • >1 focal lesions[e] on MRI studies.

CT=computed tomography; LDCT=low-dose whole body computed tomography; MRI=magnetic resonance imaging; PET-CT=positron-emission tomography with computed tomography; ULN=upper limit of normal.

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 (per IMWG criteria; however, bone marrow aspirate only is acceptable for this study); 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, then more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement.
d. These values are based on the serum Freelite assay (The Binding Site Group, Birmingham UK). The involved free light chain must be ≥100 mg/L. To avoid overcalling progression based on FLC ratio, the progression will be determined based on modified FLC criteria combining IMWG progression criteria with IMWG FLC ratio criteria, as described below.
e. Each focal lesion must be 5 mm or more in size.
f. . Per protocol Amendment 6, progressive disease identification is based on local assessment only.

From Rajkumar 2014.[29]

Free light chain criteria are designed for de novo diagnosis rather than for progression of SMM to MM. Prior experience suggests that therapy, especially with daratumumab, can in some instances preferentially reduce the uninvolved light chain, therefore suggesting progression despite actual therapeutic response/absolute reduction of the involved light chain. To avoid overcalling progression based on FLC ratio, the progression will be determined based on modified FLC criteria combining IMWG progression criteria with IMWG FLC ratio criteria:

- Serum FLC (involved/uninvolved) light chain ratio ≥100
- Involved light chain ≥100 mg/L
- Difference of involved – uninvolved light chain shows confirmed increase ≥25% from lowest value (nadir)

Assessment of Biochemical Progression

Biochemical progression is defined as an increase of 25% from nadir value in any one of the following:

- Serum M-component (absolute increase must be ≥5 g/L)
- Urine M-component (absolute increase must be ≥200 mg/24 hours).

If the lowest M component was ≥50 g/L, then a serum M-protein increase ≥10 g/L is sufficient for biochemical progression.

In subjects without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (ie, absolute difference) must be increased by 25% from nadir and the absolute increase must be >100 mg/L.

Biochemical progression is to be considered as an important risk factor to evolve to diagnostic progression and those subjects should be monitored closely. However, biochemical progression alone does not constitute a reason for discontinuing therapy.

9.2.3. CRAB Criteria-related Laboratory Assessments

The following laboratory tests must be performed at every disease assessment, including during the follow-up period, whenever disease assessments are required.

Per protocol Amendment 6, CRAB Criteria-related laboratory tests should be performed locally.

- Serum calcium corrected for albumin
- Creatinine clearance or serum creatinine
- Hemoglobin

Serum Calcium Corrected for Albumin

According to CRAB criteria, corrected serum calcium >11 mg/dL or >2.75 mmol/L indicates progression to MM, if it is not attributable to any other cause (see Table 9). Measurement of free ionized calcium is the preferred test for determining hypercalcemia. Free ionized calcium levels >1.5 mmol/L are considered to be hypercalcemic (according to CRAB criteria) for this study.

As an alternative, the serum calcium level must be adjusted for abnormal albumin levels ("corrected serum calcium"). The formula for adjustment is presented in Attachment 6.

The elevation in calcium should not be due to another reason, such as hyperparathyroidism. An appropriate workup should be performed, including, at a minimum, laboratory determination of parathyroid hormone.

Subjects who, at screening, have clinically stable hypercalcemia that has existed for several years and did not show any deterioration during the prior year, can be considered for eligibility as long as the causality of hypercalcemia is proven to be attributed to a disease other than multiple myeloma (eg, hyperparathyroidism). Prior to screening, a case-by-case discussion with the medical monitor may occur with the inclusion of prior laboratory results.

Creatinine Clearance

According to CRAB criteria, measured or estimated creatinine clearance <40 mL/min using validated equations (preferred), creatinine >2 mg/dL or >177 µmol/L indicates progression to MM if it is not attributable to any other cause. Decrease in glomerular filtration rates should not be due

to non-myeloma-related etiology; an appropriate workup should be performed. A kidney biopsy should be strongly considered when there is no increase in FLC or increase in urine Bence-Jones proteins. Measured or estimated glomerular filtration rates (according to the Modification of Diet in Renal Disease (MDRD) [Levey 2006[19]] formula; Attachment 2), as per local practice, are preferred over a fixed serum creatinine concentration. For subjects who discontinue treatment prior to PD, these measurements should continue to be analyzed every time disease assessments are performed.

Subjects who, at screening, have clinically stable renal insufficiency that has existed for several years and did not show any deterioration during the prior year, can be considered for eligibility as long as the causality of renal insufficiency is proven to be attributed to a disease other than multiple myeloma (eg, glomerulonephritis). Prior to screening, a case-by-case discussion with the medical monitor may occur with the inclusion of prior laboratory and biopsy results.

Hemoglobin

According to CRAB criteria, hemoglobin <10 g/dL or >2 g/dL lower than the lower limit of normal indicates progression to MM if it is not attributable to any other cause. Before PD is declared on the basis of anemia without other CRAB signs or symptoms, additional diagnostic tests (at a minimum, iron, ferritin, transferrin, manual smear review, Coombs testing, lactate dehydrogenase, vitamin B12, and folate) should be carried out to determine that there is no other underlying cause of anemia. Positive tests thought to at least partially explain the anemia should continue to be analyzed every time disease assessments are performed. In questionable cases, especially when there is anemia with no concomitant increase in measurable disease, a bone marrow examination must be performed to clarify the diagnosis of anemia before progression to MM can be diagnosed.

Subjects who, at screening, have anemia that has existed for several years and did not show any decline during the prior year, can be considered for eligibility as long as the anemia's causality is proven to be attributed to a disease other than multiple myeloma (eg, iron deficiency, Vitamin B12 deficiency, thalassemia). Prior to screening, a case-by-case discussion with the medical monitor may occur with the inclusion of prior laboratory results. (Refer to Appendix 18.1 for specific requirements for France.)

9.2.4. Myeloma Protein Measurements in Serum and Urine

Per protocol Amendment 6, M-protein measurements will no longer be analyzed by the central laboratory and will only be analyzed locally.

The following tests will be performed.

- Serum quantitative immunoglobulins (QIgs): 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 quantification by electrophoresis (SPEP)

- 24-hour urine M-protein quantitation by electrophoresis (UPEP)
- Serum immunofixation electrophoresis (SIFE)/urine immunofixation electrophoresis
- Serum FLC assay

Blood and 24-hour urine samples for disease assessments will be collected during screening and as specified in the Time and Events Schedule (Table 1) until the development of PD. If blood and 24-hour urine disease assessment samples collected at screening were taken within 14 days before Cycle 1 Day 1, then it is not mandatory to collect these samples again at the Cycle 1 Day 1 visit. Repeat laboratory studies in cases where screening values were obtained >14 days from Cycle 1 Day 1 only need to be obtained for Arm B subjects.

In subjects with a baseline UPEP result below the level of measurable disease (<200 mg/24 hours), UPEP analysis will be repeated only at the time of suspected CR. Serum/urine immunofixation assays will be performed at screening, and at other times if considered helpful in the interpretation of SPEP and UPEP results. In subjects without measurable disease in the urine at diagnosis who show rising involved serum FLC (or raise other clinical concerns), UPEP may be performed at the investigator's discretion to assess for excretion of light chains. Baseline value is defined as the last value prior to initiating treatment (Arm B) or prior to randomization for active-monitoring subjects (Arm A).

Daratumumab is an immunoglobulin that may interfere with clinical SPEP/SIFE assessments. In cases in which daratumumab interference is suspected, a reflex assay confirming the presence of daratumumab will be performed (Attachment 7). In cases where CR or sCR is suspected and the reflex assay confirms that daratumumab is present on SPEP/SIFE, additional clinical assessments will be triggered to confirm the CR/sCR. A subject who meets all other clinical criteria for CR/sCR, and who has daratumumab interference confirmed by the reflex assay, will be considered a CR/sCR.

9.2.5. β2-microglobulin and Lactate Dehydrogenase

As per protocol Amendment 6, β2-microglobulin and lactate dehydrogenase at time of disease progression will no longer be analyzed by the central laboratory and will only be analyzed locally.

9.2.6. Bone Marrow Examination

Per protocol Amendment 6, central lab MRD testing will be discontinued. Bone marrow aspirate should be performed locally for morphology and cytogenetics by FISH at PD per the Time and Events Schedule in Table 10.

Bone marrow aspiration will be performed for disease assessments for all subjects as specified in the Time and Events Schedule. For details of bone marrow analysis, see Table 10. The volume required for these tests will be based on laboratory standard practices. Details for performing FISH are provided in the Laboratory Manual. A portion of any bone marrow aspirates may be sent to a laboratory for MRD clone identification or molecular subtyping.

Cytogenetic FISH testing will include the specified probes [del(17p13), amp(1q21), t(4;14) and t(14;16). If the subject had a routine bone marrow aspirate performed prior to screening, and no additional aspirate is performed, (formalin-fixed paraffin-embedded (FFPE) samples are the only available sample for FISH), these samples can be analyzed by the local site laboratory where every effort should be made to obtain FISH using the specified probes [del(17p13), amp(1q21), t(4;14) and t(14;16)]. NOTE: An additional bone marrow aspirate, if feasible, should be performed within 2 months after the first date of the diagnosis of PD.

Table 10: Bone Marrow Testing

	Local Testing	**Central Testing** Per protocol Amendment 6, all central lab testing detailed below will be discontinued.
Screening	Disease characterization (morphology and either immunohistochemistry, immunofluorescence, or flow cytometry). Cytogenetics by FISH (centrally or locally [for China only in case only FFPE is available]). FISH must include probes for del(17p13), amp(1q21), t(4;14) and t(14;16) [for China only in case only FFPE is available].	Cytogenetics by FISH (centrally or locally [for China only in case only FFPE is available]). If a fresh bone marrow aspirate is collected at Screening, then a portion may be sent to a central laboratory for MRD clone identification or molecular subtyping. If a fresh bone marrow aspirate will not be performed at Screening because a sample is available within 56 days prior to randomization, then non-decalcified diagnostic tissue (bone marrow aspirate slides, touch-prep from biopsy [rolled biopsy] slides, or clot specimen slides) should be collected for MRD assessment.
On Study (every 2 years until PD or yearly if a follow-up is BMPC ≥40%. If BMPC ≥40% at screening, then obtain every 12 months**)**	Disease characterization (morphology and either immunohistochemistry, immunofluorescence, or flow cytometry) to determine extent of plasma cell infiltration (plasma cell infiltration)	
CR, sCR Per protocol Amendment 6, central lab testing will be discontinued	For response confirmation, additional bone marrow aspirates or biopsies (or both) will be performed locally (Disease characterization [morphology and either immunohistochemistry, immuno-fluorescence, or flow cytometry]) to confirm sCR or CR. For sCR: immunohistochemistry, immunofluorescence (requires kappa/ lambda ratio from analysis of ≥100 cells) or 2- to 4-color flow cytometry.	A portion may be sent to a central laboratory for potential MRD evaluation.
Maintained CR, sCR Per protocol Amendment 6, central lab testing will be discontinued	Not applicable.	If feasible for subjects who maintain CR or sCR, a bone marrow aspirate sample will be obtained 12 months after the date of the initial CR.
Disease Progression Per protocol Amendment 6, central lab testing will be discontinued Bone marrow aspirate for cytogenetics by FISH should be performed locally.	When suspected: Disease characterization: morphology and either immunohistochemistry, immunofluorescence, or flow cytometry. Cytogenetics by FISH[1] (local testing) [for China only in case only FFPE is available]). FISH at suspected PD must include probes for del(17p13), amp(1q21), t(4;14) and t(14;16) [for China only in case only FFPE is available]).	If feasible, a bone marrow aspirate may be collected from subjects at disease progression to evaluate mechanism of daratumumab resistance. Cytogenetics by FISH (centrally or locally [for China only in case only FFPE is available]).

BMPC=bone marrow plasma cell; CR=complete response; FFPE=formalin-fixed paraffin-embedded; FISH=fluorescence in situ hybridization; MRD=minimal residual disease; PD=progressive disease; sCR=stringent complete response.

9.2.7. Assessment of Bone Disease

Per protocol Amendment 6, central review of imaging studies will be discontinued. Imaging studies and review should be performed locally according to the Time and Events schedule.

The presence of bone lesions will be evaluated locally. The site will review the screening images first to confirm eligibility of study subject (no lytic lesions and/or ≤1 focal lesion with diameter ≥5 mm present unless proven benign/post-traumatic origin). After initial screening imaging assessment by the site and confirming eligibility by the site, results of imaging studies (ie, LDCT/CT/PET-CT/MRI) will be uploaded to a central repository and reviewed centrally. This central review of screening images will be used to determine eligibility of subjects for study participation (see Section 9.1.2). Presence of focal bone lesions will be evaluated by MRI, in exceptional cases by PET-CT (see below). The presence of lytic bone lesions will be evaluated by LDCT, PET-CT, or CT, including skull, entire vertebral column, pelvis, chest, humeri, femora, and any other bones in which the investigator suspects involvement by disease radiography. Local review will also be used to assess disease progression by evaluating the occurrence of bone disease. During the Active Monitoring and Treatment Phases and before disease progression is confirmed, imaging should be performed as indicated in the Time and Events Schedule (Table 1), to document response or progression.

Lytic bone lesions (LDCT, PET-CT or CT)

The preferred method of assessment for osteolytic lesions is LDCT scan. Depending on local practice, PET-CT or CT may be used as an alternative. Bone lesion assessments will be performed at Screening and every 12 months until PD.

Focal Bone lesions (MRI)

MRI (spine and pelvis) will be performed to assess focal lesions at Screening and regularly during the study, as indicated in the Time and Events Schedule. Positron emission tomography-computed tomography (PET-CT) may be used as an alternative for those subjects for whom MRI is contraindicated. However, the medical monitor is to be informed upfront about the reason why MRI is contraindicated.

Disease Progression

Identification of >1 focal lesions on MRI is considered a Myeloma Defining Event (MDE). One or more sites of osteolytic bone destruction (≥5 mm in size) seen on CT (including LDCT) or PET-CT are considered an MDE. Increased uptake on PET-CT alone in >1 location without underlying lytic lesions (focal lesions) is considered adequate for the diagnosis of MM only in subjects in whom MRI is contraindicated (other reasons for increased PET signal, such as infection, should be excluded); in all other subjects evidence of underlying osteolytic bone destruction is needed on the CT portion of the examination. If the diagnosis of disease progression is obvious by imaging investigations (LDCT, PET-CT, CT or MRI), then no repeat confirmatory imaging is necessary. In instances where changes may be more subtle, repeat imaging may be performed in 1 to 3 months per investigator discretion.

The suggested window for imaging studies is ±1 months. Studies triggered by biochemical progression or suspected PD may replace a scheduled imaging study visit if the triggering event occurs <1 month from the suggested window. If the triggering event occurs >1 month from the suggested window for the next scheduled imaging study, then a dedicated study should be performed. The suggested minimum interval between imaging studies of the same type is 3 months.

9.2.8. Best Response to First-line Multiple Myeloma Treatment

Best response to first-line MM treatment will be assessed by the investigator at 6-month intervals. The investigator will assess response based on the IMWG response criteria for MM using local lab evaluations.

9.3. Pharmacokinetics and Immunogenicity

Per protocol Amendment 6, no further Pharmacokinetics and Immunogenicity samples will be collected.

9.3.1. Evaluations

Samples to assess both the serum concentration (PK) of daratumumab and the generation of anti-daratumumab antibodies (immunogenicity) will be obtained from all subjects in the daratumumab group according to the Time and Events Schedule (Table 2). Samples will also be collected from all subjects in the daratumumab group to evaluate the immunogenicity of rHuPH20 according to the Time and Events Schedule (Table 2).

The exact dates and times of blood sampling must be documented. 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/immunogenicity of daratumumab or immunogenicity of rHuPH20 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

Samples will be analyzed to determine concentrations of daratumumab or generation of antibodies to daratumumab or rHuPH20 using validated immunoassay methods by or under the supervision of the sponsor. For the daratumumab immunogenicity assessments, serum samples will be screened for antibodies binding to daratumumab and serum titer will also be determined from confirmed positive samples. Other immunogenicity analyses (eg, assessment of neutralizing capabilities) may be performed to further characterize the immune responses that are generated.

For the rHuPH20 immunogenicity assessments, plasma samples will be screened for antibodies binding to rHuPH20 and will be assessed in confirmatory and titer assays as necessary. Neutralizing antibody assessments may also be performed to further characterize immune responses that are generated.

9.3.3. Pharmacokinetic Parameters

Pharmacokinetic samples to determine serum concentration of daratumumab will be obtained from subjects in the daratumumab group. The PK parameters are defined as:

C_{max}	Maximum observed serum concentration
C_{min}	Minimum observed serum concentration

If sufficient data are available, other PK parameters may be calculated. The C_{min} and C_{max} will be determined based on the assigned collection timepoints. If there are sufficient data, population-PK analysis of serum concentration-time data of daratumumab may be performed using nonlinear mixed-effects modeling and may include data from other clinical studies. Details will be provided in a population-PK analysis plan and results of the analysis will be presented in a separate report.

9.3.4. Immunogenicity Assessments

Serum from venous blood samples collected from all subjects in the daratumumab group will be assessed for the generation of anti-daratumumab antibodies (immunogenicity) according to the Time and Events Schedule. Daratumumab concentration will be evaluated at all immunogenicity time points to ensure appropriate interpretation of immunogenicity data. When both daratumumab serum concentration and immunogenicity analyses are specified, they will be performed on aliquots from the same blood draw and no additional sampling is required. Plasma samples will also be collected from all subjects in the daratumumab group and assessed for antibodies to rHuPH20.

When an IRR occurs associated with the second daratumumab administration or beyond, 2 blood samples should be obtained, if possible, for determination of both antibodies to daratumumab and antibodies to rHuPH20. No unscheduled samples need to be collected for IRRs associated with the first administration of daratumumab. Daratumumab serum concentration will also be determined from the daratumumab IRR sample for the purpose of interpreting immunogenicity data. These samples will be stored and evaluated if deemed necessary. If an IRR results in treatment discontinuation, then a subject should undergo all scheduled safety and efficacy evaluations. Procedures for sample collection, preparation, identification, storage, and shipment will be provided in the Laboratory Manual or equivalent document. Samples collected for the analysis of daratumumab immunogenicity/serum concentration or rHuPH20 immunogenicity 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.

Subjects who discontinue treatment or withdraw from the study before confirmation of PD should have samples collected at the time of early discontinuation. Subjects who discontinue treatment will also be asked to return for immunogenicity evaluation during the Follow-up Phase.

9.4. Biomarkers

Per protocol Amendment 6, biomarker assessments by central laboratory will be discontinued.

Biomarker assessments will focus on 3 main objectives: determining the clinical benefit (ORR, PFS, and OS) of daratumumab in subjects with genetic modifications (del(17p13), amp(1q21), t(4;14), t(14:16), or other risk-associated molecular subtypes), depth of response by the absence of MRD, and to evaluate the immunophenotype of subjects with SMM for potential immune cell contributions to daratumumab response. All biomarker assessments will be performed centrally.

Bone marrow aspirates may be collected at screening and following treatment as outlined in the Time and Events Schedule. Bone marrow aspirates may be used for DNA/RNA sequencing in subjects with genetic modifications (del(17p13), amp(1q21), t(4;14), t(14:16), or other risk-associated molecular subtypes) and to monitor for potential predictive biomarkers of response or resistance such as changes in CD38, complement inhibitor protein expression, and changes in expression patterns of genes associated with ADCC, CDC, or other mechanisms of action of daratumumab.

In addition, baseline bone marrow aspirates may be subjected to DNA sequencing in order to establish the myeloma clone for MRD monitoring. A fresh bone marrow aspirate at Screening for all subjects is required, if possible, for MRD assessments. If a fresh bone marrow aspirate will not be performed at Screening because a sample is available within 56 days prior to randomization, then non-decalcified diagnostic tissue (bone marrow aspirate slides, touch-prep from biopsy [rolled biopsy] slides, or clot specimen slides) should be collected for MRD assessment. For subjects who achieve a sCR or CR, additional bone marrow aspirate may be used for assessment of MRD by next generation sequencing (NGS) of immunoglobulin heavy and light chains (Vij 2014[35]). For subjects that maintain a sCR/CR, MRD may also be assessed at 12 months after date of initial sCR/CR in bone marrow aspirate. All MRD samples will be stored and analyzed if ORR data support testing. 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 SIFE and preventing determination of CR, subjects with VGPR may also be evaluated for MRD by NGS.

A whole blood sample will be drawn at time points indicated in the Time and Events Schedule to evaluate immune cell populations by methodologies such as cytometry by time of flight, and to reserve plasma for potential biomarker evaluations. These samples may be used to evaluate specific subsets of immune cells such as cytotoxic T cells, regulatory T cells, MDSCs, B cells, and NK cells. Cells may also be used for additional phenotypic and functional profiling. Plasma-based analyses may also be used to evaluate changes in factors such as cytokines, complement proteins, soluble CD38, soluble CD59, IFNγ, granzyme, perforin, and/or tumor associated DNA in circulation to evaluate potential biomarkers of response and resistance. Stool samples may be collected at time points indicated in the Time and Events Schedule and DNA sequencing may be performed to evaluate the gut microbiome.

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 (Table 1).

9.5. Patient-reported Outcomes

The EORTC QLQ-C30, select items from the EORTC QLQ-MY20, and the EQ-5D-5L are included to assess subject's report of symptoms, functioning, and HRQoL.

The EORTC QLQ-C30 includes functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), symptom scales (fatigue, nausea and vomiting, and pain), and a Global Health Status scale (Attachment 8). Reliability, validity, and clinically meaningful change have been demonstrated among patients with MM (Wisloff 1996[37], Wisloff 1997[38]). The EORTC Multiple Myeloma Module (QLQ-MY20) has been designed to use alongside the EORTC QLQ-C30 as a validated MM measure (Cocks 2007[4]). Only the 3 questions in the future perspective scale and the 6 questions in the disease symptoms scales will be administered (Attachment 9). The EQ-5D-5L is a generic preference-based measure of health status (Attachment 10). The 5-item questionnaire assesses mobility, self-care, usual activities, pain/discomfort and anxiety/depression to compute a single utility score plus a visual analog scale rating "health today" (Herdman 2011[10]).

PRO endpoints are to be assessed during the screening window, the Active Monitoring/study treatment phase, during pre-PD follow-up, at the time of disease progression, and during post-PD phases. PRO data collection during the Screening Phase will serve as the baseline score, to be collected after the subject signs informed consent. PRO assessments should be administered prior to any interventions that could influence subject perceptions of their health state, scheduled for the same day as PRO assessments are collected. The goal of data collection during the Active Monitoring/study treatment phase is to measure changes in emotional functioning due to receiving or not receiving treatment and to measure the impact of adverse events from daratumumab treatment on HRQoL. The goal of data collection during the pre-PD phase is to measure HRQoL after treatment and the value of potentially being in a pre-PD state longer because of treatment. The goal of data collection during the post-PD phase is to measure the onset and severity of symptoms associated with MM. Subject burden related to completion of PRO measures was a key consideration in determining the number of assessments as well as the timepoints likely to observe potential change in scores. If no in-person visit is scheduled, PROs can be interviewer-administered during tele-health (conducted via phone or video conference) visits.

9.6. Medical Resource Utilization

Medical resource utilization data associated with medical encounters (including tele-health visits [conducted via phone or video conference]), will be collected in the eCRF by the investigator and study-site personnel for all subjects at the disease assessment visits and at Months 3 and 6, post-PD. Protocol mandated procedures, tests, and encounters are excluded. The data collected will be

used to conduct exploratory analyses that may be used to support the value story and cost-effectiveness modelling for market access. The data collected include:

- Number and characteristic of diagnostic and therapeutic tests procedures (inpatient and outpatient)
- Number and duration of hospitalization (total length of stay [days], including duration by each hospital unit (intensive care unit)
- Outpatient medical encounters (including physician, nurse practitioner or emergency room visits, tests and procedures)

Please see eCRF completion guidelines for more details.

9.7. Safety Evaluations

Details regarding the IDMC are provided in Section 11.12. Safety will be measured by adverse events, physical examinations, ECGs, SC injection-site evaluations, clinical laboratory test results (hematology and chemistry), and ECOG performance status. All toxicities will be graded according to the NCI-CTCAE Version 4.03. 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, IRRs/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.

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

Adverse Events

Adverse events (with the exception of progression to MM) will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally designated representative) as specified in the Time and Events Schedule (Table 1). Adverse events will be followed by the investigator as specified in Section 12, Adverse Event Reporting.

Clinical Laboratory Tests

As per protocol Amendment 6, central laboratory assessments will be discontinued.

Local Laboratory Testing

For subjects in the daratumumab arm, blood samples for serum chemistry and hematology will be collected as outlined in the Time and Events Schedule and analyzed by the local laboratory before each dosing to determine if the subject meets daratumumab treatment criteria described in Section 6.5. The investigator must review the laboratory results, 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. Local laboratory data must be entered in the eCRF for safety evaluation.

The following tests will be performed by the local laboratory:

- Hematology Panel

  -hemoglobin
  - White blood cell count, absolute neutrophil count, and absolute lymphocyte count
  -platelet count

- Serum Chemistry Panel

  - AST
  - ALT
  -total bilirubin[a]
  -alkaline phosphatase
  -sodium
  -potassium
  -creatinine
  -glucose
  - blood urea nitrogen or urea
  -calcium and albumin-adjusted calcium

  [a] if Gilbert's disease, assessment of direct bilirubin

- Hepatitis B Virus (HBV) serology and DNA Tests

  - HBsAg, Anti-HBs, and Anti-HBc;

  - HBV DNA by PCR for patients with serologic evidence of past HBV infection (all patients during screening, arm B patients only Q12W during treatment, at the End of Treatment Visit, and Q12W for up to 6 months after the last dose of study treatment)

Serum or Urine Pregnancy Testing

- Serum or urine pregnancy testing at screening, and as clinically indicated, for women of childbearing potential only

HBV Serology

All subjects will be tested locally for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (Anti-HBs), and hepatitis B core antibody (Anti-HBc) at Screening. Additionally, subjects ongoing in the Treatment Phase (arm B only) who are within 6 months of starting study treatment when Protocol Amendment 3 is implemented will be required to have HBV serology performed locally upon signing the updated ICF. (Refer to Appendix 18.1 for specific requirements for France.)

HBV serology is not required at Screening or for subjects ongoing in the Treatment Phase (arm B only) who are within 6 months of starting study treatment if this was performed as part of standard of care within 3 months prior to first dose. For patients on treatment >6 months, testing is at investigator discretion.

HBV DNA Tests

Subjects who are positive for Anti-HBc or Anti-HBs will undergo testing for hepatitis B DNA by PCR. Subjects with serologic findings suggestive of HBV vaccination (Anti-HBs positivity as the only serologic marker) and a known history of prior HBV vaccination do not need to be tested for HBV DNA by PCR. During and following study treatment, subjects who have history of HBV infection (positive for Anti-HBc and/or Anti-HBs, have a negative HBV DNA PCR at baseline based on local laboratory assessments, and are randomized to Arm B) will be closely monitored for clinical and laboratory signs of reactivation of HBV as specified in the Time and Events Schedule (Table 1). Where required by local law, the results of HBV testing may be reported to the local health authorities.

Indirect Antiglobulin Test (IAT)

Blood Type, Rh, and indirect antiglobulin test (IAT) should be done before the first dose of daratumumab. Red blood cell (RBC) phenotyping (standard or extended) is an alternative to the IAT test, if required by a local standard.

Daratumumab interferes with the IAT, which is a routine pre-transfusion test performed to identify a subject's antibodies to minor antigens so that suitable donor blood can be given for transfusion. Daratumumab does not interfere with ABO/RhD typing. CD38 is expressed at very low levels on erythrocytes. Daratumumab binds to the CD38 on erythrocytes, which results in a positive IAT (Indirect Coombs Test). This positive result masks the detection of antibodies to minor antigens and may prevent or delay blood banks from issuing donor blood for transfusion. This effect occurs during daratumumab treatment and for up to 6 months after treatment ends. Subjects will receive a patient identification wallet card for the study that includes the blood profile (ABO, Rh, and IAT or phenotyping) determined before the first administration of daratumumab along with information on the IAT interference for healthcare providers/blood banks. Subjects are to carry this card throughout the treatment period and for at least 6 months after treatment ends. Blood banks can eliminate the daratumumab interference with IAT by treating reagent RBCs with dithiothreitol (DTT) (Chapuy 2015[3]).

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

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

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

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

Electrocardiogram (ECG)

A 12-lead ECG will be performed as specified in the Time and Events Schedule. 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 is scheduled for the same time point as ECG recording, the procedures should be performed in the following order: ECG, blood draw.

Physical Examination and ECOG Performance Status

A complete physical examination (including neurological examination) should be performed during the Screening Phase. Thereafter, only a symptom-directed physical examination is required. Abnormalities will be recorded in the appropriate section of the eCRF. ECOG performance status will be used to evaluate the effect of the disease status on the activities of daily living. Height, and weight should be measured as clinically necessary and will be recorded in the eCRF at screening only. Vital signs should be monitored as clinically necessary. Only abnormal vital signs will be recorded in the eCRF, as part of AE reporting in the AE reporting page.

Pulmonary Function Test

Subjects with known or suspected COPD must have a FEV1 test, as specified in the Time and Events Schedule (Table 1). Refer to Section 6.3.2 of the protocol for details on subjects with higher risk of respiratory complications.

9.8. Sample Collection and Handling

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

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided. 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/DISCONTINUATION OF STUDY TREATMENT/ WITHDRAWAL FROM THE STUDY

10.1. Completion

In the Active Monitoring group, a subject will be considered to have completed the study treatment if the subject has completed 36 months of Active Monitoring. In the daratumumab group, a subject will be considered to have completed study treatment if the subject has completed 39 cycles of therapy or 36 months of daratumumab, whichever occurs first. A subject will be considered to have completed the study (study completion defined in Section 17.9.1) if he or she has been followed to the end of the study or has died before the end of the study. Subjects who have been lost to follow-up, or have withdrawn consent for study participation before the end of the study, will not be considered to have completed the study.

10.2. Discontinuation of Active Monitoring (Arm A) or Study Treatment (Arm B)

Discontinuation of Active Monitoring (Arm A) or Study Treatment (Arm B)

A subject will not be automatically withdrawn from the study if he or she has to discontinue active monitoring or treatment before the end of the Active Monitoring or Treatment Phase. The End-of-Active Monitoring/End-of-Treatment Visit and Follow-up Visit assessments should continue as specified in the Time and Events Schedule (Table 1).

A subject must be discontinued from active monitoring or daratumumab treatment if:

- The investigator believes that for safety reasons or tolerability reasons (eg, adverse event) it is in the best interest of the subject to discontinue study treatment
- A subject randomized to Arm B becomes pregnant unless the subject (or the subject's legally acceptable representative), investigator, and sponsor agree the benefits outweigh the risks to the fetus and continuation of study treatment is in the best interest of the subject. A subject randomized to Arm A who becomes pregnant may remain on the study (refer to Section 4.3). For a pregnant subject who remains on the study, any study procedures deemed by the investigator to be potentially harmful to the fetus (eg, CT scans) may be deferred until the subject is no longer pregnant.
- The subject (or the subject's legally acceptable representative) withdraws consent for administration of study treatment
- The subject experiences unacceptable toxicity, including IRRs described in Section 6.4
- The subject’s daratumumab dose is held for more than 28 days due to treatment-related adverse events (Arm B only)
- The subject experiences disease progression (definition see Section 9.2.2). [Biochemical progression without meeting IMWG diagnostic criteria for MM requiring therapy (Table 9) does not constitute a reason for discontinuation of therapy.]
- A subject who experiences a second primary malignancy that cannot be treated by surgery alone must be withdrawn from the study. However, a subject who develops a malignancy that may be cured surgically may continue to receive active monitoring (Arm A) or the assigned

study treatment (Arm B) and should continue to be followed for subsequent progression of MM.

Before subjects discontinue active monitoring (Arm A) or study treatment (Arm B) due to disease progression, sites will document disease progression by completing a disease progression form as soon as possible and within 48 hours of disease progression assessment. The medical monitor will confirm that treatment should be discontinued. After confirmation from the sponsor, active monitoring (Arm A) or study treatment (Arm B) will be discontinued and the subject will enter into Follow-up after completion of the End-of-Active Monitoring Visit or End-of-Treatment Visit.

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

10.3. Withdrawal from the Study (Arm A and Arm B)

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

- Lost to follow-up
- Withdrawal of consent
- Death
- The study investigator, for any reason, stops the subject's participation in the study
- Sponsor terminates the study

If a subject discontinues active monitoring or study drug and withdraws from the study before the end of the active monitoring or treatment phase, End-of-Active Monitoring or End-of-Treatment Visit assessments should be obtained.

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

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw will not be replaced. Additional subjects will not be enrolled. If a subject withdraws from the study, assessments in the End-of-Active Monitoring or the End-of-Treatment Visit should be obtained. If the reason for withdrawal from the study is withdrawal of consent, no additional assessments are allowed. Public record searches will be conducted, if permitted by local law.

10.4. Withdrawal From the Use of Samples in Future Research

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

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 main analysis populations are:

- Intent-to treat population, defined as all randomized subjects
- Safety population, defined as all randomized subjects for subjects randomized to active monitoring or all randomized subjects who received at least one dose of daratumumab for subjects randomized to daratumumab

The intent-to-treat population will be used to summarize the study population and characteristics and efficacy; and the safety population will be used to summarize the safety data.

11.2. Sample Size Determination

The sample size calculation assumes that the median PFS for Arm A (active monitoring) is 30 months. The longer projected median PFS compared to the published 24 months was chosen to account for the fact that ultra-high risk SMM subjects, who were included in earlier studies, are now considered to have symptomatic MM according to the updated IMWG criteria, and to account for the additional risk factors included to identify high-risk SMM for this study. It was further assumed that daratumumab treatment will reduce the risk of the disease progression or death by 37.5%, ie, assuming a HR (daratumumab vs active monitoring) of 0.625, which translates to a median PFS of 48 months for daratumumab. Taking into account the interim analysis, 165 PFS events are needed to achieve a power of at least 85% to detect this hazard ratio with a log-rank test (one sided alpha=0.025). With a 24-month accrual period and an additional 24 months of follow-up, the sample size needed for the study is approximately 360 (180 in active monitoring, 180 in daratumumab) subjects. Sample size calculations were performed using ADDPLAN v6.1.1.

At the end of study, approximately 134 PFS2 events are expected in both arms (81 at the time of the primary analysis of PFS). With 134 PFS2 events, the probability of showing a positive trend, ie, estimated HR<1, is more than 95% assuming the true HR=0.75 (median PFS2: 72 vs 96 months). Note that in the hierarchical testing procedure, only superiority will be tested for this endpoint.

At the end of study, approximately 107 OS events are expected in both arms (64 at the time of the primary analysis of PFS). With 107 OS events, the probability of showing a positive trend, ie, estimated HR<1, is more than 85% assuming the true HR=0.80 (median OS: 100 vs 125 months).

11.3. Efficacy Analyses

The primary efficacy analysis will occur when approximately 165 PFS events have been observed. This is expected to occur approximately 2 years after the last subject has been randomized.

Descriptive statistics will be used to summarize data. For continuous parameters, number of observations, mean, SD, median, and range will be used. For discrete parameters, frequency will be summarized. For time-to-event parameters, Kaplan-Meier estimates will be produced. When sample sizes are small, sample listings may be provided instead.

11.3.1. 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 among the 2 groups (daratumumab vs active monitoring). The Kaplan-Meier method will be used to estimate the distribution of overall PFS for each group. The treatment effect (HR) and its 2-sided 95% confidence intervals are to be estimated using a stratified Cox regression model with treatment as the sole explanatory variable. These analyses will be stratified by the stratification factor, number of risk factors associated with progression to MM (<3 vs ≥3).

11.3.2. Secondary Endpoints

- Time to biochemical or SLiM-CRAB progression (BOD-PFS): The median time to BOD-PFS and 95% CI in each group will be estimated using the Kaplan-Meier method. The BOD-PFS distributions between the 2 groups will be compared using the stratified log-rank test. The treatment effect (HR) and its 2-sided 95% CI will be estimated using a stratified Cox regression model with treatment as the sole explanatory variable.
- ORR: The proportion of subjects who have an OR and the 95% CI will be calculated for each treatment group. The rate of OR will be compared between the 2 groups using the stratified Cochran-Mantel-Haenszel test. The Mantel-Haenszel odds ratio will be provided along with its 2-sided 95% CI.
- CR rate: The proportion of subjects who have a CR or better and the 95% CI will be calculated for each group. The rate of CR or better will be compared between the 2 groups using the stratified Cochran-Mantel-Haenszel test. The Mantel-Haenszel odds ratio will be provided along with its 2-sided 95% CI.
- Time to first-line treatment for MM: The median time to first-line treatment for active MM and 95% CI in each group will be estimated using the Kaplan-Meier method. The time to first-line treatment for MM distributions between the 2 groups will be compared using the stratified log-rank test. The treatment effect (HR) and its 2-sided 95% CI will be estimated using a stratified Cox regression model with treatment as the sole explanatory variable.
- PFS2: The median PFS2 and 95% CI in each group will be estimated using the Kaplan-Meier method. The PFS2 distributions between the 2 groups will be compared using the stratified log-rank test. The treatment effect (HR) and its 2-sided 95% CI will be estimated using a stratified Cox regression model with treatment as the sole explanatory variable.
- OS: The median OS and 95% CI in each group will be estimated using the Kaplan-Meier method. The OS distributions will be compared between the 2 groups using the stratified log-

rank test. The treatment effect (HR) and its 2-sided 95% CI will be estimated using a stratified Cox regression model with treatment as the sole explanatory variable.

- Incidence of MM with adverse prognostic features: The proportion of subjects who progress to MM with adverse prognostic features and the 95% CI will be calculated for each group.
- Duration of response: A descriptive summary for duration of response will be provided. No statistical comparison will be made.
- Time to response: A descriptive summary for time to response will be provided. No statistical comparison will be made.

In the event that the primary endpoint is statistically significant, details of the hierarchical testing of the secondary endpoints will be provided in the Statistical Analysis Plan.

11.4. Pharmacokinetic Analyses

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

Descriptive statistics will be used to summarize daratumumab serum concentrations at each sampling time point. C_{min} is defined as the minimum concentration observed immediately before daratumumab administration and C_{max} is defined as the maximum concentration observed following daratumumab administration, as presented in the summary of serum concentration by sampling time point. Other PK parameters, if available, may also be summarized.

If sufficient data are available, population-PK analysis of serum concentration-time data of daratumumab may be performed and may be combined with data from other studies. If the population-PK analysis is conducted, details will be given in a population-PK analysis plan and the results of the analysis will be presented in a separate report. Exposure-response analyses may also be performed and may use data from other studies; if performed, details will be provided in a separate analysis plan and report.

11.5. Immunogenicity Analyses

The incidence of anti-daratumumab antibodies will be summarized for all subjects who receive at least 1 dose of daratumumab and have appropriate samples for detection of antibodies to daratumumab (ie, subjects with at least 1 sample obtained after their first dose of daratumumab). The incidence of anti-rHuPH20 antibodies will be summarized for all subjects who receive a dose of daratumumab and have appropriate samples for detection of anti-rHuPH20 antibodies. A listing of subjects who are positive for anti-daratumumab or anti-rHuPH20 antibodies will be provided.

11.6. Biomarker Analyses

Biomarker studies are designed to identify markers predictive of response (or resistance) to daratumumab. Analyses will be stratified by clinical covariates or molecular subgroups using the appropriate statistical methods (eg, parametric or non-parametric, univariate or multivariate, analysis of variance, or survival analysis, depending on the endpoint). Correlation of baseline expression levels or changes in expression levels with response to time-to-event endpoints will identify responsive (or resistant) subgroups in addition to genes and pathways attenuated following treatment with daratumumab.

Any pharmacodynamic measures will be listed, tabulated, and where appropriate, plotted. Subjects may be grouped by cohort, dose schedule, or clinical response. As this is an open-label study with an active monitoring control arm, statistical analyses will be done to aid in the understanding of the results.

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.

11.7. Pharmacokinetic/Pharmacodynamic Analyses

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

11.8. Patient-reported Outcomes

The EORTC-QLQ-C30 (Attachment 8) and EORTC QLQ-MY20 (Attachment 9) scale scores and EQ-5D-5L (Attachment 10) utility and visual analog scores will be descriptively summarized by treatment group at each time point. Within-group and between-group treatment effects of the PRO endpoints will be assessed by change from baseline using mixed models for repeated measures.

11.9. Medical Resource Utilization Analyses

Medical resource utilization will be summarized descriptively by treatment group. Additional analyses may be conducted; details and results of any additional analyses will be presented in a separate report.

11.10. 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. Treatment-emergent adverse events are adverse events with onset during the active monitoring or treatment phase or that are a consequence of a pre-existing condition that has worsened since baseline. All reported adverse events will be included in the analysis. For each adverse event, the percentage of subjects who experience at least

1 occurrence of the given event will be summarized by treatment group. In addition, comparisons between treatment groups will be provided if appropriate.

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

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the Statistical Analysis Plan) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point. Changes from baseline results will be presented in pre- versus posttreatment cross-tabulations (with classes for below, within, and above normal ranges). Parameters with predefined NCI-CTCAE toxicity grades will be summarized. Change from baseline to the worst adverse event grade experienced by the subject during the study will be provided as shift tables. 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.

Electrocardiograms

Electrocardiogram data will be summarized based on categories of normal, abnormal either clinically significant or not clinically significant and listed.

11.11. Interim Analysis

There will be one interim analysis for futility. This analysis will occur when approximately 60% of the PFS events (99) have occurred. This is expected to occur approximately 8 months after the last subject has been randomized. The purpose of this interim analysis is to evaluate cumulative interim safety and efficacy data. The non-binding futility boundary at this interim analysis will be determined using the Kim-Demets power spending function with parameter p=4.0. The beta spent at this analysis will be 0.0194.

11.12. Data Monitoring Committee

An IDMC will be established to monitor data on an ongoing basis to ensure the continuing safety of the subjects enrolled in this study. The committee will meet periodically to review interim data. After the review, the IDMC will make recommendations regarding the continuation of the study. In addition, the IDMC will review cumulative safety data (ie, serious adverse events) after the first 60 subjects have been randomized and treated or observed for 8 weeks, 6 months later, and thereafter every 12 months until the primary analysis. In addition, the IDMC will review the efficacy data after 99 PFS events have occurred and will make recommendations regarding the continuation of the study. The details will be provided in a separate IDMC charter.

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

The IDMC will be discontinued once the primary analysis endpoint has been achieved.

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

Although no medicinal product is administered, adverse events and serious adverse events will be reported for subjects in Arm A (active monitoring).

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational/auxiliary) 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/auxiliary) product, whether or not related to that medicinal (investigational or non-investigational/auxiliary) 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 European Union 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 drug and the event (eg, death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

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

Adverse Event Associated With the Use of the Drug

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

12.1.2. Attribution Definitions

Not Related

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

Doubtful

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

Possible

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

Probable

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

Very Likely

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

12.1.3. Severity Criteria

The severity assessment for an adverse event or serious adverse event should be completed using the NCI-CTCAE Version 4.03.

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

12.2. Special Reporting Situations

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

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

Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious 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 as specified in the Time and Events Schedule. Beyond the adverse event reporting period, only adverse events that are considered to be possibly, probably, or very likely related to study drug need to be reported.

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). For adverse events that result in death, death should be recorded as an outcome of the adverse event and should not be recorded as an adverse event or serious adverse event. The adverse event that resulted in the death should be reported as a serious adverse event. All events that meet the definition of a serious adverse event will be reported as serious adverse events, regardless of whether they are protocol-specific assessments.

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

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

Subjects (or their designees, if appropriate) must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following, at a minimum:

- 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 IAT (as described in Section 9.7).

12.3.2. Serious Adverse Events

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

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

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

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

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

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

Expected progression of disease should not be considered an adverse event (or serious adverse event). However, if determined by the investigator to be more likely related to the study treatment than the underlying disease, the clinical signs or symptoms of progression and the possibility that the study treatment is enhancing disease progression, should be reported per the usual reporting requirements (see Section 12 Adverse Event Reporting).

12.3.3. Pregnancy

All initial reports of pregnancy in female subjects or partners of male subjects must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study treatment unless the subject (or the subject's legally acceptable representative), investigator, and sponsor agree the benefits outweigh the risks to the fetus and continuation of study treatment is in the best interests of the subject. A subject randomized to Arm A who becomes pregnant may remain on the study (refer to Section 4.3). For a pregnant subject who remains on the study, any study procedures deemed by the investigator to be potentially harmful to the fetus (eg, CT scans) may be deferred until the subject is no longer pregnant. Because the effect of the study drug on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported, as noted above. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

12.4. Contacting Sponsor Regarding Safety

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

13. PRODUCT QUALITY COMPLAINT HANDLING

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

13.1. Procedures

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

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

13.2. Contacting Sponsor Regarding Product Quality

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

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drug

The daratumumab supplied for this study is a colorless to yellow liquid and sterile concentrate of 120 mg/mL daratumumab + 2000 U/mL rHuPH20 in a vial. The study agent should be essentially free of visible particulate matter at the time of syringe preparation and drug product administration. It will be manufactured and provided under the responsibility of the sponsor. Refer to the Investigator's Brochure[11] for a list of excipients.

14.2. Packaging

Daratumumab is supplied in glass vials containing daratumumab at a concentration of 120 mg/mL and rHuPH20 at a concentration of 2000 U/mL (~20 μg/mL). It will be supplied to the site/pharmacy as open-label supply.

14.3. Labeling

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

14.4. Preparation, Handling, and Storage

Daratumumab must be stored in the original carton in a refrigerator at controlled temperatures ranging from 2°C to 8°C until it is removed for dose preparation. Study drug must not be used after the expiry date printed on the label. The product must be protected from light and must not be frozen. The product does not contain preservatives; therefore any unused portion remaining in the vial must be discarded. Refer to the IPPI and Site Investigational Product Procedures Manual for additional guidance on study drug preparation, handling, and storage.

14.5. Drug Accountability

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

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

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

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

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

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Investigator's Brochure for daratumumab (and rHuPH20, where required per local regulations)
- Investigational Product Preparation Instructions
- Investigational Product and Procedures Manual
- Laboratory manual
- PRO questionnaires and PRO completion guidelines
- IWRS Manual
- eCRF completion guidelines
- Sample ICF
- Subject diaries for recording predose and postdose medications that are administered at home (Section 6.3)
- Subject identification wallet card indicting blood type and IAT result
- Other manuals and guidance documents as needed.

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

The current standard of care for patients with SMM is observation. The QuiRedex study has provided some evidence that therapeutic intervention administering therapy designed for MM in SMM is beneficial. However, changes in the disease definition and concerns that QuiRedex may have, in fact, included some subjects with fully developed MM have contributed to ongoing questions in the field. These deliberations support the presence of clinical equipoise in this trial.

An argument for the early treatment of myeloma at the pre-symptomatic SMM stage is the prevention of organ damage, especially with regards to bone fractures and kidney failure. Both treatment arms in this study are aiming to accomplish this goal, either by active monitoring with frequent disease evaluations or with pre-emptive therapy. It is truly unknown if one approach is superior (clinical equipoise); however, both study arms have a reasonable likelihood of benefitting the subjects enrolled.

The primary safety profile of daratumumab is predominantly characterized by IRRs; see Section 6.2, 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 administration. 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.

In a previous study with SC administration of daratumumab (MMY1004), a lower incidence of IRRs was observed compared to IRR rate reported from studies with IV administration of daratumumab. However, IRRs may still occur and may develop at a later time point than previously observed with IV administration due to the more gradual absorption. Subjects will therefore be observed for at least 6 hours on their first day of SC daratumumab administration. Apart from IRRs, a similar toxicity profile has been shown for SC versus IV administration for anemia, thrombocytopenia, and other toxicities. During this study local tolerability at the SC injection site will be closely monitored as well.

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

The total blood volume to be collected is outlined in Section 9.1.1. A total volume corresponding to 1 to 2 blood donations will be collected over the entire study duration. The blood volumes collected are not burdensome.

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

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

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

16.2.2. Independent Ethics Committee or Institutional Review Board

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

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

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

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

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- New edition(s) of the Investigator's Brochure and amendments/addenda

- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of adverse events that are serious, unlisted/unexpected, and associated with the study drug
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

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

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

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion (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, which includes permission to obtain information about his or her survival status. It also denotes that the subject agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, and subsequent disease-related treatments, if needed, 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.

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/territories.

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 or make requests concerning his or her personal data in accordance with applicable data protection law. 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.

In the event of a data security breach, the sponsor will apply measures to adequately manage and mitigate possible adverse effects taking into consideration the nature of the data security breach as

necessary to address other obligations such as notifying appropriate authorities in accordance with applicable data protection law.

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

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

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

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

16.2.6. Country/Territory Selection

This study will only be conducted in those countries/territories where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, 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 IEC/IRB (where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except

in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

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

17.2.2. Required Prestudy Documentation

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

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

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

- Completed investigator financial disclosure forms from all subinvestigators

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

17.3. Subject Identification, Enrollment, and Screening Logs

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

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification and date of birth (as allowed by local regulations). In cases where the subject is not enrolled 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 documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: subject identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; concomitant medication; drug receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

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

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

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

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

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

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

17.5. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each subject in electronic format. All eCRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. Electronic Data Capture (eDC) will be used for this study. Study site personnel must log into eDC via a secure manner (ie, using a personal password). The individual password must be kept confidential for personal use). The investigator must verify that all data entries in the eCRF are accurate and correct. The study data will be transcribed by study-site personnel from the source documents onto an eCRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

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

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

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

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

17.6. Data Quality Assurance/Quality Control

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

Guidelines for eCRF completion will be provided and reviewed with study-site personnel before the start of the study. The sponsor will review eCRF 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 eCRF and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

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

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

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

17.8. Monitoring

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

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the eCRF with the source documents (eg, hospital/clinic/physician’s office medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the 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 documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

17.9. Study Completion/Termination

17.9.1. Study Completion/End of Study

The study is considered completed approximately 8 years after the first subject is randomized or when the sponsor decides to stop the study. 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. 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 data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator 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, 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 disclose the existence of and the results of clinical studies as required by law.

18. COUNTRY/TERRITORY-SPECIFIC REQUIREMENTS

18.1. Requirements for France

Requirements for France		
Section	**Requirement**	**Amendment Number**
Time and Events Schedule Table 1: Active Monitoring (Arm A) and Daratumumab (Arm B): Active Monitoring/Treatment Phase, End-of-Active Monitoring/End-of-Treatment, Pre-PD Follow-up, and Post-PD Follow-up; 9.7 Safety Evaluations HBV Serology	All subjects will be tested locally for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (Anti-HBs), and hepatitis B core antibody (Anti-HBc) at Screening. Additionally, subjects ongoing in the Treatment Phase (arm B only) with unknown hepatitis B serologic status, HBsAg, Anti-HBs, and Anti-HBc testing is recommended if the subject is still receiving daratumumab (or is within 6 months after the last dose).	Amendment 3/FRA-2 (12 June 2019)
4.2 Exclusion Criteria (1d); 9.2.3 CRAB Criteria-related Laboratory Assessments	Anemia, defined as hemoglobin <10 g/dL or >2 g/dL below lower limit of normal or both; transfusion support or concurrent treatment with erythropoietin stimulating agents is not permitted. The following is not relevant for France: Subjects who have clinically stable anemia attributable to a disease other than multiple myeloma (eg, thalassemia, vitamin B12 deficiency, iron deficiency) may be considered for inclusion after a case by case review by the medical monitor (see Section 9.2.3).	Amendment 2/FRA-1 (14 November 2018)

19. PROTOCOL AMENDMENT HISTORY

This protocol has been amended 5 times globally and 2 times for France (prior to creation of the consolidated protocol amendment [Amendment 5/EEA-1]). The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment 5/EEA-1 (14 August 2023)

Overall Rationale for the Amendment

The overall reason for the amendment is to update the protocol to comply with EU CTR requirements. In addition, country-specific requirements for France from 2 prior country-specific amendments to the protocol have been consolidated within a country/territory-specific appendix.

Applicable Section(s)	Description of Change(s)
Rationale: To conform with EU CTR and indicate which country/territories are affected by each protocol amendment.	
Protocol Amendments	Converted the Protocol version table to a Document History table with a **Country/Territory Affected** column.
Rationale: To conform with EU CTR by describing the Benefit and Risks of this study	
Synopsis; 1.3. Benefit-Risk Assessment	Added Sections 1.3, 1.3.1, and 1.3.2 to describe benefits and risks.
Rationale: To clarify medicinal product designations and conform with the definitions under EU CTR.	
5. Treatment Allocation; 12.1.1. Adverse Event Definitions and Classifications	Revised Section 5 to include a table (Table 6) providing designations of the study medicinal products (IMP, non-IMP/AxMP). Amended text in Section 12.1.1. as follows: (investigational or non-investigational/auxiliary).
Rationale: To conform with EU CTR concerning data privacy.	
16.2.4. Privacy of Personal Data	Amended text on privacy of personal data and included the sponsor's responsibilities in the event of a data security breach, based on EU CTR. Added **pharmacodynamic** to the list of types of exploratory research that are not appropriate for the return of data to subjects/
Rationale: To consolidate country/territory-specific requirements per current sponsor protocol template and in line with EU CTR requirements.	
18. Country/ Territory-specific Requirements	New appendix added.

Applicable Section(s)	Description of Change(s)
Rationale: To align with the current sponsor protocol template requirement to list all changes pertaining to a country or territory in an appendix.	
Throughout the protocol	Added cross-references within the body of the document to country-specific requirements listed in Appendix 18 (Country/Territory-specific Requirements).

Rationale: To align with the current sponsor protocol template.	
Throughout the protocol	Added country/**territory** and countries/**territories**.

Rationale: To update protocol with current sponsor template.	
Protocol Amendments; 19. Protocol Amendment History	New appendix added and the protocol history transferred from the Protocol Amendments section to there.

Amendment 5 (14 January 2021)

The overall reason for the amendment: The overall reason for the amendment is to indicate that only the futility analysis will be performed during the interim analysis. The superiority analysis will not be conducted during the interim analysis to ensure data are sufficiently mature prior to unblinding per feedback from Health Authorities.

Applicable Section(s)	Description of Change(s)
Rationale: Text regarding the interim analysis was updated to remove the superiority analysis to ensure data are sufficiently mature prior to unblinding.	
Synopsis Statistical Methods; 3.1. Overview of Study Design; 11.11. Interim Analysis	Text regarding the interim superiority analysis was removed.
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 4 (22 June 2020)

The overall reason for the amendment: The overall reason for the amendment is to permit home health care and tele-health (conducted via phone or video conference) visits. Home health care and tele-health visits may be implemented per the clinical judgement of the investigator, in consultation with the sponsor, and where feasible and permissible by local policy and regulations.

Applicable Section(s)	Description of Change(s)
Rationale: To specify that home health care and tele-health (conducted via phone or video conference) visits are permitted for subjects with no safety concerns per the clinical judgement of the investigator, in consultation with the sponsor, and where feasible and permissible by local policy and regulations.	
Synopsis; Time and Events Schedule (Tables 1 and 2); 9.1.1. Overview	Text was added to indicate that home health care and tele-health visits are permitted.
3.1. Overview of Study Design	The following text was modified to permit home health care and tele-health visits: For subjects randomized to active monitoring (Arm A), no disease-specific treatment will be given and subjects ~~**will return to the study**~~ **are to be evaluated** every 12 weeks.
9.2. Efficacy Evaluations; 9.3.2. Analytical Procedures; 9.4. Biomarkers	Information was added to indicate that samples for protocol-specified assessments may be collected during home health care visits per the clinical judgement of the investigator. Information was provided regarding sample processing, shipment to the central laboratory, and sample handling.
9.5. Patient-reported Outcomes	Home health care and tele-health visits were added as a means by which PROs can be administered.
9.6. Medical Resource Utilization	Specified that medical encounters include home health care and tele-health visits.
Rationale: To specify assessments that should be performed at the study site or designated facilities.	
Time and Events Schedule (Table 1)	Footnote m was added.
Time and Events Schedule (Table 2)	Footnote g was added.
Rationale: To specify that data from the central laboratory remain the primary source for efficacy assessment and progressive disease identification.	
9.2. Efficacy Evaluations	The following text was added: Data from the central laboratory remain the primary source for efficacy assessment and progressive disease identification.
9.2.2. Assessment of Disease Progression to Multiple Myeloma (Table 7)	Footnote f was added.
Rationale: The definition of the baseline value that will be used in the study analysis was clarified.	
9.2.4. Myeloma Protein Measurements in Serum and Urine	The following text was added: Baseline value is defined as the last value prior to initiating treatment (Arm B) or prior to randomization for active monitoring subjects (Arm A).
Rationale: To eliminate the possibility of inconsistency between the NCI-CTCAE version numbering used in the protocol and the standard grade descriptions included in the protocol.	
12.1.3 Severity Criteria	Eliminated definitions of severity criteria; the definitions are specified in NCI-CTCAE version 4.03.
Rationale: Alignment of text with recent protocol template changes.	

Applicable Section(s)	Description of Change(s)
12.3.1. All Adverse Events	Revised text related to sponsor's responsibility for reporting anticipated events.
Rationale: Text was added for clarity.	
Time and Events Schedule (Table 1)	Footnote n was added to indicate that if the end of active monitoring/end-of-treatment visit is performed due to PD, the PRO assessments do not need to be performed twice if the visits take place on the same day.
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 3/FRA-2 (12 June 2019)

The overall reason for the amendment: The overall reason for the amendment is to incorporate feedback from the Agence nationale de sécurité du medicament et des produits de santé (ANSM), who requested to add further guidance on testing for hepatitis B in subjects with unknown serology status.

Applicable Section(s)	Description of Change(s)
Rationale: The text for hepatitis B serology testing for any subject in the daratumumab arm (Arm B) with unknown hepatitis B serology and monitoring and managing of hepatitis B virus (HBV) reactivation was added in response to a request from ANSM.	
Time and Events Schedule Table 1: Active Monitoring (Arm A) and Daratumumab (Arm B): Active Monitoring/Treatment Phase, End-of-Active Monitoring/End-of-Treatment, Pre-PD Follow-up, and Post-PD Follow-up; 9.7 Safety Evaluations HBV Serology	Added the following information detailing the conduct of HBV serology testing: All subjects will be tested locally for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (Anti-HBs), and hepatitis B core antibody (Anti-HBc) at Screening. Additionally, subjects ongoing in the Treatment Phase (arm B only) ~~who are within 6 months of starting study treatment when Protocol Amendment 3 is implemented will be required to have HBV serology performed locally upon signing the updated ICF.~~ **with unknown hepatitis B serologic status, HBsAg, Anti-HBs, and Anti-HBc testing is recommended if the subject is still receiving daratumumab (or is within 6 months after the last dose)**'.

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

Amendment 3 (25 January 2019)

The overall reason for the amendment: The overall reason for the amendment is in response to identification of a new important risk (hepatitis B virus [HBV] reactivation).

Applicable Section(s)	Description of Change(s)
Rationale: The text for identification of HBV reactivation, testing, and management of subjects with the potential for HBV reactivation was added or modified in response to identification of a new important risk (HBV reactivation).	
Time and Events Schedule – Table 1	Added row for HBV serology, modified text for HBV DNA test, and identified the timepoints at which HBV serology and HBV DNA test would be conducted.
Time and Events Schedule – Table 2	Deleted the row for HBV DNA test as this assessment is now elaborately covered under Table 1 Time and Events Schedule.
Section 4.2 Exclusion Criteria (Criterion # 6.2)	Clarified language to exclude subjects who are seropositive for hepatitis B. Modified the following sentence: Subjects with resolved infection (ie, subjects who are **HBsAg negative but** positive for antibodies to hepatitis B core antigen [Anti-HBc] and/or antibodies to hepatitis B surface antigen [Anti-HBs]) must be screened using real-time polymerase chain reaction (PCR) measurement of hepatitis B virus (HBV) DNA levels.
Section 8.4 Management of Hepatitis B Virus Reactivation	Added a new section for information for the management of Hepatitis B virus reactivation.
Section 9.1.1 Overview	Corrected the maximum blood volume to be collected during screening to approximately 55 mL, thus accounting for HBV serology.
Section 9.7 Safety Evaluations	Mentioned Hepatitis B Screening (for HBsAg, Anti-HBc, and Anti-HBs) and HBV DNA tests under local laboratory testing. Added information detailing the conduct of HBV serology and updated information on HBV DNA tests.
References	Deleted reference # 7 and renumbered and updated the numbering of other references.
Rationale: Minor errors were noted	
Table 1 Time and Events Schedule	Clarified that the frequency for whole blood and stool collection for biomarker assessments during Cycle 1 – Cycle 39 is every 12 months from C1D1 (±1 **month** with disease evaluations) and at Week 24 and at suspected CR (±1 **month** with disease evaluations), respectively.
Table 2 Time and Events Schedule	Corrected the End of Treatment as 30 (±3) days after the last Daratumumab dose instead of 28 (±3) days after the last Daratumumab dose so as to be consistent with Table 1 of the Time and Events Schedule
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 2/FRA-1 (14 November 2018)

The overall reason for the amendment: The overall reason for the amendment is to address specific concerns from the Health Authority in France.

Applicable Section(s)	Description of Change(s)
Rationale: The Health Authority in France recommended modification of the Exclusion Criterion 1.d in order to prevent subjects with anemia (hemoglobin <8g/dL) to be treated with daratumumab, given its known safety profile.	

Applicable Section(s)	Description of Change(s)
4.2 Exclusion Criteria (1d); 9.2.3 CRAB Criteria-related Laboratory Assessments	Removed text describing exceptions to the limitations on allowed hemoglobin levels: Anemia, defined as hemoglobin <10 g/dL or >2 g/dL below lower limit of normal or both; transfusion support or concurrent treatment with erythropoietin stimulating agents is not permitted. ~~Subjects who have clinically stable anemia attributable to a disease other than multiple myeloma (eg, thalassemia, vitamin B12 deficiency, iron deficiency) may be considered for inclusion after a case by case review by the medical monitor (see Section 9.2.3).~~

Amendment 2 (19 September 2018)

The overall reason for the amendment: To implement a central review of screening images in order to confirm subject eligibility. Updates to the inclusion and exclusion criteria and study assessments were also made for clarity.

Applicable Section(s)	Description of Change(s)
Rationale: A central review of screening images is being implemented to confirm subject eligibility.	
Table 1 Active Monitoring (Arm A) and Daratumumab (Arm B): Active Monitoring/ Treatment Phase, End-of-Active Monitoring/End-of-Treatment, Pre-PD Follow-up, and Post-PD Follow-up, Demography/Medical History/benign/post-traumatic pre-existing bone lesions row, footnote d; 3.1 Overview of Study Design; 9.1.2 Screening Phase	Confirmation of eligibility will be based on central disease, hematology, and chemistry laboratory assessments and will also include assessment of ECG, ECOG, medical history, concomitant medications, adverse events, and screening images. Bone lesions assessment at screening will be done by an independent reviewer after subject eligibility is confirmed by the site (no lytic lesions and/or ≤ 1 focal lesion with diameter ≥5 mm present unless proven benign/post-traumatic origin). This central review of screening images will be used to determine the subject's eligibility. For optimal assessment of the screening images by the independent reviewers, additional clinical data, including benign/post-traumatic pre-existing bone lesions, data of recent bone marrow procedures, and general medical history, will be included in the independent review. Details (diagnosis, location, duration) on benign/post-traumatic pre-existing bone lesions that can be seen on the screening images (eg, old fractures) and were also present on previous imaging are to be reported in the CRF (see also Sections 9.1.2 and section 9.2.7). Imaging from routine standard of care assessments can be used only if these meet the minimum requirements as set by the current version of the Image Acquisition Guidelines.

Applicable Section(s)	Description of Change(s)
9.2.7 Assessment of Bone Disease	The presence of bone lesions will be evaluated **both** locally **and centrally.** Imaging studies should be performed per Imaging Acquisition Guidelines provided by the central imaging provider and will be read centrally in addition to the local read ~~(see IRC Charter)~~. **The site will review the screening images first to confirm eligibility of study subject (no lytic lesions and/or ≤1 focal lesion with diameter ≥5 mm present unless proven benign/post-traumatic origin). After initial screening imaging assessment by the site and confirming eligibility by the site,** results of imaging studies (ie, LDCT/CT/PET-CT/MRI) will be uploaded to a central repository and reviewed centrally. **This central review of screening images will be used to determine eligibility of subjects for study participation (see Section 9.1.2).** Presence of focal bone lesions will be evaluated by MRI, in exceptional cases by PET-CT (see below). The presence of lytic bone lesions will be evaluated by LDCT, PET-CT, or CT, including skull, entire vertebral column, pelvis, chest, humeri, femora, and any other bones in which the investigator suspects involvement by disease radiography. **Central review will also be used to assess disease progression by evaluating the occurrence of bone disease**. During the Active Monitoring and Treatment Phases and before disease progression is confirmed, imaging should be performed as indicated in the Time and Events Schedule (Table 1), to document response or progression.
Rationale: The screening window has been increased from 28 days to 35 days to ensure there is enough time to complete all screening assessments within the screening period.	
Table 1; 3.1 Overview of Study Design; 4 Subject Population; 9.1.2 Screening Phase	Screening of subjects will be performed within **35** ~~28~~ days before randomization.
Rationale: To include additional instructions for when a subject's scheduled administration is delayed within 1 cycle.	
Table 1; 6 Dosage and Administration; 6.5.2 Toxicity Management	**All subsequent days within that cycle and** Day 1 of subsequent cycles should be adjusted accordingly to maintain the 28-day cycle duration. **In case of dose delays affecting days other than Day 1, because of reasons other than toxicity, administration should occur within the prespecified window. If an administration does not commence within the prespecified window 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. Every effort should be made to avoid dose delays because of reasons other than toxicity (refer to Section 6.5.3 for details on interrupted or missed doses).**

Applicable Section(s)	Description of Change(s)
Rationale: To clarify the End-of-Active-Monitoring and End-of-Treatment visit timing.	
Table 1, footnote c; 9.1.3 Active Monitoring Phase or Treatment Phase	**For subjects in the Active Monitoring (Arm A), the End-of-Active Monitoring visit is to be performed within 30 days (±3 days) of confirmation of disease progression by investigator.** If disease progression is confirmed in a subject in the daratumumab arm, then the subject will discontinue study treatment, complete the End-of-Treatment Visit **(30 days ±3 days after the last dose of daratumumab, or before starting subsequent therapy, if earlier),** and enter the Follow-up Phase. For subjects in Arm A, the End-of Active Monitoring Visit is to occur after 36 months (±3 days) (from the date of randomization) of active monitoring **if disease progression was not yet confirmed earlier, or if the subject did not meet other criteria for discontinuation prior to 36 months (refer to Section 10.2). In case of discontinuation because of reasons other than disease progression, the End-of-Active Monitoring/End-of-Treatment Visit is to be performed within 30 days (±3 days) after notification that the subject will discontinue Active Monitoring/treatment.** For subjects in the Arm B, the End-of-Treatment Visit is to occur ~~28~~ **30** (±3) days after the last dose of daratumumab.
Rationale: To update biomarker assessment timepoints, add a new microbiome assessment, and clarify the handling samples for FISH analysis.	
Table 1, Biomarker Assessments subsection	Updated the assessment timepoints for cytometry, PBMCs, and plasma, and added a new microbiome (stool sample) assessment. Also, as it's exploratory, moved the cytogenetics by FISH assessment row from its prior location as part of "morphology and additional diagnostic tests" subsection so it is now included as part of the biomarker assessments subsection.
Table 1, footnote k; 9.2.6 Bone Marrow Examination; Table 8 Bone Marrow Testing	Samples for FISH are required to be sent to the central laboratory for further analysis. For sites in China, every effort should be made to collect fresh samples for FISH to be sent to central laboratory. If the subject had a routine bone marrow aspirate performed prior to screening, and no additional aspirate is performed, (formalin-fixed paraffin-embedded (FFPE) samples are the only available sample for FISH) these samples can be analyzed by the local site laboratory.
Synopsis, Other Evaluations; 3.2 Study Design Rationale; 9.4 Biomarkers; References	As a new microbiome (stool sample) has been added to the biomarker assessments, an introduction to the potential role of the gut microbiome in influencing clinical outcomes has been added. Two new reference citations supporting the addition of the microbiome assessment have been added.
Attachment 7: Interpretation of the SEBIA Hydrashift 2/4 Daratumumab IFE Interference test	An attachment describing the new SEBIA Hydrashift 2/4 Daratumumab IFE Interference test has been added to replace the prior Daratumumab Interference Reflex Assay.

Applicable Section(s)	Description of Change(s)
Rationale: To clarify that it is acceptable for the screening FEV1 test to be performed as part of the standard of care as long as it is performed within 35 days before randomization. Also, to clarify that specific postdose medications are to be considered for subjects with higher risk of respiratory complications, as per investigator discretion.	
Table 1, FEV1 test row	Added a statement indicating that it's acceptable to be considered as a screening assessment if performed as part of the standard of care within 35 days before randomization.
6.3.2 Postdose Medication	For subjects with higher risk of respiratory complications (eg, subjects with COPD who have a FEV1 <80% and subjects with asthma), the following postdose medications should be considered, **as per investigator discretion.**
9.7 Safety Evaluations	In the Pulmonary Function Test subsection, deleted the reference to FEV1 test having to be done at screening and added a cross-reference to the Time and Events Schedule (Table 1).
Rationale: Clarification on the timing of PRO collection during screening, and related ECOG wording has been revised to increase operational flexibility.	
Table 1, Patient Reported Outcomes row; 9.1.1 Overview; 9.5 Patient-Reported Outcomes	Added text to clarify that PRO collection should be completed after informed consent forms are signed, but before any tests, procedures, or other consultations that may influence subject perception scheduled for the same day as the PRO assessments are collected.
9.7 Safety Evaluations	Revised ECOG wording to remove text indicating that ECOG assessments should occur prior to any other study procedures planned for the same day.
Rationale: To clarify the approach on lowering pre- and postdose steroid dose in case of an occurrence of an IRR. Also, additional wording was added to emphasize the use of conversion rules when a different steroid than methylprednisolone is used for this purpose.	
6.3.1 Predose Medication	A corticosteroid: methylprednisolone 100 mg PO or IV or equivalent for the first 2 doses and 60 mg for all subsequent doses ~~(in the absence of IRR adverse events in the first 2 doses)~~. **This reduction in steroid dose can only be done in the absence of IRR adverse events in both of the first 2 doses.** Substitutions for methylprednisolone are allowed, **but conversion rules have to be taken into account** (refer to Attachment 5).
6.3.2 Postdose Medication	~~In the absence of~~ **Only when no** IRR adverse events **occurred during** ~~after~~ the first 3 doses, postdose corticosteroids should be administered per investigator discretion.
Rationale: Text added, as per the algorithm, to clarify the process for confirming disease progression to align with the IMWG criteria to confirm disease progression.	
9.2 Efficacy Evaluations	A repeated investigation for confirmation of disease progression does not need to occur within a specified timeframe and could potentially occur on the same date (at a later timepoint). However, the original value meeting disease progression and the confirmation value must be consecutive (ie, no intermediate values that do not meet the definition of disease progression). It is not a requirement to have a repeat investigation if disease progression is based on at least 2 of the laboratory tests of Hb, calcium, renal function and FLC at the same assessment date (eg, when Hb <10 g/dL and creatinine clearance <40 mL/min are present on the same day).

Applicable Section(s)	Description of Change(s)
Table 6 International Uniform Response Criteria Consensus Recommendations, new footnote a	Subjects will continue in the last confirmed response category until there is confirmation of progression or improvement to a higher response status; subjects cannot move to a lower response category.
Table 7 Diagnostic Criteria for Progression to Multiple Myeloma, footnote a	A clarifier regarding collection of a bone marrow aspirate was added to align with the current study conduct: Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen (**per IMWG criteria; however, bone marrow aspirate only is acceptable for this study**); in case of a disparity between the aspirate and the core biopsy, the highest value should be used.
new footnote d	New footnote to state that the determination of progression will be based on modified FLC criteria combining IMWG progression criteria with IMWG FLC ratio criteria.
Rationale: To ensure that sites use PET-CT appropriately as an alternative for subjects whom MRI is contraindicated, as MRI is the preferred method of assessment.	
9.2.7 Assessment of Bone Disease	MRI (spine and pelvis) will be performed to assess focal lesions at Screening and regularly during the study, as indicated in the Time and Events Schedule. Positron emission tomography-computed tomography (PET-CT) may be used as an alternative for those subjects for whom MRI is contraindicated. **However, the medical monitor is to be informed upfront about the reason why MRI is contraindicated.**
Rationale: Minor, miscellaneous edits made throughout the protocol for clarity and consistency.	
3.1 Overview of Study Design; 11.12 Date Monitoring Committee	An additional IDMC Data Review Meeting will be scheduled 6 months (approximately March 2019) after the first IDMC Data Review.
4.1 Inclusion Criteria, Criterion #2.1	Clarified that the diagnosis of SMM (per IMWG criteria) for ≤5 years with measurable disease is to be as of the time of randomization.
Criterion #3.1	Clarified the immunoparesis risk factor definition to align with IMWG criteria in that only IgA, IgM, and IgG should be considered in determination for immunoparesis and that IgD and IgE are not considered in this assessment.
4.2 Exclusion Criteria, Criteria #1.1a to 1.1d	Provided expanded details relating to the requirements that must be met for inclusion in the study as it pertains to the definition of multiple myeloma; specifically, for bone lesions, hypercalcemia, renal insufficiency, and anemia.
Criterion #3.1b; 8 Prestudy and Concomitant Therapy; 8.2 Permitted Therapies	Added reference to "**denosumab", as applicable,** as denosumab is an approved treatment for osteoporosis, and treatment with denosumab is to be handled the same way as bisphosphonates.
New Criterion #3.1e; 8.3 Prohibited Therapies	As the sponsor has received several questions from sites regarding the allowability of certain monoclonal antibodies and immunomodulators, a new exclusion criterion has been added: **Ongoing treatment with other monoclonal antibodies (eg, infliximab, rituximab), immunomodulators (eg, abatacept, methotrexate, azathioprine, cyclosporine) or other treatments that are likely to interfere with the study procedures or results**

Applicable Section(s)	Description of Change(s)
Criterion #7;	To avoid unnecessary screening, the criterion wording was clarified to provide a more specific exclusion of subjects with active system disease, as follows: Medical or psychiatric condition or disease (eg, active systemic disease **[including presence of auto-antibodies]**, uncontrolled diabetes) 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.
Criteria #4, #9.1, #13	Very minor updates added for clarity and increased understanding of requirements.
9.1.1 Overview	Updates have been made to the blood volume paragraph to reflect the additional blood collection being implement with this protocol amendment.
9.2.2 Assessment of Disease Progression to Multiple Myeloma	Updated the subsection heading for specificity to: Assessment of Progression to Multiple Myeloma **(diagnostic progression).**
9.2.2 Assessment of Disease Progression to Multiple Myeloma	Added statement that biochemical progression is to be considered as an important risk factor to evolve to diagnostic progression and those subjects should be monitored closely.
9.2.3 CRAB Criteria-related Laboratory Assessments	Text updated to allow consideration of subjects who, at screening, have clinically stable hypercalcemia, renal insufficiency, or anemia that has existed for several years and did not show any deterioration during the prior year, on a case-by-case basis after discussion with the medical monitor.
9.7 Safety Evaluations	Updated the HBV DNA Test wording to clarify that the assessment is based on local laboratory assessments
10.2 Discontinuation of Active Monitoring (Arm A) or Study Treatment (Arm B)	As discontinuation in IWRS will only happen after the sponsor's confirmation of PD, text has been revised as follows: Before subjects discontinue active monitoring (Arm A) or study treatment (Arm B) due to disease progression, sites will document disease progression by completing a disease progression form ~~or by contacting the IWRS~~ as soon as possible and within 48 hours of disease progression assessment.
12.3.2 Serious Adverse Events	Updated the definition of expected progression of disease to align with the current protocol template wording.
12.3.3 Pregnancy	In alignment with other protocols across the daratumumab compound, provided details on the requirements if a subject becomes pregnant during the study.
Rationale: Minor errors were noted.	
3.2 Study Design Rationale	Removed erroneous language specifying that certain high-risk cytogenetic modifications will be used for stratification in the study.
4.2 Exclusion Criteria, Criterion #6.1	Updated erroneous numbering of Criterion #6.1, which had previously been numbered as #6.b.1 when updated at Amendment 1. The content remains unchanged.
9.7 Safety Evaluations	Deleted the erroneous statement indicating that the central laboratory results will be recorded in the eCRF and clarified that local laboratory data must be entered into the eCRF
Attachment 2: Modified Diet in Renal Disease Formula	Updated an error in the formula for creatinine in µmol/L.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 1 (30 January 2018)

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 overall reason for the amendment is to address feedback from Health Authorities from the original protocol submission.

Applicable Section(s)	Description of Change(s)
Rationale: To clarify that daratumumab administered subcutaneously contains rHuPH20, which is considered an active agent by some Health Authorities.	
Synopsis, Dosage and Administration; 3.1. Overview of Study Design; 6. Dosage and Administration; 6.2. Treatment Schedule and Administration	Added rHuPH20 (2000 U/mL) to daratumumab SC description (daratumumab 1800 mg + rHuPH20 [2000 U/mL]).
Rationale: To clarify the management of HBV infection to align with other daratumumab protocols.	
Table 1; Table 2; 4.2 Exclusion Criteria, Criterion #6.b.1; 9.7. Safety Evaluations – HBV DNA Tests	Added text to clarify which subjects need to be tested and/or followed for HBV infection. Timepoints for HBV DNA tests for subjects, if necessary, added at Screening, every 12 weeks during the Treatment Phase, and at the End-of-Treatment Phase.
Rationale: To clarify duration for Active Monitoring (Arm A) and Treatment Phase (Arm B).	
Synopsis, Dosage and Administration; Table 1; 3.1. Overview of Study Design; 6.2 Treatment Schedule and Administration; 10.1. Completion	Added text to clarify that subjects could complete 39 cycles or up to 36 months of treatment, whichever occurs first. Added text to clarify Arm A disease evaluations were every 12 weeks. Added text to clarify that 36 months of adverse event and concomitant medication monitoring should occur for Arm A.
Rationale: To update the data available for infusion-related reactions from the current Investigator's Brochure.	
3.1. Overview of Study Design	Updated the date of the data available to reflect the current Investigator's Brochure (Edition 14, October 2017).
Rationale: Daratumumab SC formulation includes recombinant human hyaluronidase (rHuPH20).	
4.2. Exclusion Criteria, Criterion #9.1.	Added hyaluronidase to list of possible items that a patient might be intolerant to.
Rationale: To clarify if both treatment arms needed to have repeat laboratory studies in cases where screening values were obtained >14 days from Cycle 1 Day 1 (C1D1).	
Table 1; 9.2.4. Myeloma Protein Measurements in Serum and Urine	In the event that central laboratory screening values are ≤14 days from C1D1, subjects randomized to the active monitoring arm (Arm A) would not be required to return to the clinic for their C1D1 visit.

Rationale: Change the time of the baseline PRO assessment to prevent mixed modes data collection (telephone and in-person PRO assessments) at baseline and to prevent missing data in Arm A, if scheduled at the C1D1 visit.	
Table 1; 9.5. Patient-reported Outcomes	Updated the baseline PRO assessment for all subjects to occur in-person during the Screening visit and not at C1D1. A time point at screening was added and it was noted that it will serve as the baseline score. It was clarified that the PRO assessments will be collected during Active Monitoring as well as during study treatment.
Table 1	Added text to clarify that the PRO assessments during Active Monitoring/study treatment should be performed with disease evaluations and administered before any other study procedures for that visit.
Rationale: Clarification made for the sake of completeness and clarity.	
9.1.1. Overview	Added statement that reason for not completing PRO assessments is now to be documented.
Rationale: To clarify how dose delays resulting from toxicity management should be handled and to clarify how to handle subjects with missed doses.	
6.5.2. Toxicity Management; Table 5	Added guidance for dose delays affecting Day 1 of a cycle and dose delays affecting days other than Day 1.
6.5.3. Interruption or Missed Doses	Specified that subjects missing ≥3 consecutive planned doses of daratumumab for reasons other than daratumumab-related toxicity should be withdrawn from treatment.
Rationale: To clarify when use of a local laboratory is acceptable for efficacy and safety evaluations.	
9.2. Efficacy Evaluations	Addition of statement clarifying that if central laboratory evaluations fail, the test should be performed again at the central laboratory; local laboratory results should only be used in exceptional cases after discussion with the medical monitor.
9.7. Safety Evaluations – Central Laboratory Testing	Addition of statement clarifying that if central laboratory tests fail, it will be acceptable to substitute local laboratory results for safety monitoring purposes
Rationale: To ensure that disease progression to multiple myeloma is not over-represented.	
3.1. Overview of Study Design; 9.2.2. Assessment of Disease Progression to Multiple Myeloma	Changed progression determination from IRC adjudication to IMWG FLC progression criteria combined with IMWG FLC ratio criteria.
Rationale: Clarification made to prevent false positive diagnosis of progression to multiple myeloma.	
9.2.3. CRAB Criteria-related Laboratory Assessments, Serum Calcium Corrected for Albumin	Added text to determine reason for elevation in calcium.
Creatinine Clearance	Added text to determine reason for decrease in glomerular filtration rates.
Hemoglobin	Added text to clarify the diagnosis of anemia before progression to MM can be diagnosed.

Rationale: To clarify the timing of bone lesion assessments.	
Table 1; 9.2.7. Assessment of Bone Disease Lytic bone lesions (LDCT, PET-CT or CT)	Clarified that bone lesion assessments will be performed at Screening and every 12 months until PD. Deleted Figure 4, Schedule for Lytic Lesion Assessments. Added text to clarify that MRI should be performed per Imaging Acquisition Guidelines provided by the central imaging provider.
Disease Progression	Added information regarding reasons for an increased PET signal other than markers of disease progression has been added.
Rationale: To clarify laboratory assessments for UPEP.	
Table 1; 9.2.4. Myeloma Protein Measurements in Serum and Urine	Added text to clarify level of measurable disease and clarified when UPEP analysis is performed.
Rationale: To clarify study completion for Arm A.	
10.1 Completion	Added a definition for study completer for Arm A.
Rationale: Added to address a Health Authority request.	
3.2. Study Design Rationale	Added summary of benefits and risks.
4.1. Inclusion Criteria, Criterion #2.1.	Clarified the basis for diagnosis of SMM by adding ‘per IMWG criteria’.
4.1. Inclusion Criteria, Criterion #3.1.	Added clarification of ‘clonal’ to BMPCs.
11.3.1 Primary Endpoint	Added text to clarify stratification by number of risk factors associated with progression to MM (<3 vs ≥3).
Table 1; 9.1.4. Follow-up Phase	Survival will be followed until the end of the study and at a frequency of at least every 12 weeks until PD. After PD, survival is to be followed at least every 6 months.
8.1. Recommended Therapies	Prophylaxis for pneumocystis carini/jirovecci pneumonia, according to institutional guidelines, should be considered for subjects in Arm B (daratumumab).
Rationale: To add an antihistamine that may be used for daratumumab predose medication.	
Attachment 4 Antihistamine Medications	Added chlorphenamine as an antihistamine that may be used for daratumumab predose medication.
Rationale: Alignment of text with recent protocol template changes.	
10.3. Withdrawal from the Study (Arm A and Arm B)	Revised text related to subjects withdrawing from the study and added text regarding public record searches.
12.3.1. All Adverse Events	Added text related to sponsor's responsibility for reporting anticipated events and about reporting a SUSAR.
12.3.3 Pregnancy	Deleted text related to the unknown effect of study drug on sperm.
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	Changed the time for submitting study results for publication from 'within 12 months of the availability of the final data (tables, listings, graphs)…' to '18 months after study end date…'. Changed authorship guidelines from Uniform Requirements for Manuscripts Submitted to Biomedical Journals to ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals.
Rationale: For clarity and consistency, minor grammatical and formatting changes were made throughout the protocol.	
Synopsis, Other Evaluations; Table 1 and Table 2; 3.1. Overview of Study Design; 6.2. Treatment Schedule and Administration; 9.7. Safety Evaluations; 11.10. Safety Analysis	Height and weight assessments updated to be performed at screening only. In some sections, this meant that text describing vital signs assessments was deleted.
9.2.6. Bone Marrow Examination, Table 8	Added text to clarify bone marrow tissue for MRD testing when taken from archive tissue.
9.2.8 Best Response to First-line Multiple Myeloma Treatment	Updated text to reflect using local lab evaluations to assess best response to first-line MM.
4. Subject Population	Added text to clarify randomized subjects are considered enrolled subjects.
4.1. Inclusion Criteria, Criterion #7.1.; Attachment 11	Added definition of women of childbearing potential
Table 1; 6. Dosage and Administration	Added text to clarify minimal interval of days between daratumumab doses.
Synopsis; 6. Dosage and Administration	Added text to clarify that all doses should be administered at outpatient visits.
Attachment 2 Modified Diet in Renal Disease Formula	Updated the modified diet in renal disease formulas.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

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Attachment 1: ECOG Performance Status Scale

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

Reference: Oken 1982[27]

Attachment 2: Modified Diet in Renal Disease Formula

For creatinine in **mg/dL**, the estimated glomerular filtration rate (e-GFR) for the modified diet in renal disease (MDRD) formulas is:

e-GFR (MDRD) mL/min per 1.73 m^2= 175 × [serum creatinine mg/dL]$^{-1.154}$ × [age]$^{-0.203}$ × [1.212 if black] × [0.742 if female]

For creatinine in **µmol/L**, the estimated glomerular filtration rate (e-GFR) for the modified diet in renal disease (MDRD) formulas is:

e-GFR (MDRD) mL/min per 1.73 m^2= 175 × [serum creatinine µmol/L/88.4]$^{-1.154}$ × [age]$^{-0.203}$ × [1.212 if black] × [0.742 if female]

(Levey 2006[19])

Attachment 3: Asthma Guidelines

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	
	SABA use for symptom control (not prevention of EIB)	≤ 2 days/week			≤ 2 days/week but not daily		>2 days/ week but not daily, and not more than 1x	Daily			Several time per day		
	Interference with normal activity	None			Minor limitation			Some limitation			Extremely limited		
Normal FEV_1/FVC: 8-19 yr 85% 20-39 yr 80% 40-59 yr 75% 60-80 yr 70%	Lung function	N/A	Normal FEV1 between exacerbations	Normal FEV1 between exacerbations	N/A			N/A			N/A		
	FEV1		> 80%	> 80%		> 80%	> 80%		60-80%	60-80%		< 60%	< 60%
	FEV1/FVC		> 85%	Normal		> 80%	Normal		75-80%	Reduced 5%		< 75%	Reduced
Risk	Exacerbations requiring oral systemic corticosteroids	0-1/year			≥ 2 exacerbations in 6 months requiring oral steroids or >4 wheezing episodes/1 year lasting >1 day and risk factors for persistent asthma	≥ 2/year Relative annual risk may be related to FEV_1.	≥ 2/year Relative annual risk may be related to FEV_1.	≥ 2 exacerbations in 6 months requiring oral steroids or >4 wheezing episodes/1 year lasting >1 day and risk factors for persistent asthma	≥ 2/year Relative annual risk may be related to FEV_1.	≥ 2/year Relative annual risk may be related to FEV_1.	≥ 2 exacerbations in 6 months requiring oral steroids or >4 wheezing episodes/1 year lasting >1 day and risk factors for persistent asthma	≥ 2/year Relative annual risk may be related to FEV_1.	≥ 2/year Relative annual risk may be related to FEV_1.
		Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category.											
Recommended Step for Initiating Treatment		Step 1			Step 2			Step 3 and consider short course of oral steroids	Step 3: medium dose ICS and consider short course of	Step 3 and consider short course of oral steroids	Step 3 and consider short course of oral steroids	Step 3: medium dose ICS OR Step 4 and consider short course of oral steroids	Step 4 or 5 and consider short course of oral steroids
		In 2-6 weeks, evaluate level of asthma control that is achieved. 0-4 years: If no clear benefit is observed in 4-6 weeks, stop treatment and consider alternate diagnosis or adjusting therapy. 5-11 and 12+ years: adjust therapy accordingly.											

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

Attachment 4: Antihistamine Medications

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

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

* The IV use of promethazine should be avoided.

Attachment 5: Conversion Table for Glucocorticosteroid Dose

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

Attachment 6: 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 1998[2]

Attachment 7: Interpretation of the SEBIA Hydrashift 2/4 Daratumumab IFE Interference test

Background: Clinical response assessment in myeloma relies on serum protein electrophoresis (SPEP) and immunofixation electrophoresis (IFE). As daratumumab is a monoclonal IgG kappa antibody, the SPEP and IFE can be positive for daratumumab at the serum levels anticipated during this protocol.

Implementation: To mitigate this interference, the sponsor will use the SEBIA Hydrashift 2/4 Daratumumab IFE Interference test to distinguish a positive SPEP/IFE due to the presence of daratumumab versus the presence of the underlying (endogenous) monoclonal protein. The SEBIA Hydrashift 2/4 Daratumumab IFE Interference test will be sent automatically to the central laboratory if a subject with IgG kappa multiple myeloma has an SPEP at or below 0.2 g/dL on 2 or more consecutive cycles. In addition, the SEBIA Hydrashift 2/4 Daratumumab IFE Interference test will be sent automatically to the central laboratory if a subject has an SPEP of zero, but persistently positive IFE for IgG kappa on 2 or more occasions.

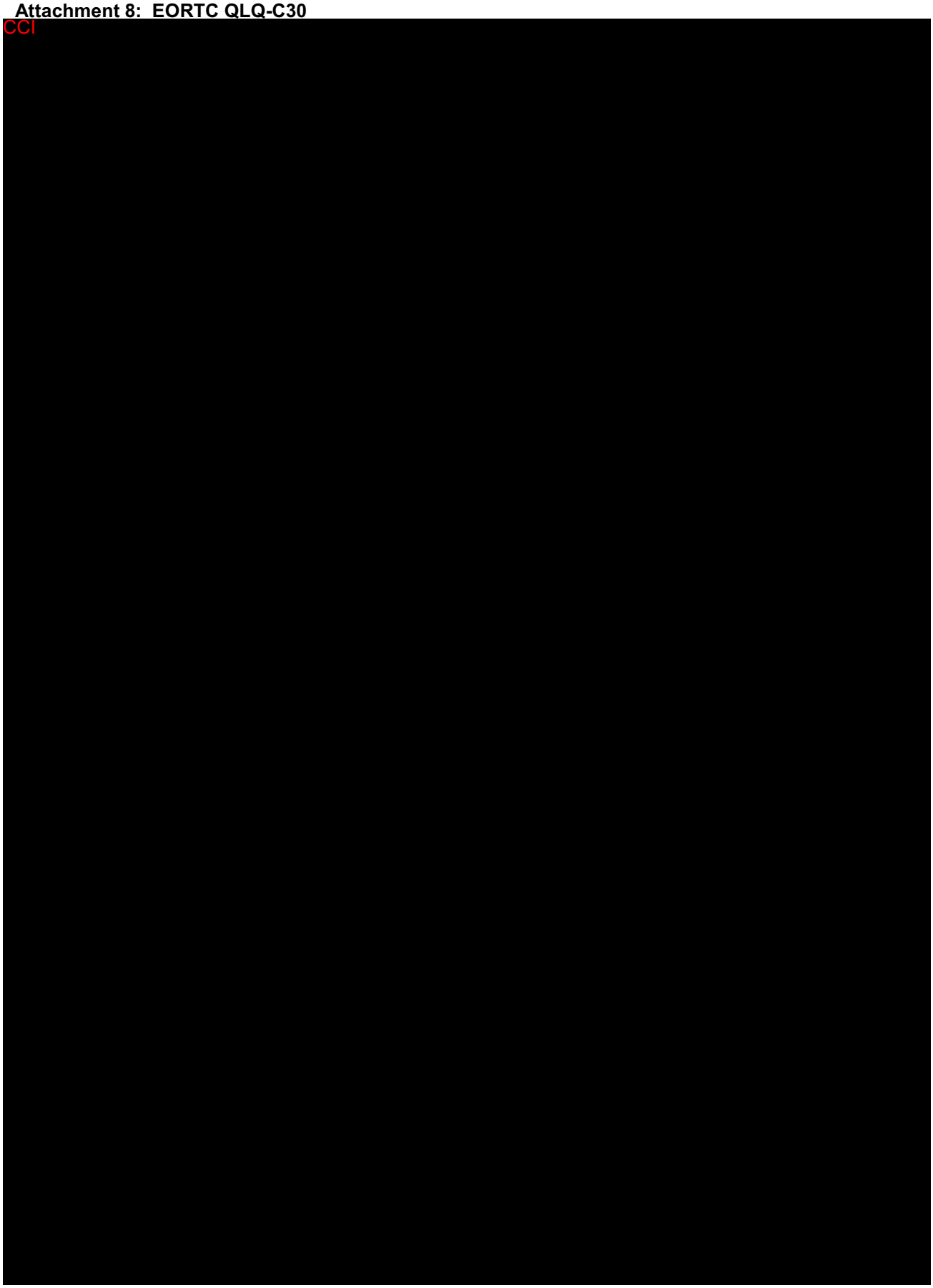
Interpretation of results:
The results will be available to the investigator via the central laboratory interface and will be reported as follows:

DARAHydra Impress1: result defined as "DARA detected", "DARA not detected", OR "DARA indeterminate"
DARAHydra Impress2: result defined as "M-protein not detected" OR the specific protein detected (i.e. "IgG,k" or "IgA")
DARAHydra Impress3: result defined as "M-protein not detected" OR the specific protein detected (i.e. "IgG,k" or "IgA")

– If Impress1 result is "DARA detected" and Impress2 and 3 results are "M-protein not detected", the patient may be in complete response (CR) if the other criteria for CR (including negative bone marrow aspirate/biopsy) are achieved.
– If Impress1 result is "DARA not detected" or "DARA indeterminate", the patient is still positive for underlying (endogenous) monoclonal protein and Impress2 and 3 can inform as to the type of endogenous protein still present. Therefore, this patient is not in a complete response (CR), because the CR response criteria requires a negative SPEP and serum IFE.
– If Impress1 result is "DARA detected" but there is also protein present and reported by Impress2 or 3, the patient is still positive for underlying (endogenous) monoclonal protein and Impress2 and 3 can inform as to the type of endogenous protein still present. Therefore, this patient is not in a complete response (CR), because the CR response criteria requires a negative SPEP and serum IFE.

Attachment 8: EORTC QLQ-C30

CCI



CCI

[redacted]

Attachment 9: EORTC QLQ-MY20

CCI

[redacted]

CCI

[redacted]

Attachment 10: EQ-5D-5L

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

Attachment 11: Women of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women Not of Childbearing Potential:

Premenarchal:
A premenarchal state is one in which menarche has not yet occurred.

Postmenopausal:
A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy, however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

Permanently sterile:
Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy.

Note: If the childbearing potential changes after start of the study (eg, a premenarchal woman experiences menarche) or the risk of pregnancy changes (eg, a woman who is not heterosexually active becomes active), a woman must begin a highly effective method of contraception, as described throughout the inclusion criteria. If reproductive status is questionable, additional evaluation should be considered.

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 intervention, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

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 study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

Signature

User	Date	Reason
PPD	24-Sep-2024 11:13:45 (GMT)	Document Approval