Janssen Research & Development *

Clinical Protocol

A Randomized Phase 3 Study to Evaluate the Efficacy and Safety of Daratumumab in Combination with Cyclophosphamide, Bortezomib and Dexamethasone (CyBorD) Compared With CyBorD Alone in Newly Diagnosed Systemic AL Amyloidosis

Protocol 54767414AMY3001; Phase 3
AMENDMENT 3

JNJ-54767414 daratumumab

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This compound is approved for marketing in multiple myeloma.

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

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TABLE OF CONTENTS

TABLE OF CONTENTS **2**

LIST OF IN-TEXT TABLES AND FIGURES **6**

PROTOCOL AMENDMENTS **7**

SYNOPSIS **22**

TIME AND EVENTS SCHEDULES **26**

ABBREVIATIONS **33**

1. INTRODUCTION **35**
1.1. Amyloidosis 35
1.1.1. Bortezomib-based Treatment Options for Amyloidosis 36
1.1.2. Background on Bortezomib in Combination with Cyclophosphamide and Dexamethasone (CyBorD regimen) 36
1.2. Daratumumab 37
1.2.1. Daratumumab in AL Amyloidosis 38
1.3. Overall Rationale for the Study 39

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESIS **40**
2.1. Objectives 40
2.2. Endpoints 41
2.3. Hypothesis 43

3. STUDY DESIGN AND RATIONALE **43**
3.1. Overview of Study Design 43
3.2. Study Design Rationale 45
3.2.1. Rationale for Dose and Subcutaneous Administration 45
3.2.2. Rationale for Study Treatment Regimen 47
3.2.3. Rationale for Run-in Phase 48
3.2.4. Rationale for Biomarker Collection 49
3.2.5. Rationale for Patient-Reported Outcome Measures 49

4. SUBJECT POPULATION **49**
4.1. Inclusion Criteria 50
4.2. Exclusion Criteria 52

5. TREATMENT ALLOCATION AND BLINDING **55**

6. DOSAGE AND ADMINISTRATION **55**
6.1. Treatment Cycles 55
6.2. Daratumumab 56
6.2.1. Treatment Schedule and Administration 56
6.2.2. Dose Delays and Dose Modification 57
6.2.2.1. Dose Modification 57
6.2.2.2. Toxicity Management 57
6.2.2.3. Interruption or Missed Doses 58
6.2.3. Guidelines for Prevention and Management of Daratumumab Infusion-related Reactions 58
6.2.3.1. Preinfusion Medication 58
6.2.3.2. Postinfusion Medication 58
6.2.3.3. Management of Infusion-Related Reactions 59
6.2.3.3.1. Infusion-Related Reactions of Grade 1 or Grade 2 60
6.2.3.3.2. Infusion-Related Reactions of Grade 3 or Higher 60

6.2.3.3.3. Recurrent Infusion-Related Reactions 60
6.2.4. Guidelines for Management of Daratumumab Administration-related Reactions 60
6.3. Cyclophosphamide 61
6.3.1. Dose Adjustments for Cyclophosphamide 61
6.3.2. Urinary Tract and Renal Toxicity 62
6.4. Bortezomib 62
6.4.1. Dose Adjustments of Bortezomib 62
6.4.2. Neurologic Toxicity 63
6.4.3. Other Grade 3 or 4 Adverse Events 63
6.5. Dexamethasone 63

7. TREATMENT COMPLIANCE 64

8. PRESTUDY AND CONCOMITANT THERAPY 65
8.1. Recommended Therapies 65
8.1.1. Prophylaxis for *Pneumocystis carinii (jirovicii)* 65
8.1.2. Prophylaxis for Herpes Zoster Reactivation 65
8.1.3. Prophylaxis or Management of Hemorrhagic Cystitis 65
8.1.4. Management of Hepatitis B Virus Reactivation 65
8.1.5. Management of Peripheral Edema, Pulmonary Edema, Congestive Heart Failure. 66
8.2. Permitted Therapies 66
8.3. Prohibited Therapies During the First 6 Cycles of Therapy 66

9. STUDY EVALUATIONS 67
9.1. Study Procedures 67
9.1.1. Overview 67
9.1.1.1. Bone Marrow Biopsy/Aspirate Considerations 67
9.1.2. Screening Phase 68
9.1.2.1. Histopathological Diagnosis of Amyloidosis 68
9.1.2.2. Factor X Deficiency 69
9.1.3. Treatment Phase 69
9.1.3.1. Safety Run-In 69
9.1.3.2. Randomized Study 70
9.1.3.3. Autologous Stem Cell Collection Considerations 70
9.1.4. End-of-Treatment 71
9.1.4.1. Subsequent Therapy 71
9.1.4.2. End-of-Treatment Visits 72
9.1.5. Post-Treatment Observation Phase and Long-Term Follow-up 72
9.2. Efficacy Evaluations 72
9.2.1. Hematologic Response Categories 73
9.2.2. Monoclonal Protein (M-protein) Measurements in Serum and Urine 74
9.2.3. Determination of Organ Response 75
9.2.4. Bone Marrow Assessment 76
9.3. Pharmacokinetics and Immunogenicity 76
9.3.1. Evaluations 76
9.3.2. Analytical Procedures 76
9.3.3. Pharmacokinetic Parameters 77
9.3.4. Immunogenicity Assessments 77
9.4. Pharmacokinetic/Pharmacodynamic Evaluations 77
9.5. Biomarkers 78
9.6. Sample Collection and Handling 78
9.7. Medical Resource Utilization 78
9.8. Patient-Reported Outcomes 79
9.9. Safety Evaluations 80

10. SUBJECT COMPLETION/DISCONTINUATION OF STUDY TREATMENT/ WITHDRAWAL FROM THE STUDY 84
10.1. Completion 84

10.2. Discontinuation of Study Treatment/Withdrawal from the Study 84

11. STATISTICAL METHODS 85
11.1. Subject Information 86
11.2. Sample Size Determination 86
11.3. Efficacy Analyses 86
11.4. Pharmacokinetic Analyses 87
11.5. Immunogenicity Analyses 87
11.6. Pharmacokinetic/Pharmacodynamic Analyses 87
11.7. Biomarker Analyses 88
11.8. Patient-Reported Outcomes 88
11.9. Safety Analyses 88
11.10. Interim Analysis 89

12. ADVERSE EVENT REPORTING 89
12.1. Definitions 90
12.1.1. Adverse Event Definitions and Classifications 90
12.1.2. Attribution Definitions 91
12.1.3. Severity Criteria 91
12.2. Special Reporting Situations 92
12.3. Procedures 92
12.3.1. All Adverse Events 92
12.3.2. Serious Adverse Events 94
12.3.3. Pregnancy 95
12.4. Contacting Sponsor Regarding Safety 95

13. PRODUCT QUALITY COMPLAINT HANDLING 95
13.1. Procedures 95
13.2. Contacting Sponsor Regarding Product Quality 95

14. STUDY DRUG INFORMATION 96
14.1. Physical Description of Study Drug(s) 96
14.2. Packaging 96
14.3. Labeling 96
14.4. Preparation, Handling, and Storage 96
14.5. Bortezomib, Cyclophosphamide, and Dexamethasone 96
14.6. Drug Accountability 96

15. STUDY-SPECIFIC MATERIALS 97

16. ETHICAL ASPECTS 98
16.1. Study-Specific Design Considerations 98
16.2. Regulatory Ethics Compliance 99
16.2.1. Investigator Responsibilities 99
16.2.2. Independent Ethics Committee or Institutional Review Board 99
16.2.3. Informed Consent 100
16.2.4. Privacy of Personal Data 101
16.2.5. Long-Term Retention of Samples for Additional Future Research 102
16.2.6. Country Selection 102

17. ADMINISTRATIVE REQUIREMENTS 102
17.1. Protocol Amendments 102
17.2. Regulatory Documentation 103
17.2.1. Regulatory Approval/Notification 103
17.2.2. Required Prestudy Documentation 103
17.3. Subject Identification, Enrollment, and Screening Logs 104
17.4. Source Documentation 104
17.5. Case Report Form Completion 105
17.6. Data Quality Assurance/Quality Control 106

17.7. Record Retention 106
17.8. Monitoring 107
17.9. Study Completion/Termination 107
17.9.1. Study Completion/End of Study 107
17.9.2. Study Termination 107
17.10. On-Site Audits 108
17.11. Use of Information and Publication 108

REFERENCES 110

ATTACHMENT 1: ECOG PERFORMANCE STATUS SCALE 113

ATTACHMENT 2: DEFINITION OF ORGAN INVOLVEMENT BASED ON AMYLOIDOSIS CONSENSUS CRITERIA 114

ATTACHMENT 3: NYHA CLASSIFICATION 115

ATTACHMENT 4: CONVERSION TABLE FOR GLUCOCORTICOID DOSE 116

ATTACHMENT 5: CALCULATED CREATININE CLEARANCE AND ESTIMATED GLOMERULAR FILTRATION RATE 117

ATTACHMENT 6: GUIDELINE FOR ASTHMA ELIGIBILITY CRITERIA 118

ATTACHMENT 7: BODY SURFACE AREA NOMOGRAM 119

ATTACHMENT 8: EORTC QLQ-C30 120

ATTACHMENT 9: SUPPLEMENTAL ITEMS TO EORTC QLQ-C30 (FROM EORTC ITEM BANK) 122

ATTACHMENT 10: EQ-5D-5L 123

ATTACHMENT 11: SF-36V2 126

ATTACHMENT 12: ANTICIPATED EVENTS 132

ATTACHMENT 13: PROTOCOL 54767414AMY3001 STUDY RISK/BENEFIT ASSESSMENT 134

ATTACHMENT 14: MAYO CLINICAL CARDIAC STAGING SYSTEM 148

ATTACHMENT 15: LIST OF CYP3A INDUCERS AND INHIBITORS 149

INVESTIGATOR AGREEMENT 150

LIST OF IN-TEXT TABLES AND FIGURES

TABLES

Table 1: Time and Events Schedule 26
Table 2: Time and Events Schedule: Study Treatment Dosing 31
Table 3: Efficacy of Daratumumab in AL Amyloidosis and Multiple Myeloma with AL Amyloidosis 39
Table 4: Daratumumab-Related Toxicity Management 57
Table 5: Cyclophosphamide Dose Adjustment 61
Table 6: Recommended Dose Modification for Bortezomib-related Neuropathic Pain or Peripheral Sensory or Motor Neuropathy 63
Table 7: Dexamethasone Dose Modification Based on Toxicity 64
Table 8: Recommendations for Subsequent Therapy After Cycle 6 72
Table 9: International Amyloidosis Consensus Criteria 73
Table 10: Organ Response and Progression Criteria[a] 75

FIGURES

Figure 1: Schematic Overview of the Safety Run-In 44
Figure 2: Schematic Overview of the Randomized Study 45
Figure 3: Daratumumab Dosing Schedule 56

PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	6 April 2017
Amendment 1	03 April 2018
Amendment 2	23 January 2019
Amendment 3	10 October 2019

Amendments below are listed beginning with the most recent amendment.

Amendment 3 (10 October 2019)

The overall reason for the amendment: The overall reason for the amendment is to clarify that an aggregated (hematologic and organ) progression-free survival (PFS) for this study is now split into a specific hematologic progression-free survival (HemPFS) which is moved to an exploratory objective, while retaining organ-specific response rate and duration of response as secondary objectives; add a complete hematologic response (CHR) analysis at 6 months; revise Severity Criteria for adverse events to align with National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.03 severity definitions; update anticipated events in Attachment 12; and provide other revisions, updates, and clarifications based on increased knowledge since the start of protocol development.

Applicable Section(s)	Description of Change(s)
Rationale: Progression in amyloidosis can occur by both hematologic progression and organ progression, and there are currently no publications available to assess for clinical meaningfulness of aggregated (hematologic and organ) PFS as an endpoint in treatment of AL amyloidosis. A 6-month landmark analysis of organ-specific response and progression will be reported. The PFS endpoint in this study will be specific for hematologic parameters and renamed HemPFS.	
Synopsis (OBJECTIVES AND HYPOTHESIS); 2.1 Objectives	PFS was removed from the list of secondary objectives and HemPFS was added as an exploratory objective.
Synopsis (STATISTICAL METHODS); 2.1 Objectives (Secondary Objectives); 9.5 Biomarkers; 11.3 Efficacy Analyses	"PFS" was revised to "HemPFS".
2.2 Endpoints (Secondary Endpoints)	The definition of PFS was deleted.
2.2 Endpoints (Exploratory Endpoints)	The definition of HemPFS was added.
Rationale: To add a CHR analysis at 6 months.	
Synopsis (STATISTICAL METHODS); 11.3 Efficacy Analyses	Specified that analysis of CHR rate at 6 months will be performed similarly to the primary endpoint CHR rate.
2.2 Endpoints (Secondary Endpoints)	The definition of CHR rate at 6 months was added.

Applicable Section(s)	Description of Change(s)
Rationale: To revise Severity Criteria for adverse events to align with NCI-CTCAE v4.03 severity definitions.	
12.1.3 Severity Criteria	Definitions for Grade 1 through Grade 4 severity criteria were revised, and definitions were added accordingly for activities of daily living (ADL).
Rationale: An anticipated event is an AE (serious or non-serious) that commonly occurs as a consequence of the underlying disease or condition under investigation (disease-related) or background regimen. Some events that are already listed as adverse drug reactions for daratumumab can be deleted.	
Attachment 12 (Anticipated Events)	Anemia, neutropenia, and thrombocytopenia were deleted from the anticipated events list. The review and reporting requirements for anticipated events were clarified. Revised "Anticipated Event Review Committee" (ARC) to "Safety Assessment Committee" (SAC).
Rationale: Discordance in organ response within an individual subject can occur. Subjects with involvement in more than 1 organ may have discordance in organ response or progression. At baseline, a subject may have advanced organ damage in one organ that will progress (ie, the subject cannot overcome the existing level of damage). However, the same subject can have improvement in another organ.	
Synopsis (STATISTICAL METHODS); 11.3 Efficacy Analyses	Specified that organ response/progression analysis will be performed separately for each organ involved at baseline, specifically for heart, kidney, and liver, and that descriptive statistics will be provided to summarize organ response/progression at 6 months, time to organ response, and time to organ progression.
2.2 Endpoints (Secondary Endpoints)	Revised the definition of time to organ response to individually list time to cardiac response, time to renal response, and time to liver response. Added a definition for time to cardiac progression, time to renal progression, and time to liver progression. Clarified that organ response rate (OrRR) for kidney, heart, liver is defined as the proportion of baseline organ involved subjects who achieve **confirmed** organ response in each corresponding organ.
11.3 Efficacy Analyses	Specified that a transient increase in NT-proBNP, troponin T, 24-hour proteinuria, and alkaline phosphatase, or a transient decrease in eGFR meeting organ progression criteria are not considered for organ progression if it persisted less than 6 months, and levels returned to baseline level or better.
Rationale: Patients with AL amyloidosis often experience an intolerance to or adverse events with steroid treatment. Infusion-related reactions (IRRs) typically occur during initial treatment cycles of daratumumab.	
6.2.3.2 Postinfusion Medication	Revised the instructions for receiving postinfusion corticosteroids.
Rationale: During the conduct of this study, it became apparent that the Comenzo 2012[7] guidelines require clarifications. Based on a deeper understanding of disease biology and outcomes (Manwani 2018, Muchtar 2019)[27,31] as well as the impact of daratumumab on serum free light chains (Comenzo 2019)[6] that affect the definition of a complete hematologic response, CCI [redacted]	
Table 9 (International Amyloidosis Consensus Criteria)	Clarified that for progression, **involved** light chain must double. A footnote was added that if iFLC<ULN and serum and urine IFE are negative, then neither a normal uFLC level nor a normal FLC ratio are required for complete response (CR).

Applicable Section(s)	Description of Change(s)
Rationale: To provide updates to pharmacokinetic, pharmacodynamic, and immunogenicity assessments.	
9.3.3 Pharmacokinetic Parameters	Revisions were made to align text with the sparse sampling conducted in this study.
9.4 Pharmacokinetic/ Pharmacodynamic Evaluations; 11.6 Pharmacokinetic/ Pharmacodynamic Analyses	Clarified that pharmacokinetic/pharmacodynamic modeling may be performed to gain understanding of the relationship between serum concentrations of daratumumab and endpoints of clinical efficacy **or safety**.
11.4 Pharmacokinetic Analyses	Revisions and clarifications were made to how PK data will be summarized.
11.5 Immunogenicity Analyses	Deleted redundant text: ~~Separate listings of subjects who are positive for antibodies to daratumumab or positive for antibodies to rHuPH20 will be provided.~~
Rationale: Laboratory values can fluctuate for a variety of reasons.	
9.2.1 Hematologic Response Categories	Added text to strongly recommend that hematologic disease progression be confirmed in a subsequent disease evaluation visit via central laboratory values prior to determining MOD-PFS.
Rationale: Revisions, updates, and clarifications were provided.	
Synopsis (DOSAGE AND SC-ADMINISTRATION); 6.3 Cyclophosphamide	Clarified that the maximum **absolute** weekly dose of cyclophosphamide is 500 mg**, irrespective of body surface area (BSA)**.
Table 5 (Cyclophosphamide Dose Adjustment)	Text revised to clarify that cyclophosphamide dose could be adjusted or held if neutrophil ~~and/~~or platelet counts **or both** met values specified in Table 5.
Table 1 (Patient-Reported Outcome)	Noted that the first 6-month post-treatment ePRO assessment should occur 6 months after the EOT visit. Extended the collection window for PRO in the LTFU phase to ±14 days to provide subjects more flexibility and improve compliance.
Table 1 (HBV DNA test); 9.9 Safety Evaluations (Hepatitis B Virus (HBV) DNA Tests)	Specified that subjects who tested positive for Anti-HBc or Anti-HBs or both will undergo testing for hepatitis B DNA by PCR.
9.1.3.2 Randomized Study	Added instructions that if continued treatment is desired after MOD-PFS is met, a discussion between the investigator and medical monitor should occur about whether further study treatment would benefit a subject, without safety concerns. If disease progression is confirmed by the sponsor **and no benefit is expected from further treatment**, the subject will discontinue study treatment, complete the End-of-Treatment visit, and enter the Long-Term Follow-up Phase.
9.2.3 Determination of Organ Response	Modified text to clarify that organ disease that is considered to be quantifiable for response be evaluated by the central laboratory.
9.9 Safety Evaluations (HBV Serology)	Added text that if the Hepatitis B serologic status of a subject in the daratumumab plus CyBorD arm is unknown, HBsAg, Anti-HBs, and Anti-HBc testing is recommended if the subject is still receiving daratumumab or is within 6 months of the last dose.

Applicable Section(s)	Description of Change(s)
9.9 Safety Evaluations (Hematology Panel)	Specified that Factor X testing is optional, but recommended if a subject will have an invasive procedure or experiences a clinically significant bleeding event.
10.2 Discontinuation of Study Treatment/Withdrawal from the Study	A subject's study treatment must be discontinued if: 8. The subject meets criteria for MOD-PFS endpoint (See Section 2.2)**, provided no benefit is expected from continuing treatment (see Section 9.1.3.2)**.
Table 9 (International Amyloidosis Consensus Criteria); Table 10 (Organ Response and Progression Criteria)	A definition of baseline measurement was added as a footnote, where appropriate.
Table 9 (International Amyloidosis Consensus Criteria); References	Three new references were added to footnote "a". Citations for 3 new references were added to the list of references.
Synopsis (OVERVIEW OF STUDY DESIGN, DOSAGE AND SC-ADMINISTRATION); 3.1 Overview of Study Design; 6.2.1 Treatment Schedule and Administration; 9.1.3.2 Randomized Study; 9.1.3.3 Autologous Stem Cell Collection Considerations; 9.1.4 End-of-Treatment	24 cycles is defined as approximately 2 years of daratumumab treatment ; treatment duration was provided as cycles from the first dose of study treatment; not years from the start of the study.
Rationale: Minor errors and inconsistencies were noted.	
Throughout the protocol	Minor errors and inconsistencies were revised, and grammatical, formatting, or spelling changes were made.

Amendment 2 (23 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). Additionally, revisions and clarifications were made to disease assessment, PK and immunogenicity, and biomarker timings and definitions, as well as other parameters throughout the Protocol.

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).	

Applicable Section(s)	Description of Change(s)
Table 1 Time and Events Schedule	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.
4.2 Exclusion Criteria (Criterion 9)	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.
8.1.4 Management of Hepatitis B Virus Reactivation	Added a new section providing information for the management of hepatitis B virus reactivation.
9.1.1 Overview; 16.1 Study-Specific Design Considerations	Corrected the blood volume to be collected during the Screening Visit to approximately 25 mL, thus accounting for HBV serology.
9.9 Safety Evaluations	Added and revised information detailing the conduct of hepatitis B virus serology and DNA tests.
Attachment 13; References	Removed original Attachment 13: JSH Guidelines for the Management of Hepatitis B Virus Infection. Removed Reference: Drafting Committee for Hepatitis Management Guidelines and the Japan Society of Hepatology (JSH). Guidelines for the management of hepatitis B virus infection. Hepatol Res. 2014;44(Suppl S1):1-58.
Rationale: Clarifications were made to disease assessment, PK and immunogenicity, and biomarker timings and definitions.	
Table 1 Time and Events Schedule	The timing windows for EOT and long-term follow-up were modified to +/-3 days and +/-7 days, respectively. Removed assessment at -28 Days for Clinical Evaluation of MOD-PFS endpoint.
Table 2 Time and Events Schedule	Revised measurement of vital signs: **Arm A**: Vital signs will be measured **before study drug administration. Arm B: Vital signs will be measured** immediately before and after daratumumab SC-administration start and end.
Table 1 Time and Events Schedule; 9.2 Efficacy Evaluations; Table 9; 9.7 Medical Resource Utilization	Moved and clarified the instructions for the Medical Encounters Summary (From Section 9.2 Efficacy Evaluations to Section 9.7 Medical Resource Utilization); updated notation in Table 1. Clarified the following sentence: To mitigate this interference, the sponsor has developed a reflex assay that utilizes anti-idiotype antibody to bind daratumumab and confirm its interference on IFE. For all subjects **on Arm B (daratumumab plus CyBorD)** with VGPR, and a negative M-protein by SPEP, reflex IFE testing may be performed by the central laboratory to confirm daratumumab interference on IFE.
9.2.1 Hematologic Response Categories (Table 9)	Added clarification to the definitions of the hematologic response categories.

Applicable Section(s)	Description of Change(s)
Table 1 Time and Events Schedule	Indicated that the biomarker FISH may be sent to central lab in China, and certain other biomarker samples will not be collected in China. A window of +/-1 week was added to PK and immunogenicity frequency during the Observation Phase for Safety Run-in and Arm B only.
Table 1 Time and Events Schedule; 9.2.3 Determination of Organ Response; Attachment 14	Added clarification: **Note: only HS Troponin T sent to central laboratory in China.** Also made correction to troponin **T** in Attachment 14.
Rationale: Clarifications were made to the diagnosis of amyloidosis.	
9.1.2 Screening Phase; 9.1.2.1 Histopathological Diagnosis of Amyloidosis	The clarification was added: **Retesting of abnormal screening values that lead to exclusion are allowed only once during the screening period (to reassess eligibility). The last result known prior to Cycle 1 Day 1 will be used to determine eligibility.** Added clarification that mass spectrometry is not available in China.
Rationale: Clarification was made to the dosing of daratumumab with regard to management of toxicity.	
6.2.2.2 Toxicity Management	The clarification was added: **Note: there should be at least 4 days between each daratumumab administration**.
Rationale: Minor changes and clarifications were made throughout.	
Table 2 Time and Events Schedule	Revised dexamethasone premedication for Treatment Arm B: Dexamethasone 20 mg. May be given ~~up~~ **1** to 3 hours before the dose of daratumumab
4.2 Exclusion Criteria (Criterion 19)	Added the clarification that **strong** CYP3A4 inducers must discontinue their use at least 5 half-lives prior to the first dose of study treatment.
4.1 Inclusion Criteria (Criterion 3)	Changed the units of measure for free light chain.
3.1 Overview of Study Design	Clarified the treatment cycle: All treatment cycles are 4 weeks (28 days **with a +/-5 day window**) in length.
9.1.1.1 Bone Marrow Biopsy/Aspirate Considerations	Modified the timing of sample collection: If a fresh bone marrow aspirate will not be performed at Screening because a sample is available within 56 days prior to ~~randomization~~ **Cycle 1 Day 1**.
9.1.4.1 Subsequent Therapy	The clarification was added: **For Treatment Arm A subjects who continue CyBorD post 6-cycles, the continued CyBorD treatment will be considered subsequent therapy.**
Table 1 Time and Events Schedule; 12.3.1 All Adverse Events	The clarification was made: For subjects who have received additional treatment with therapeutic intent for AL amyloidosis during the AE reporting period, only AEs that are considered to be possibly, probably, or ~~definitely~~ **very likely** related to study drug must be reported.
17.4 Source Documentation	The clarification was made: (EORTC QLQ-C30, EQ-5D-5L, SF-36**v2** Health Survey.
Rationale: Minor errors were noted.	
Attachment 15	The spellings of CYP3A inducers and inhibitors were corrected.
Abbreviations	Added to the Abbreviations Table: Anti-HBc, Anti-HBs

Applicable Section(s)	Description of Change(s)
Throughout the Protocol	Other minor corrections/ clarifications were made throughout the document.

Amendment 1 (03 April 2018)

The overall reason for the amendment: The overall reason for the amendment is to align with Health Authority requests and to revise the AL Amyloidosis response consensus criteria.

Applicable Section(s)	Description of Change(s)
Rationale: To clarify that the informed consent form must be signed before any study-specific procedures are performed.	
9.1.2 Screening Phase; 16.2.3 Informed Consent	Clarified that the signed ICF must be obtained from the subject before any study-specific procedures (not Standard of Care procedures) are performed.
Rationale: To clarify the censoring of data for secondary endpoints of time to complete hematologic response and time to organ response.	
2.2 Endpoints	Removed data censoring for time to complete hematologic response and time to organ response.
Rationale: Stratification by cardiac stage will be based on the Mayo Clinic Cardiac Staging System.	
Synopsis; 3.1 Overview of Study Design; 5 Treatment Allocation and Blinding	Stratification of subjects by Mayo Clinical Cardiac Stating (I, II, and IIIa) was specified and sources (Dispenzieri 2014 and Palladini 2016) were cited.
Rationale: To clarify the definition of hematologic progressive disease based on the recommendation of the AMY3001 Steering Committee that detectable monoclonal protein must be above a pre-defined quantitative level as described below, to qualify for progression.	
2.2 Endpoints; 9.2.1 Table 9 International Amyloidosis Consensus Criteria	Changed the definition of hematologic progressive disease to the following: From CHR, ~~any detectable monoclonal protein or~~ abnormal free light chain ratio (light chain ratio must double) ~~Note: the development of a IgG Kappa spike on SPEP/IFE will not be considered disease progression for subjects who have received daratumumab, DIRA testing may be indicated.~~ ~~From PR,~~ **or from CHR/VGPR/PR**, 50% increase in serum M-protein to >0.5 g/dL or 50% increase in urine M-protein to >200 mg/day (a visible peak must be present) Free light chain increase of 50% to >100 mg/L
Rationale: To provide additional details regarding observation of subjects after the end of study drug administration during Cycle 1.	
Synopsis; 3.1 Overview of Study Design; 6.2.1 Treatment Schedule and Administration	Clarified that once the randomized portion of the study begins, subjects in Treatment Arm B (CyBorD plus daratumumab) will be observed for at least 6 hours after the end of study drug administration during Cycle 1 Day 1 and, if deemed necessary by the investigator, after consecutive administrations.

Applicable Section(s)	Description of Change(s)
Rationale: To capture post-progressive disease patient-reported outcome assessment.	
Table 1 Time and Events Schedule: Patient-Reported Outcome	Column: Post-treatment Week 8 and after: ~~Q6 months until~~ **Start of** subsequent therapy. ~~Immediately before subsequent therapy is started, and 8 wks after;~~ **Q6 mos until MOD-PFS** Column: q16 wks: **16 weeks post MOD-PFS; 32 weeks post MOD-PFS**
Rationale: To ensure accurate recording of medical encounters.	
9.8 Table and Events Schedule, Medical Encounters Summary	Clarified visits at which a Medical Encounters eCRF page must be completed.
Rationale: "Dizziness" is non-specific and not attributable to amyloidosis.	
9.8 Patient-Reported Outcomes; Attachment 9 Supplemental Items to EORTX QLQ-C30	"Dizziness" has been removed from the supplemental EORTC QLQ-C30 item bank.
Rationale: To update the renal organ response criteria to the criteria as detailed in Palladini 2014.	
9.2.3 Determination of Organ Response	~~The~~ **Cardiac and liver** organ response must be monitored by the International Amyloidosis Consensus Criteria (Comenzo 2012)[6] ~~shown in.~~ **Renal organ response must be monitored by Palladini criteria (Palladini 2014). Refer to** Table 10. For kidney response, **the recent Palladini criteria response is defined as** a ~~50%~~ decrease in ~~24-hour urine protein (at least~~ **proteinuria by ≥30% or below 0.5 g/day** ~~when pre-treatment urine protein is >0.5 g/day)~~ in **24 hours without renal progression; renal progression is** ~~required. In addition, the creatinine clearance must not worsen by~~ defined as a ≥25% ~~over baseline~~ **eGFR decrease (Palladini 2014).**
9.2.3, Table 10, Kidney Response Row	~~Response column: 50% decrease (at least 0.5 g/day) of 24-h urine protein (urine protein must be >0.5 g/day) pre-treatment. Creatinine and creatinine clearance must not worsen by 25% over baseline.~~ **≥30% decrease in proteinuria or drop in proteinuria below 0.5 g/24 hours in the absence of renal progression.** Progression column: ~~50% increase (at least 1 g/day) of 24-h urine protein to >1 g/day or 25% worsening of serum creatinine or creatinine clearance~~ **≥25% decrease in eGFR**. Footnotes: Footnote a: Based on Comenzo 2012 consensus criteria **(Comenzo 2012)** Footnote b added: **Based on Palladini 2014 criteria (Palladini 2014)**

Applicable Section(s)	Description of Change(s)
Rationale: Exclusion criteria and safety follow-up for HBV were revised to align with regional guidelines for management of HBV infection.	
4.2. Exclusion Criteria 9.1.a	Revised exclusion text to define hepatitis B as hepatitis B surface antigen [HBsAg] positive, or antibodies to hepatitis B surface or core antigens [antiHBs or anti-HBc] with hepatitis B virus [HBV]-DNA quantitation positive). In addition, subjects who are positive for anti-HBs or anti-HBc must have a negative polymerase chain reaction (PCR) for HBV-DNA quantitation result at screening, PCR positive subjects are to be excluded. Subjects with serologic findings suggestive of prior HBV vaccination and known history of prior vaccination do not require PCR testing.
Table 1 Time and Events Schedule – HBV DNA Test; 9.9. Safety evaluations; Attachment 13 JSH Guidelines for the Management of Hepatitis B Virus Infection	Added a new section for safety follow-up for subjects who are positive for anti-HBc or anti-HBs. During the study, subjects who are positive for anti-HBc or ant-iHBs will undergo testing for hepatitis B DNA by PCR every 12 weeks. During and following study treatment, subjects who have history of HBV infection will be closely monitored for clinical and laboratory signs of reactivation of HBV. Added reference: JSH Guidelines for the Management of Hepatitis B Virus Infection 2014. Clarified that 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.
Rationale: PH20 is handled as an active agent in Japan	
1.2 Daratumumab; 3.1 Overview of Study Design; 3.2.1 rationale for Dose and Subcutaneous Administration; 4.2 Exclusion Criterion #14.1;	Clarification that daratumumab is co-formulated with rHuPH20 has been added throughout the protocol.
Rationale: To clarify that daratumumab monotherapy is approved in the United States, European Union, and other countries.	
3.2.1 Rationale for Dose and Subcutaneous Administration	Daratumumab monotherapy for subjects with multiple myeloma **is approved for the treatment of patients with relapsed/refractory multiple myeloma in the United States, European Union, and other countries** at **a dose of** 16 mg/kg (weekly for 8 weeks, then every 2 weeks for 16 weeks, then every 4 weeks thereafter) administered via IV infusion until disease progression, start of subsequent therapy, or unacceptable toxicity ~~in the United States, European Union, and other countries.~~
Rationale: To align with Health Authority requirements for increased safety monitoring around treatment with bortezomib.	
Table 1: Time and Events Schedule – Chest X-Ray	A chest x-ray was added at Screening.
Table 2: Time and Events Schedule – Hematology; Study Drug Dosing	Hematology testing was added at Days 8 and 22 for Cycles 1 through 6.

Applicable Section(s)	Description of Change(s)
Rationale: To align with Health Authority requests for increased contraception duration after discontinuation of cyclophosphamide.	
4.1 Inclusion Criteria 9.1	A man who is sexually active with a woman of childbearing potential and has not had a vasectomy must agree to use a barrier method of birth control; eg, either condom with spermicidal foam/gel/film/cream/suppository or partner with occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository during and up to ~~4~~ **6** months after discontinuation of cyclophosphamide or 3 months after discontinuation of daratumumab, whichever is longer. All men must also not donate sperm during the study and for ~~4~~ **6** months after discontinuation of cyclophosphamide or 3 months after discontinuation of daratumumab, whichever is longer.
Rationale: To align with Health Authority requests to exclude subjects with hypersensitivity or contraindications to cyclophosphamide or any of its metabolites.	
4.2 Exclusion Criteria 11.1	Criterion 11.1 Known hypersensitivity **or contraindications** to **any of the study drugs** including bortezomib, boron, mannitol, **or cyclophosphamide or any of its metabolites**.
Rationale: Serum is the preferred sample type for pregnancy testing.	
Table 1 Time and Events Schedule – Pregnancy Test; 4.1 Inclusion Criteria Criterion 10.1; 9.1.1 Overview; 9.1.2 Screening Phase; 9.9 Safety Evaluations	(Serum preferred) has been added to every location in which pregnancy testing is discussed.
Rationale: To align with Health Authority requests for the addition of the benefit/risk assessment to be included in the protocol.	
Attachment 14	Inserted new Attachment 14, which consists of the benefit/risk assessment specific to this study.
Rationale: To provide greater detail surrounding the prevention and management of daratumumab infusion-related reactions.	
6.2.3.1 Preinfusion Medication	**In an effort to prevent infusion-related reactions, all subjects will receive the following medications 1 to 3 hours prior to each daratumumab administration (1 hour prior to daratumumab administration is preferred):** Preinfusion medications include the following: • Dexamethasone 20 mg IV or PO (an equivalent of long-acting corticosteroid may substitute [see Attachment 4 for conversion table]) • **Antipyretic:** Paracetamol (acetaminophen) 650 to 1000 mg PO or IV • An antihistamine (diphenhydramine 25 to 50 mg, or equivalent) either given IV or PO. Avoid IV use of promethazine. • Montelukast (leukotriene inhibitor): **Predose administration of a leukotriene inhibitor** (**montelukast** 10 mg **PO or equivalent) is optional** on Cycle 1 Day 1~~,~~ and ~~optional~~ **can be administered up to 24 hours** before ~~all other doses of daratumumab~~ **SC-infusion as per investigator discretion.** If necessary, oral preinfusion medications may be administered ~~at~~ **outside** the ~~subject's home~~ **clinic** on the day of the daratumumab treatment, provided they are taken within 3 hours prior to the administration of daratumumab SC infusion.

Applicable Section(s)	Description of Change(s)
6.2.3.2 Postinfusion Medication	**Consider administering low-dose oral methylprednisolone (≤20 mg) or equivalent, the day after the SC-infusion.** **However, if a background regimen-specific corticosteroid (eg, dexamethasone) is administered the day after the SC-infusion, additional postinfusion steroids are not required, but may be considered by the investigator.** **Subjects who continue daratumumab monotherapy after completing 6 cycles in Treatment Arm B will receive long or intermediate-acting corticosteroid orally (20 mg methylprednisolone or equivalent in accordance with local standards) starting in Cycle 7 on the 2 days following daratumumab SC administrations (beginning the day after the SC-infusion) for the prevention of delayed IRRs.** Note: Subjects will continue to receive 20 mg of dexamethasone, or equivalent, as pretreatment medication prior to each dose of daratumumab. In the absence of infusion-related AEs after 3 cycles of monotherapy (Cycles 7 to 9), postinfusion corticosteroids may be administered per investigator discretion. For subjects with a higher risk of respiratory complications (eg, subjects with mild asthma or subjects with COPD who have an FEV1 <80% at Screening or developed FEV1 <80% during the study without any medical history), the following postinfusion medications should be considered: • Antihistamine (diphenhydramine or equivalent) ~~on the first and second days after all daratumumab SC administration~~ • **Leukotriene inhibitor (montelukast or equivalent)** • Short-acting β2 adrenergic receptor agonist such as salbutamol aerosol • Control medications for lung disease (eg, inhaled corticosteroids plus long-acting β2 adrenergic receptor agonists for subjects with asthma; long-acting bronchodilators such as tiotropium or salmeterol ~~plus~~ + inhaled corticosteroids for subjects with ~~chronic obstructive pulmonary disease~~ **COPD**). Investigators may prescribe bronchodilators, **H1-**antihistamines, and corticosteroids that are deemed necessary to provide adequate supportive care in the event a bronchospasm occurs after subjects are released from the hospital/clinic. If an at-risk subject experiences no major ~~infusion-related reactions~~ **IRRs**, then these postinfusion medications may be omitted after 4 doses at the investigator's discretion. ~~Subjects who continue daratumumab monotherapy after completing 6 cycles in Treatment Arm B will receive long or intermediate-acting corticosteroid orally (20 mg methylprednisolone or equivalent in accordance with local standards) starting in Cycle 7 on the 2 days following all daratumumab SC administrations (beginning the day after the infusion) for the prevention of delayed infusion-related reactions. Note: Subjects will continue to receive 20mg of dexamethasone, or equivalent, as pre-treatment medication prior to each dose of daratumumab. In the absence of infusion-related AEs after 3 cycles of monotherapy (Cycles 7 to 9), postinfusion corticosteroids may be administered per investigator discretion.~~ **Any postinfusion medication will be administered after the SC-infusion has completed.**

Applicable Section(s)	Description of Change(s)
6.2.3.3 Management of Infusion-Related Reactions	If an ~~infusion-related reaction~~ **IRR** develops, then the administration of daratumumab should be temporarily interrupted~~.~~ **(see IPPI for further details)**. Subjects who experience ~~adverse events~~ **AEs** during daratumumab SC administration must be treated ~~according to the investigator's judgment and best clinical practice~~ **for their symptoms**. The following recommendations apply: • In the event of a life-threatening ~~infusion-related reaction~~ **IRR** (which may include pulmonary or cardiac events) or anaphylactic reaction, daratumumab should be discontinued and ~~after consultation with the sponsor,~~ no additional daratumumab should be administered to the subject. ~~Aggressive symptomatic treatment should be applied.~~
6.2.3.3.1 Infusion-Related Reactions of Grade 1 or Grade 2	If the investigator assesses ~~an adverse event~~ **a Grade 1-2 IRR** to be related to the daratumumab SC administration, then the administration of daratumumab 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.
6.2.3.3.2 Infusion-Related Reactions of Grade 3 or Higher	For **SC**-infusion-related ~~adverse events~~ AEs **(other than laryngeal edema or bronchospasm)** that are Grade 3 ~~or higher~~, the daratumumab SC administration must be stopped and the subject must be observed carefully until resolution of the ~~adverse event~~ **AE or until** the intensity ~~of any other adverse event remains at Grade 3 or 4 after 2 hours, then the subject must be withdrawn from treatment. If the intensity of any other adverse~~ the event decreases to Grade 1 ~~or 2 within 2 hours, then~~, **at which point** daratumumab SC-administration may be restarted at the investigator's discretion. **If the intensity of the AE returns to Grade 3 after restart of daratumumab administration, then the subject must be withdrawn from daratumumab treatment.** ~~If the intensity of the adverse event returns to~~ **For IRR AEs that are** Grade ~~3 or~~ 4, ~~after restart of~~ the daratumumab administration~~, then the procedure described in this section may be repeated at the investigator's discretion. Should the intensity of the adverse event increase to Grade 3 or 4 for a third time, then~~ **must be stopped and** the subject ~~must be~~ withdrawn from **daratumumab** treatment.
6.2.3.3.3 ~~Recommendations~~ Recurrent Infusion-Related Reactions	**If a Grade 3 IRR (or Grade 2 or higher) event of laryngeal edema or bronchospasm recurs during or within 24 hours after a subsequent daratumumab SC-administration, daratumumab treatment must be discontinued.**
6.2.4 **Guidelines** ~~Recommendations~~ for Management of Daratumumab Administration-related Reactions	For the purpose of this protocol, "administration-related reactions" are defined as localized reactions at the injection site (eg, erythema, local tenderness, swelling, etc). **In Study MMY1004 Part 1,** SC-administration ~~related reactions have been mild (Grade 1) and consist~~ of **daratumumab in abdominal SC tissue was associated with** local ~~pain or burning at the~~ injection-site~~, erythema, and~~ reactions such as induration ~~to the abdomen. Treatment for~~ and erythema in some subjects. The reactions usually resolved within 60 minutes. Local injection site reactions ~~may include the administration of oral antihistamines. Topical application of cool compresses, antihistamines, or corticosteroids is not recommended within 4 hours of drug administration, to avoid any changes in pharmacokinetics. After 4 hours, any topical treatment should be applied gently to avoid unnecessary friction to the site~~ should be **managed per institutional standards.**

Applicable Section(s)	Description of Change(s)

Rationale: To clarify dose adjustments for cyclophosphamide**.**

6.3.1 Dose Adjustments for Cyclophosphamide Table 5

Neutrophil count/mm^3	Platelet count/µL	Dosage
>1500	>100,000	100% of the planned dose
1500 – 1000	50,000 – 100,000	50% of the planned dose[a]
<1000	<50,000	Dose should be held[b]

[a.] **Cyclophosphamide dose should remain at 50% of planned dose if subject's neutrophil and/or platelet counts meet these values. If count ~~improves~~ increases to required levels for 100% of planned dose, then dose may be re-escalated to 100% of planned dose.**

[b.] **Cyclophosphamide dose should be held if subject's neutrophil and/or platelet counts meet this value. However, if counts ~~improve~~ increase to required levels for 50% of the planned dose or 100% of the planned dose, then dose may be re-escalated as appropriate.**

Rationale: To clarify dexamethasone administration in select populations.

6.5 Dexamethasone

For subjects who are older than 70 years, underweight (BMI <18.5), have hypervolemia, poorly controlled diabetes mellitus, or prior intolerance/~~adverse event~~ **AE** to steroid therapy, the dexamethasone dose may be administered at a dose of 20 mg weekly. **For subjects receiving dexamethasone 20 mg weekly, on days of daratumumab treatment, it is recommended that dexamethasone 20 mg be administered as premedication.**

Rationale: To add criteria for the use of CYP3A4 inducers and inhibitors with the use of bortezomib.

8.3 Prohibited Therapies <u>During the First 6 Cycles of Therapy</u>

Concomitant administration of strong CYP3A4 inducers is prohibited with the use of bortezomib. Administration of strong CYP3A4 inhibitors (eg, ketoconazole, ritonavir) should be avoided and is not recommended in patients receiving bortezomib. If a strong CYP3A4 inhibitor must be given in combination with bortezomib, monitor patients for signs of bortezomib toxicity and consider a bortezomib dose reduction. For a list of CYP3A inhibitors and inducers, see Attachment 16**.**

Attachment 16

Added Attachment 16 to provide a list of CYP3A inducers and inhibitors.

Rationale: To make minor clarifications throughout the protocol.

Synopsis (Secondary Objectives, Endpoints, and Hypothesis)

To evaluate the clinically observable **composite** endpoint for major organ deterioration progression-free survival (MOD-PFS) following treatment with daratumumab in combination with CyBorD compared with CyBorD alone

Synopsis (Hypothesis)

The primary hypothesis of this study is that daratumumab in combination with CyBorD will improve the overall complete hematological response ~~rate compared to CyBorD alone, in subjects with newly diagnosed AL amyloidosis. The primary hypothesis of this study is that daratumumab in combination with CyBorD will improve the overall complete hematological response~~ **(CHR)** rate compared to CyBorD alone, in subjects with newly diagnosed AL amyloidosis.

3.2.4 Rationale for Biomarker Collection

As this is the first study of daratumumab in **treatment-naïve** amyloidosis and **additional information** ~~little is known~~ about CD38 expression on malignant plasma cells in amyloidosis **is warranted** ~~compared~~ to **better understand the disease** ~~multiple myeloma~~.

Immune populations such as immunosuppressive Treg~~,~~ ~~Breg,~~ and MDSC have not been well studied in amyloidosis.

Applicable Section(s)	Description of Change(s)
6.2.1 Treatment Schedule and Administration	To clarify the location at which doses are to be administered (opposite (right and left sides).
7 Treatment Compliance	~~Study drug (daratumumab)~~**Daratumumab** and bortezomib will be administered by qualified site staff. ~~Cyclophosphamide~~ Dexamethasone and ~~dexamethasone~~ cyclophosphamide will be administered by qualified site staff if ~~these drugs will be~~ given as an IV dose.
11.5 Immunogenicity Analyses	~~A listing~~ Separate listings of subjects **who are** positive for antibodies to daratumumab **or positive for antibodies to rHuPH20 will be provided**. **The maximum titers of antibodies to daratumumab** and rHuPH20 will ~~also be presented~~.**be summarized for subjects who are positive for antibodies to daratumumab and rHuPH20.**
12.3.1 All Adverse Events	Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study ~~drug~~ treatment, and those that are considered related to ~~daratumumab~~ **the study treatment** within the Follow-up Phase, must be reported using the Serious Adverse Event Form. Anticipated events will be recorded and reported as described in Attachment 12 **in countries where required**.
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 **from last patient out** (or according to local regulations) for additional research.
Attachment 7	The DuBois Formula can be used as an alternative formula for the calculation of body surface area. Approval from the Sponsor is required if a site wishes to use a body surface area formula other than the standard calculation or the DuBois formula.
Global	Differentiated study drug from study treatment.
Global	Updated drug administration to indicate subcutaneous injection or other administration.
Global and Attachment 11	Updated all instances of SF-36 to SF-36v2. Replaced prior SF-36 with SF-36 v2.
Rationale: Alignment of text with recent protocol template changes.	
Title page	Added 'Janssen Pharmaceutica NV' and 'Janssen, Inc.' to the list of legal entities, and removed 'Janssen Infectious Diseases BVBA, Inc.'.
9.8 Safety Evaluations – Adverse Events 12.3.1 All Adverse Events	Revised text to clarify that disease progression should not be considered an adverse event.
12.3.1. All Adverse Events	Revised text related to sponsor's responsibility for reporting anticipated events.
12.3.3. Pregnancy	Deleted text related to the unknown effect of study drug on sperm.
17.3. Subject Identification Enrollment and Screening Logs	Added '(as allowed by local regulations)' following 2 instances of 'date of birth'.

Applicable Section(s)	Description of Change(s)
17.11 Use of Information and Publication	Revised text related to ICMJE: Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals.
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

SYNOPSIS

A Randomized Phase 3 Study to Evaluate the Efficacy and Safety of Daratumumab in Combination with Cyclophosphamide, Bortezomib and Dexamethasone (CyBorD) Compared With CyBorD Alone in Newly Diagnosed Systemic AL Amyloidosis

Daratumumab is a human IgG1κ monoclonal antibody (mAb) that binds with high affinity to a unique epitope on CD38, a transmembrane glycoprotein. It is a targeted immunotherapy directed towards tumor cells that express high levels of CD38, such as plasma cells from patients with AL amyloidosis.

OBJECTIVES AND HYPOTHESIS

Primary Objective

The primary objective is to evaluate the efficacy of daratumumab plus CyBorD compared with CyBorD alone in the treatment of newly diagnosed AL amyloidosis patients.

Secondary Objectives

- To evaluate the clinically observable composite endpoint for major organ deterioration progression-free survival (MOD-PFS) following treatment with daratumumab in combination with CyBorD compared with CyBorD alone
- To evaluate the following efficacy measures following treatment with daratumumab in combination with CyBorD compared with CyBorD alone:
  - Organ response rate (OrRR)
  - Overall survival (OS)
  - Time to and duration of response
- To evaluate fatigue, mental functioning, and health-related quality of life following treatment with daratumumab in combination with CyBorD compared with CyBorD alone
- To assess the safety and tolerability of daratumumab when administered in combination with CyBorD
- To assess the pharmacokinetics of daratumumab and the immunogenicity of daratumumab and rHuPH20
- To explore minimal residual disease (MRD) status in amyloidosis patients as a surrogate for PFS and OS and as a biomarker for relapse

Exploratory Objectives

- To evaluate hematologic progression-free survival (HemPFS)
- To evaluate biomarkers of response following treatment with daratumumab in combination with CyBorD compared with CyBorD alone
- To evaluate physical functioning, symptom improvement, functional improvement and health utility following treatment with daratumumab in combination with CyBorD compared with CyBorD alone
- To evaluate diastolic function following treatment with daratumumab in combination with CyBorD compared with CyBorD alone
- To explore the pharmacokinetic/pharmacodynamic relationship of daratumumab, such as exposure response relationship for efficacy/safety endpoints or disease-related or mechanism-based biomarkers

Hypothesis

The primary hypothesis of this study is that daratumumab in combination with CyBorD will improve the overall complete hematological response (CHR) rate compared to CyBorD alone, in subjects with newly diagnosed AL amyloidosis.

OVERVIEW OF STUDY DESIGN

This is a randomized, open-label, active-controlled, multicenter Phase 3 study in subjects with newly diagnosed amyloid light chain amyloidosis. Approximately 360 subjects will be stratified by cardiac stage based on the Mayo Clinical Cardiac Staging System (Dispenzieri 2014[11]; Palladini 2016[36]) (Stages I, II, and IIIa) (Attachment 14), countries that typically offer transplant for patients with AL amyloidosis (List A or List B), and renal function (creatinine clearance [CrCl] ≥60 mL/min or CrCl <60 mL/min) and then assigned to receive either CyBorD or CyBorD in combination with daratumumab. Subject participation will include a Screening Phase, a Treatment Phase, a Post-Treatment Observation Phase, and a Long-term Follow-up Phase.

Given the potential safety concern with regards to the use of IV daratumumab in the amyloidosis population (ie, volume overload), this study will utilize the daratumumab SC co-formulation. Although the risk of volume overload is predicted to be lower with SC daratumumab than with IV infusion, patients with newly diagnosed AL amyloidosis may still develop adverse events (AEs) attributable to hypervolemia (for example, dyspnea, peripheral edema, etc) secondary to amyloid-induced cardiac or renal insufficiency. Additionally, daratumumab has not been co-administered with CyBorD. Therefore, prior to the start of the randomized portion of the study, a safety run-in will be conducted. Dosing of these subjects will be staggered so that no subject will receive their first dose sooner than 48 hours after the previously enrolled subject. Safety evaluation will be performed by the sponsor (and external academic hematologists) after at least 10 subjects have received at least 1 cycle of treatment If no safety signal is observed, particularly in regard to volume overload, the randomized portion of the study will begin. Once the randomized portion of the study begins, subjects in Treatment Arm B (CyBorD plus daratumumab) will be observed for at least 6 hours after the end of study drug administration during Cycle 1 Day 1 and, if deemed necessary by the investigator, after consecutive administrations.

The safety run-in data have been assessed by the Study 54767414AMY3001 Steering Committee members consisting of 4 academic hematologists with expertise in AL amyloidosis. The Steering Committee members concur that the combination of daratumumab with CyBorD appears to be safe and tolerable for the first 15 subjects with newly diagnosed AL amyloidosis treated in the safety run-in of Study 54767414AMY3001 and support the start of the randomized portion of the study.

In the randomized portion of the study, subjects randomized to Treatment Arm A will receive study treatment with CyBorD. All treatment cycles are 4 weeks (28 days) in length. CyBorD will be administered for a maximum of 6 cycles (24 weeks).

Subjects randomized to Treatment Arm B will receive CyBorD plus daratumumab at a fixed dose of 1800 mg. A maximum of 6 cycles (24 weeks) of CyBorD plus daratumumab will be administered. After Cycle 6, subjects will continue to receive daratumumab as monotherapy on Day 1 of subsequent 28-day cycles until disease progression, start of subsequent therapy, or a maximum of 24 cycles (~2 years) from the first dose of study treatment.

SUBJECT POPULATION

Adult subjects age 18 and older with newly diagnosed AL amyloidosis are eligible for the study. Diagnosis will be based on histopathological or electron microscopy criteria, one or more organs need to be affected, and disease must be measurable (by free light chain criteria or serum monoclonal protein [M-protein]). Eligible subjects will have an ECOG performance score of 0, 1, or 2 and adequate organ function. Key exclusion criteria include previous or current diagnosis of symptomatic multiple myeloma, evidence of significant cardiovascular conditions, any form of non-AL amyloidosis, or planned stem cell transplant during first 6 cycles of protocol therapy.

DOSAGE AND SC-ADMINISTRATION

Daratumumab 1800 mg co-formulated with recombinant hyaluronidase PH20 (rHuPH20) 2000 U/mL will be administered subcutaneously through a syringe by a manual push over approximately 5 minutes. Daratumumab will be administered weekly for the first 8 weeks (2 cycles), then every 2 weeks for 4 cycles (Cycles 3-6), and then every 4 weeks until progression of disease or subsequent therapy for a maximum of 24 cycles (~2 years) from the first dose of study treatment.

Subjects will receive 300 mg/m^2 cyclophosphamide as an oral or IV weekly dose (NOTE: maximum absolute weekly dose of cyclophosphamide is 500 mg, irrespective of body surface area [BSA]) and 1.3 mg/m^2 VELCADE® (bortezomib) as an SC injection weekly (Days 1, 8, 15, 22) in every 28-day cycle for a maximum of 6 cycles.

Dexamethasone will be administered at a total dose of 40 mg weekly (ie, Days 1, 8, 15, 22). On days of daratumumab dosing, subjects in Treatment Arm B will receive 20 mg on the day of daratumumab dosing as premedication and 20 mg on the day after daratumumab dosing. On weeks that daratumumab is not administered, or for subjects randomized to Treatment Arm A, dexamethasone is to be given 40 mg weekly on a single day or divided into 2 days.

EVALUATIONS

Disease evaluations must be performed every 4 weeks during Cycles 1 through 6 and every 8 weeks from Cycle 7 and beyond, on the scheduled assessment day (±5 days). Samples to assess both the serum concentration (pharmacokinetics) of daratumumab and the generation of anti-daratumumab antibodies (immunogenicity) will be obtained from all subjects in the safety run-in and in Treatment Arm B according to the Time and Events Schedule. Samples will also be collected from all subjects in the safety run-in and in Treatment Arm B to evaluate the immunogenicity of rHuPH20 according to the Time and Events Schedule. Biomarker evaluations will focus on the evaluation of CD38 expression by IHC on the malignant plasma cells from core diagnostic biopsies to determine if CD38 expression correlates with response to daratumumab. Safety will be assessed measured by AEs, laboratory test results, ECGs, echocardiograms, vital sign measurements, physical examination findings, and ECOG performance status.

STATISTICAL METHODS

The sample size for this study is based on the alternative hypothesis of a 15% improvement in overall CHR. Taking an overall CHR rate estimated to be 25% for the CyBorD arm, adding a 15% improvement translates to an overall CHR rate of 40% for the CyBorD plus daratumumab arm. Approximately 360 subjects (180 subjects per arm) would provide more than 85% power to detect a 15% improvement in overall CHR using a likelihood ratio test with a 2-sided alpha of 0.05. Analysis of CHR rate at 6 months will be performed similarly to the primary endpoint CHR rate.

The primary comparison of the 2 randomized treatments will be made with respect to overall CHR based on Independent Review Committee (IRC) assessment using the Cochran-Mantel-Haenszel (CMH) chi square test in the intent-to-treat (ITT) population stratified by cardiac risk (Stages I, II, and IIIa), countries that typically offer transplant for patients with AL amyloidosis (List A or List B), and renal function (CrCl ≥60 mL/min or CrCl <60 mL/min). A Mantel-Haenszel odds ratio, along with its 2-sided 95%

confidence interval, will be calculated. All binary secondary endpoints will be analyzed using the CMH chi-square test.

For time-to-event endpoints (eg, MOD-PFS, HemPFS, OS, etc.), Kaplan-Meier estimates will be presented, along with a log-rank test stratified by cardiac risk (Stages I, II, and IIIa), countries that typically offer transplant for patients with AL amyloidosis (List A or List B), and renal function (CrCl ≥60 mL/min or CrCl <60 mL/min) comparing the 2 treatment arms. Median along with corresponding 95% CIs will be obtained from the Kaplan-Meier estimates. Cox's regression will be applied to obtain the hazard ratio estimate and the corresponding 95% CI.

Organ response/progression analysis will be performed separately for each organ involved at baseline, specifically for heart, kidney, and liver. Descriptive statistics will be provided to summarize organ response/progression at 6 months, time to organ response, and time to organ progression.

Two interim analyses are planned for this study. An Independent Data Monitoring Committee (IDMC) will assess the results of the interim analyses. The primary endpoint of overall CHR and secondary efficacy endpoints will be adjudicated by an IRC.

TIME AND EVENTS SCHEDULES

Table 1: Time and Events Schedule

			Treatment Phase		Post-Treatment Phase		Long-Term Follow-Up +/-7 days
		Screening Phase	**Arm A Arm B Cycles 1-6**	**Arm B C7+**	**EOT**	**Observation Arm A, Cycle 7+ Arm B, post -dara**	
	Notes	-28 days before C1D1	D1 of each cycle	D1	Post-treatment 30 days (+/-3 days)	Post-treatment Week 8 and after	q16wks
Study treatment should be initiated within 72 hours after randomization. Cycles are approximately 28 days in duration. The start of each cycle may occur ±5 days of the scheduled day. Run-in patients should follow schedule for Treatment Arm B.							
Procedures							
Informed consent	ICF must be signed before any study-related procedures are performed.						
Eligibility criteria	If mass spectrometry is necessary, Screening period is extended to 42 days before C1D1.	X					
Demographics/ medical history		X					
Issue Subject Study ID Card		X					
Height		X					
Chest X-Ray	Pretreatment chest X-ray performed locally to establish baseline pulmonary status.	X					
Assessment of lytic disease	To exclude multiple myeloma; skeletal survey or other imaging modality	X -42 days					
FEV1 test	Subjects with known or suspected COPD or asthma, FEV1 should be measured	X					
ECOG	See Attachment 1	X	X		X		
LVEF assessment	Echocardiogram preferred, other cardiac evaluation of LVEF also acceptable	X		C7D1 and when clinically indicated	X (if before C7D1)	C7D1 at start of Observation	
12-lead ECG		X			X		
Physical examination	Including neurological examination. Clinically significant abnormalities during the study should be reported as AEs.	X	Symptom and disease directed examination as clinically indicated				
Vital signs, Weight		X	Please see Table 2				

			Treatment Phase		Post-Treatment Phase		Long-Term Follow-Up +/-7 days
		Screening Phase	**Arm A Arm B Cycles 1-6**	**Arm B C7+**	**EOT**	**Observation Arm A, Cycle 7+ Arm B, post -dara**	
	Notes	-28 days before C1D1	D1 of each cycle	D1	Post-treatment 30 days (+/-3 days)	Post-treatment Week 8 and after	q16wks
Patient-Reported Outcome	Electronic PRO (EORTC QLQ, EQ-5D-5L and SF-36v2) before any other study procedures. Window for all PRO assessments is 4 days prior to dosing. Note: first 6-month post-treatment ePRO assessment should occur 6 months after the EOT visit. Not required in the safety run-in phase.		X	Q8wks	X	Start of subsequent therapy; Q6 months until MOD-PFS	16 weeks post MOD-PFS±14 d 32 weeks post MOD-PFS±14 d
Blood type, Rh and IAT	**Arm B only**. Obtain sample before first dose of daratumumab.		C1D1 Arm B only				
Study Treatment Administration: Please see Table 2 for detailed procedures.							
CyBorD			See Table 2				
Daratumumab	Arm B ONLY		See Table 2	See Table 2			
Laboratory Assessments							
Pregnancy test	For women of childbearing potential only. Serum sample preferred.	within 14 days prior to randomization	X	X	X		
Hematology	To be done by local laboratory.	X	See Table 2		X		
Serum chemistry	Including TSH and T4 at Screening and subsequently if clinically indicated. To be done by local laboratory.	X	See Table 2		X		
Hepatitis B (HBV) serology	Local testing for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (Anti-HBs), and hepatitis B core antibody (Anti-HBc). Refer to Section 9.9.	X					
HBV DNA test	For subjects with serologic evidence of resolved HBV infection (ie, positive Anti-HBs or positive Anti-HBc) or both, HBV DNA testing by PCR must be performed locally. Refer to Section 9.9. Performed locally at screening, every 12 weeks (Q12W) during treatment, at the End of Treatment visit, and Q12W for up to 6 months after last dose of study treatment in Arms A and B.	X	Q12W	Q12W	X	Q12W for up to 6 months after last dose of study treatment	

			Treatment Phase		Post-Treatment Phase		Long-Term Follow-Up +/-7 days
		Screening Phase	**Arm A Arm B Cycles 1-6**	**Arm B C7+**	**EOT**	**Observation Arm A, Cycle 7+ Arm B, post -dara**	
	Notes	-28 days before C1D1	D1 of each cycle	D1	Post-treatment 30 days (+/-3 days)	Post-treatment Week 8 and after	q16wks
Disease Assessments: To be performed throughout all phases of the randomized study (during treatment, post-treatment, and subsequent therapy) until MOD-PFS is observed.							
Clinical Evaluation of MOD-PFS endpoint	The MOD-PFS endpoint is defined in Section 2.1 and includes clinical manifestation of cardiac or renal failure, or hematologic PD, or death.		X	Every 8 weeks until disease progression			
NYHA Functional Classification	See Attachment 3	X	X	Every 8 weeks until disease progression			
Serum disease evaluations (SPEP)	Sample to be sent to central laboratory. Not required C1D1 if Screening laboratory assessments were within 14 days C1D1.	X	X	Every 8 weeks until disease progression			
Urine disease evaluations (UPEP)	Sample to be sent to central laboratory. Not required C1D1 if Screening laboratory assessments were within 14 days of C1D1.	X	X	Every 8 weeks until disease progression			
Serum FLC	Sample to be sent to central laboratory.	X	Cycle 1: D1, D8, D15, D22. Cycle 2 to 6: D1 only.	Every 8 weeks until disease progression			
NT-proBNP assay	Sample to be sent to central laboratory.	X	X	Every 8 weeks until disease progression			
Troponin T, HS Troponin T	Sample to be sent to central laboratory. Note: only HS Troponin T sent to central laboratory in China.	X	X	Every 8 weeks until disease progression			
Medical Resource Utilization (MRU)	Site to answer question in the eCRF at every disease assessment. If subject has required any additional encounters other than those mandated per protocol since the last disease evaluation visit, a Medical Encounters eCRF page must be completed.	X	Cycles 1-6: Every 28 days Cycle 7+ and during the post-treatment observation phase: Every 8 weeks; Q16W during the long-term follow-up phase				
Subsequent Therapy	Record anticancer therapy and response to therapy.		Throughout study, and at least every 16 weeks during long-term follow-up				
Stem Cell Collection	Autologous stem cell transplant is prohibited prior to the completion of Cycle 6.		Stem cell collection permitted. Record mobilization agents and stem cell yield (number of CD34+ cells per kg) and time to engraftment. See protocol Section 9.1.3.3.				
Other malignancies			Throughout study, and at least every 16 weeks during long-term follow-up				
Survival			Throughout study, and at least every 16 weeks during long-term follow-up				

			Treatment Phase		Post-Treatment Phase		Long-Term Follow-Up +/-7 days
		Screening Phase	**Arm A Arm B Cycles 1-6**	**Arm B C7+**	**EOT**	**Observation Arm A, Cycle 7+ Arm B, post -dara**	
	Notes	-28 days before C1D1	D1 of each cycle	D1	Post-treatment 30 days (+/-3 days)	Post-treatment Week 8 and after	q16wks
Biomarkers							
Bone Marrow Biopsy/Aspirate	Morphology, immunohistochemistry, karyotype or FISH required by local laboratory (del17p, t(4;14), etc). A portion of all aspirates collected may be used to evaluate MRD (central laboratory). For screening, fresh aspirate (3 mL) preferred. If not available, obtain 3 non-decalcified aspirate slides (smears or clots). Note: FISH may be sent to central laboratory in China and MRD will not be collected in China.	X (-56 days from C1D1)	When clinically feasible, bone marrow aspirate will be collected at CHR for MRD assessment				
Archived Bone Marrow Biopsy	3 unstained FFPE or biopsy slides, or 2 unstained and 1 H&E slides, sent to central laboratory. Note: not collected in China.	Any time predose					
Whole blood biomarkers	Must be obtained before administration of study treatment, Samples to be sent to the central laboratory. Note: EOT sample not collected in China.		C1D1 C6D1		X		
Plasma biomarkers	Must be obtained before administration of study treatment. Samples to be sent to the central laboratory. Note: plasma biomarker samples not collected in China.		C1D1 C6D1		X		
Pharmacokinetics and Immunogenicity, Safety Run-in and ARM B ONLY: The 8-week post-dose sample should be obtained even if a subject has started subsequent therapy.							
Daratumumab PK	Sample to be sent to central laboratory. Predose sample collection may occur up to 2 hours before but not after the start of the SC-infusion. Samples collected on dosing days with visit windows should be collected on the actual day of study drug administration.		C1D1 Pre C1D4 (+/- 1 day) C1D8 Pre C2D1 Pre C3D1 Pre C3D4 (+/- 1 day)	C7D1 Pre C12D1 Pre	X	8 weeks after last dose of dara (+/-1 week)	
Daratumumab immunogenicity	No additional sample needed; will be taken from PK sample. In addition, for IRRs associated with 2nd SC-infusion or beyond, obtain unscheduled blood sample as soon as possible; send to central laboratory.		C1D1 Pre C2D1 Pre C3D1 Pre	C7D1 Pre C12D1 Pre	X	8 weeks after last dose of dara (+/-1 week)	
rHuPH20 immunogenicity (plasma)	In addition, for IRRs associated with 2nd SC-infusion or beyond, obtain unscheduled blood sample as soon as possible. Samples to be sent to central laboratory.		C1D1 Pre C2D1 Pre C3D1 Pre	C7D1 Pre C12D1 Pre	X	8 weeks after last dose of dara (+/-1 week)	

			Treatment Phase		Post-Treatment Phase		Long-Term Follow-Up +/-7 days
		Screening Phase	**Arm A Arm B Cycles 1-6**	**Arm B C7+**	**EOT**	**Observation Arm A, Cycle 7+ Arm B, post -dara**	
	Notes	-28 days before C1D1	D1 of each cycle	D1	Post-treatment 30 days (+/-3 days)	Post-treatment Week 8 and after	q16wks
Ongoing Subject Review							
Adverse Events	See Section 12 for detailed instructions.	Continuous from the time of signing of ICF until 30 days after last dose of study treatment. Subsequently, only AEs considered possibly, probably, or very likely related to the study treatment need to be reported. Ongoing SAEs should be followed to resolution.					
Concomitant Medications	See Section 8 for detailed instructions.	Continuous from the time of signing of ICF until 30 days after last dose of last study treatment.					

Abbreviations to the Time and Events Schedule: AE=adverse event; Anti-HBc=hepatitis B core antibody; Anti-HBs=hepatitis B surface antibody; C=cycle; CCO=clinical cutoff for PFS analysis; CHR=complete hematologic response; COPD=chronic obstructive pulmonary disease; CyBorD=cyclophosphamide-bortezomib-dexamethasone; D=day; dara=daratumumab; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; eCRF=electronic case report form; EORTC QLQ= European Organization for Research and Treatment of Cancer Quality of Life Questionnaire EOT= End-of-Treatment; EQ-5D-5L= European Quality of Life Five Dimensions Questionnaire; FEV= Forced Expiratory Volume (in 1 second); FFPE=formalin fixed paraffin embedded; FISH=Fluorescence immunohistochemistry; FLC=free light chain; HBV=hepatitis B virus; HBsAg=hepatitis B surface antigen; HS=high sensitivity; IAT=indirect antiglobulin testing; ICF=informed consent form; ID=identification card; IRR=daratumumab infusion-related reaction; LVEF=left ventricular ejection fraction; MOD-PFS=major organ deterioration progression-free survival; MRD=minimal residual disease; NHYA=New York Heart Association; H&E=hematoxylin and eosin; NT-ProBNP=N-terminal pro-brain natriuretic peptide; rHuPH20=recombinant hyaluronidase PH20; PD=progressive disease; PK=pharmacokinetics; PRO=patient-reported outcome; Q12W=every 12 weeks; SAE=serious adverse event; SF-36=36-item short-form survey; SPEP=serum M-protein quantitation by electrophoresis; T4=thyroxine; TSH=thyroid-stimulating hormone; UPEP=urine M-protein quantitation by electrophoresis.

Table 2: Time and Events Schedule: Study Treatment Dosing

	Notes	Cycle 1-2				Cycle 3-6				Cycle 7+ (Arm B only)	EOT (within 30 days of last dose)
		D1	D8	D15	D22	D1	D8	D15	D22	D1	
Hematology	For Cycle 1 Day 1, no need to repeat tests if they have been performed within the past 7 days. Testing may be performed up to 2 days prior to study treatment administration. Results of hematology tests must be evaluated before each study treatment administration. Perform at additional time points, as clinically indicated. To be done by local laboratory.	X	X	X	X	X	X	X	X	X	X
Serum Chemistry		X		X		X		X		X	X
Vital Signs	Vital signs (blood pressure, pulse, and temperature) measured in sitting position. Arm A: Vital signs will be measured before study drug administration. Arm B: Vital signs will be measured immediately before and after daratumumab SC-administration start and end.	X	X	X	X	X		X		X	
Weight	Weight should be assessed at every visit to monitor for possible volume overload. Diuretic therapy is recommended should a subject develop weight gain as related to volume overload. If weight changes by more than 10% from baseline, recalculate study treatment doses.	X	X	X	X	X		X		X	X
Preinfusion Medications for Daratumumab, Treatment Arm B											
Antihistamine	Diphenhydramine 25-50 mg or equivalent. paracetamol or acetaminophen 650mg-1000mg. May be given up to 3 hours before the dose of daratumumab.	X	X	X	X	X		X		X	
Paracetamol		X	X	X	X	X		X		X	
Montelukast	Montelukast 10 mg PO recommended Cycle 1 Day 1, optional for all other doses.	X									
Dexamethasone (premedication)	Dexamethasone 20 mg. May be given 1 to 3 hours before the dose of daratumumab.	For dexamethasone dosing during Cycles 1-6, see CyborD regimen below								X	
Study Treatment Administration, Treatment Arm A and Arm B											
Study Drug Accountability	Accountability/exposure check	D1, D8, D15, D22 of Cycles 1-6								X	X
Cyclophosphamide	Administer PO or IV. Dispense on Day 1 after daratumumab SC administration if applicable.	300 mg/m^2 PO or IV weekly (maximum weekly dose 500 mg) for each cycle until a maximum of 6 cycles (D1, D8, D15, D22)									
Bortezomib	Administer by SC injection. Dose may be delayed up to 48 hrs, adjust subsequent doses as all bortezomib doses should be at least 72 hrs apart. Doses that need to be withheld are skipped and will not be made up later in the cycle.	1.3 mg/m^2 SC, weekly of each cycle (28 days) until a maximum of 6 cycles. (D1, D8, D15, D22)									
Dexamethasone (treatment)	Dispense on Day 1 for self-administration. Subjects in Arm B should receive 20 mg dexamethasone IV or PO prior to daratumumab dosing as a premedication to prevent SC- infusion-related reactions, and 20 mg the day after dosing.	40 mg weekly (or 20 mg weekly for some subjects) see Section 6.5 for further details until a maximum of 6 cycles									

	Notes	Cycle 1-2				Cycle 3-6				Cycle 7+ (Arm B only)	EOT (within 30 days of last dose)
		D1	D8	D15	D22	D1	D8	D15	D22	D1	
Study Drug Administration, Treatment Arm B											
Daratumumab	Maximum 2 yr. Refer to IPPI for preparation and SC-administration of daratumumab.	X	X	X	X	X		X		X	

Abbreviations: D=day; EOT= End-of-Treatment; hr=hour; IPPI= Investigational Product Preparation Instructions; IV-intravenous; PO=oral; SC=subcutaneous; yr=year;

ABBREVIATIONS

ADL	Activities of daily living
AE	Adverse event
AL amyloidosis	Light chain amyloidosis
ALT	Alanine aminotransferase
Anti-HBc	Antibodies to hepatitis B core antigen
Anti-HBs	Antibodies to hepatitis B surface antigen
AST	Aspartate aminotransferase
ATTR	Amyloidosis due to transthyretin (TTR) gene mutation
BMDex	Melphalan and dexamethasone plus bortezomib
BSA	Body surface area
CCO	Clinical cutoff
CHR	Complete hematologic response
CI	Confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMH	Cochran-Mantel-Haenszel
COPD	Chronic obstructive pulmonary disease
CR	Complete response
CrCl	Creatinine clearance
CTCAE	Common Terminology Criteria for Adverse Events
CTD	Cyclophosphamide, thalidomide, dexamethasone
CyBorD	Cyclophosphamide, bortezomib and dexamethasone
CyP	Cytochrome P450
DARA-MD	Dara-mix and deliver
dFLC	Difference between involved and uninvolved free light chains
DNA	Deoxyribonucleic acid
DVd	Daratumumab, bortezomib, and dexamethasone
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
eDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EORTC QLQ	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
EQ-5D-5L	European Quality of Life Five Dimensions Questionnaire
EU	European Union
FEV1	Forced Expiratory Volume in 1 second
FFPE	Formalin fixed paraffin embedded
FLC	Free light chain
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HemPFS	Hematologic progression-free survival
HIV	Human immunodeficiency virus
HRQOL	Health-related quality of life
IABP	intra-aortic balloon pump
IAT	Indirect antiglobulin testing
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFE	Immunofixation electrophoresis
IHC	Immunohistochemistry

IPPI	Investigational product preparation instructions
IRB	Institutional Review Board
IRC	Independent Review Committee
IRR	Infusion-related reaction(s)
ITT	Intent-to-treat
IV	Intravenous
IWRS	Interactive web-based randomization system
LVAD	Left ventricular assist device
LVEF	Left ventricular ejection fraction
MDex	Melphalan and dexamethasone
MDSC	Myeloid derived suppressor cells
MOD	Major organ deterioration
MOD-PFS	Major organ deterioration-progression-free survival
MRD	Minimal residual disease
MTD	Maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
ORR	Overall response rate
OrRR	Organ response rate
OS	Overall survival
PCR	Polymerase chain reaction
PD	Progression of disease
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PO	Oral administration
PQC	Product quality complaint
PR	Partial response
PRO	Patient-reported outcome
PS20	Polysorbate 20
PT	Prothrombin time
PTT	Partial thromboplastin time
RBC	Red blood cell
rHuPH20	Recombinant hyaluronidase PH20
S-IFE	Serum immunofixation
SAC	Safety Assessment Committee
SAE	Serious adverse event
SC	Subcutaneous
SF-36v2	36-Item Short Form Survey version 2
SIPPM	Site Investigational Product and Procedures Manual
SmPC	Summary of Product Characteristics
SPEP	Serum protein electrophoresis
TEAE	Treatment-emergent adverse event
TNT	Time to next treatment
TTE	Transthoracic echocardiogram
U-IFE	Urine immunofixation
ULN	Upper limit of normal
UPEP	Urine protein electrophoresis
Vd	Bortezomib and dexamethasone
VGPR	Very good partial response

1. INTRODUCTION

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. Amyloidosis

Amyloidosis refers to a disease in which there is extracellular deposition of insoluble fibrillar proteins in tissues and organs. These are part of a growing group of diseases now thought to be caused by misfolded proteins (Chaulagain 2013).[4] Systemic light chain (AL) amyloidosis is an acquired plasma cell disorder caused by insoluble protein produced by clonal expansion of CD38+ plasma cells.

The goal of therapy for amyloidosis is to achieve "complete hematologic response (CHR) or at a minimum very good partial response (VGPR) in order to prevent further end-organ damage, reverse existing organ dysfunction, and prolong overall survival (Chaulagain 2013).[4] In AL amyloidosis, achieving a partial hematologic response or stable disease may not offer a clinical benefit, because ongoing light chain production may result in further organ damage. Therefore, partial response (PR) should always be viewed in conjunction with organ response in the evaluation of treatment outcomes (Comenzo 2012).[7]

All current treatments for AL amyloidosis involve the destruction of plasma cells responsible for the production of the light chains. There are several regimens utilized for AL amyloidosis; all derived from the treatment experience of patients with multiple myeloma (Anderson 2014).[1] However, the National Comprehensive Cancer Network (NCCN) recommends that treatment should be in the context of a clinical study when possible because there are insufficient data to recommend optimal treatment of amyloidosis. (Anderson 2014).[1]

Medications that target the malignant plasma cell are part of the treatment armamentarium for myeloma and have clinical efficacy in amyloidosis. High dose melphalan followed by stem cell transplant is one of the treatments; however, it is associated with significant treatment-related mortality. Phase 2 studies have shown that lenalidomide in combination with dexamethasone is active in frontline and relapsed/refractory settings (Sanchorawala 2007, Dispenzieri 2007).[43,12] Severe cardiac and renal toxicities were observed in these patients, which underscores the need for careful monitoring of patients on this regimen. In another Phase 2 study in newly diagnosed patients, a combination of cyclophosphamide, lenalidomide and dexamethasone, resulted in an overall hematologic response rate of 60% (VGPR or better) (Kumar 2012).[19] In this study, hematologic toxicities were the predominant adverse events (AEs). Proof of concept and Phase 2 studies have shown that regimens like cyclophosphamide, thalidomide, dexamethasone (CTD), RevDex, and VELCADE® (bortezomib) have clinical utility in AL amyloidosis (Kumar 2012, Kastritis 2012, Sanchorawala 2013, Palladini 2013).[19,15,42,37]

1.1.1. Bortezomib-based Treatment Options for Amyloidosis

Results of the first prospective, randomized, Phase 3 trial comparing melphalan and dexamethasone (MDex) with MDex plus bortezomib (BMDex) in newly diagnosed AL amyloidosis were recently presented (Kastritis 2016).[16] The primary endpoint, hematologic response at 3 months, was reached in 51% (28% CR/VGPR) of subjects with MDex versus 78% (53% CR/VGPR) with BMDex (P=0.001). Overall hematologic response at the end-of-treatment (median of 5 cycles) was 56% for MDex and 81% for BMDex (P=0.001), with 38% CR/VGPR and 64% CR/VGPR, respectively. Cardiac response was achieved in 24% (8/33) of MDex evaluable subjects and 38% (10/26) BMDex evaluable subjects. There was a numerically higher proportion of cardiac progression (32% vs 15%, p=0.054) in the MDex arm. Renal response was 48% in both arms. After a median follow-up of 25 months, there was no significant difference in survival. Achievement of hematologic response at 3 months was associated with improved survival which further validates this biomarker endpoint as a surrogate for benefit. The conclusion of the study is that the introduction of novel therapy (bortezomib) results in superior efficacy compared to alkylating therapy plus steroid alone.

1.1.2. Background on Bortezomib in Combination with Cyclophosphamide and Dexamethasone (CyBorD regimen)

The use of CyBorD is recommended by the NCCN, British Society of Haematology, and consensus guidelines (Comenzo 2012, Anderson 2014; Mahmood 2014, Wechalekar 2008).[7,1,26,49] The majority of data published on safety and efficacy of bortezomib for the treatment of AL amyloidosis is derived from uncontrolled, retrospective analyses. The regimen of cyclophosphamide, bortezomib, and dexamethasone, known as CyBorD, is commonly used for the treatment of newly diagnosed patients with AL Amyloidosis (Anderson 2014).[1] For example, Mikhael et al presented a retrospective study utilizing bortezomib (1.5 mg/m^2 weekly), cyclophosphamide (300 mg/m^2 orally weekly), and dexamethasone (40 mg weekly) (Mikhael 2012).[30] Response was observed in 16 (94%) patients, with 71% achieving CHR and 24% achieving PR. Time to response was 2 months. In a separate study with 48 patients with untreated or relapsed AL, Venner et al reported an overall hematologic response rate of 81.4%, including CR in 41.9%, and very good partial response with >90% decrease in difference between involved and uninvolved light chains (VGPR-dFLC) in 51.4% (Venner 2012).[47] Patients treated upfront had higher rates of CR (65.0%) and VGPR-dFLC (66.7%). The estimated 2-year progression-free survival was 66.5% for patients treated upfront and 41.4% for relapsed patients.

The largest experience published to date was a retrospective study of 230 front line AL amyloidosis patients who received CyBorD at 2 academic centers (Palladini 2015).[38] By intent-to-treat, hematologic response was achieved in 138 of 230 patients (60%), with CR in 54 cases (23%). Among 201 patients with measurable disease, 125 (62%) responded (CR in 42, 21%; VGPR, in 45, 22%). Overall, 55% of patients are projected to survive 5 years, and median time to second line therapy or death was 13 months. Hematologic response significantly improved survival with deeper responses (CR and VGPR) correlating with improvements in overall survival.

The dose of VELCADE chosen in the 54767414AMY3001 study is based on consensus guidelines and best available evidence. Specifically, the VELCADE dosing in AMY3001 protocol is based on the above published efficacy and safety data of VELCADE 1.3 mg/ m^2 once weekly in the treatment regimen CyBorD for newly diagnosed AL amyloidosis (Palladini 2015)[38]. While the dose of 1.3mg/m^2 twice weekly has been attempted in AL Amyloidosis (Reece 2014)[41], there is a significant concern for treatment emergent peripheral neuropathy. Patients with AL amyloidosis have increased risk and suffer from significant peripheral neuropathy secondary to amyloid deposition in the peripheral nervous system and this symptom may be exacerbated by VELCADE. Therefore, the company has selected 1.3 mg/m^2 once weekly dose of VELCADE in the AMY3001 study, which is consistent with the recommendations from members of the Steering Committee who are international amyloidosis experts and have written the consensus guidelines for AL amyloidosis.

1.2. Daratumumab

Daratumumab is a human IgG1κ monoclonal antibody (mAb) that binds with high affinity to a unique epitope on CD38, a transmembrane glycoprotein. It is a targeted immunotherapy directed towards tumor cells that express high levels of CD38, such as plasma cells from patients with AL amyloidosis.

The mechanisms of action of daratumumab comprise immune-mediated effects, including complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, antibody-dependent cellular phagocytosis, and apoptosis by means of cross-linking (de Weers 2011, Overdijk 2016, Overdijk 2015, Lammerts 2014, Laubach 2015).[9,33,34,20,21] Moreover, daratumumab also induces immunomodulatory effects via several different pathways that contribute to killing CD38+ immune cells that modulate T cell activity, namely MDSC, TReg, and BReg (Krejcik 2016).[18] Daratumumab's converging mechanisms of actions are hypothesized to lead synergistically to the deep responses observed in patients with multiple myeloma.

As of 30 Jun 2016, approximately 3,147 subjects have been enrolled in 14 ongoing clinical studies of daratumumab. Among the 156 subjects treated with 16 mg/kg daratumumab IV monotherapy, the most frequently reported TEAEs (incidence more than 20%) were fatigue; nausea and anemia, back pain, cough, neutropenia, pyrexia, upper respiratory tract infection, and thrombocytopenia. Six subjects (4%) were withdrawn from treatment prematurely due to TEAEs, none of which were considered by the investigator to be related to daratumumab. Daratumumab as IV combination therapy has been administered to approximately 1,310 subjects. The safety profile of daratumumab in combination with standard background regimens (bortezomib, lenalidomide, pomalidomide, dexamethasone, melphalan, prednisone, thalidomide) is consistent with those of the background regimens and single agent daratumumab. With the exception of SC-infusion related reactions and neutropenia/thrombocytopenia, the safety profiles of daratumumab in combination with lenalidomide and dexamethasone (Rd), bortezomib and dexamethasone (Vd), or pomalidomide and dexamethasone (Pom-dex) were similar to those of the background regimens.

Subcutaneous (SC) administration of daratumumab has been investigated in Study MMY1004. Preliminary data from this study show that daratumumab SC-administration is feasible and has a substantially shortened infusion time compared with standard IV administration. In addition, the data show that the incidence of IRRs is reduced with SC-administration compared with IV administration. Further details of the safety and efficacy of daratumumab administered SC are provided in Section 3.2.1. In the current study, daratumumab will be administered as an SC dose with recombinant hyaluronidase PH20 (rHuPH20).

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

1.2.1. Daratumumab in AL Amyloidosis

The phenotype of plasma cells in the bone marrow of patients with AL amyloidosis was investigated using flow cytometry (Matsuda 2003).[28] Samples from 10 patients with AL amyloidosis and control samples from 4 patients with M-protein (positive controls) and 8 patients without M-protein (negative controls) were evaluated. On flow cytometry CD38++CD19+CD56- cells (polyclonal plasma cells) showed no significant difference between patients and either control group, while CD38++CD19-CD56+ cells (monoclonal plasma cells) showed a significantly higher level in patients compared with either negative ($p < 0.005$) or positive controls ($p < 0.05$). Thus, monoclonal plasma cells in AL amyloidosis express CD38, the target of daratumumab.

There are very limited data published on daratumumab in the treatment of AL Amyloidosis. Twelve previously treated patients with AL amyloidosis who received daratumumab monotherapy at the Stanford University Amyloid Center, were retrospectively studied for evidence of hematologic and organ response (Kaufman 2016).[17] Based on consensus criteria (Comenzo 2012),[7] 10 of 12 patients (83%) achieved objective responses (3 CHR, 3 VGPR, 4 PR) after a median duration of therapy of 4 months. Seven subjects were evaluable for cardiac response based on N-terminal pro-brain natriuretic peptide (NT-proBNP) criteria; of these, 3 patients achieved cardiac organ response (>30% reduction and >300 ng/L decrease in NT-proBNP).

Weiss 2016[50] reported efficacy data from 4 patients with AL amyloidosis (AL) or multiple myeloma with AL (MM/AL) who were treated with daratumumab. Patients P[redacted] and P[redacted] received the following modification from the standard daratumumab treatment: daratumumab 8 mg/kg in 500 mL on Cycle 1 Day 1, then 16 mg/kg in 500 mL on Day 8 and thereafter. Patients P[redacted] and P[redacted] received the standard daratumumab treatment of 16 mg/kg. Patients PPD received montelukast on the day prior, the day of and 2 days after daratumumab. Hematologic response was assessed by consensus criteria (Comenzo 2012).[7]

Table 3: Efficacy of Daratumumab in AL Amyloidosis and Multiple Myeloma with AL Amyloidosis

Subject ID	Diagnosis	No. Prior Regimens	Best Hematologic Response
PPD	MM/AL	6	CHR
	AL	4	PR
	AL	4	unmeasurable
	MM/AL	3	VGPR

CR=complete remission, PR=partial remission, VGPR=very good partial remission.

The Mayo Clinic reported safety and efficacy of daratumumab in 2 patients with multiple myeloma whose disease was complicated by development of co-morbid AL amyloidosis (Sher 2016).[44] Both patients achieved an objective hematologic response, which helps confirm the efficacy of daratumumab in AL amyloidosis observed at other institutions.

1.3. Overall Rationale for the Study

AL amyloidosis is a rare disease with a poor prognosis. The median survival of untreated patients is 13 months from diagnosis (Sanchorawala 2007, Chaulagain 2013).[43,4] Therapy for AL amyloidosis should include eradication of plasma cells that produce toxic protein deposits leading to organ failure. These plasma cells express CD38 (Matsuda 2003, Shimojima 2005)[28,45] and could be targeted by antibodies such as daratumumab that binds and eliminates CD38 expressing cells.

Safety data is available from the ongoing single agent daratumumab study (GEN501), from the combination study of daratumumab and bortezomib-containing regimens (MMY1001 and MMY3004), and from the label for bortezomib. The safety profile of daratumumab, which predominantly involves IRRs, is not considered to contribute to the known adverse effects of the CyBorD regimen. The combination of daratumumab and CyBorD is therefore expected to have an acceptable safety profile. In addition, the safety run-in portion of this study will further validate the safety assumptions and provide information on the safety of daratumumab in combination with CyBorD in the AL amyloidosis patient population.

In summary, there is a strong rationale for evaluating daratumumab in AL amyloidosis:

- There is a medical need for new treatments for AL amyloidosis, given the high morbidity and mortality in this patient population, because no specific standard of care exists in the frontline or relapsed setting.
- Flow cytometric data suggest that malignant plasma cells in AL amyloidosis express CD38 and therefore can be targeted by daratumumab.

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

2.1. Objectives

Primary Objective

The primary objective is to evaluate the efficacy of daratumumab plus CyBorD compared with CyBorD alone in the treatment of newly diagnosed AL amyloidosis patients.

Secondary Objectives

The secondary objectives are:

- To evaluate the clinically observable composite endpoints for major organ deterioration-progression-free survival (MOD-PFS) following treatment with daratumumab in combination with CyBorD compared with CyBorD alone
- To evaluate the following efficacy measures following treatment with daratumumab in combination with CyBorD compared with CyBorD alone:
  - Organ response rate (OrRR)
  - Overall survival (OS)
  - Time to and duration of response
- To evaluate fatigue, mental functioning, and health-related quality of life following treatment with daratumumab in combination with CyBorD compared with CyBorD alone
- To assess the safety and tolerability of daratumumab when administered in combination with CyBorD
- To assess the pharmacokinetics of daratumumab and the immunogenicity of daratumumab and rHuPH20
- To explore minimal residual disease (MRD) status in amyloidosis patients as a surrogate for hematologic progression-free survival (HemPFS) and OS or as a biomarker for relapse

Exploratory Objectives

The exploratory objectives are:

- To evaluate HemPFS
- To evaluate biomarkers of response following treatment with daratumumab in combination with CyBorD compared with CyBorD alone
- To evaluate physical functioning, symptom improvement, functional improvement and health utility following treatment with daratumumab in combination with CyBorD compared with CyBorD alone
- To evaluate diastolic function following treatment with daratumumab in combination with CyBorD compared with CyBorD alone

- To explore the pharmacokinetic/pharmacodynamic relationship of daratumumab, such as exposure response relationship for efficacy/safety endpoints or disease-related or mechanism-based biomarkers

2.2. Endpoints

Primary Endpoint

The primary endpoint is overall CHR rate.

Secondary Endpoints

The secondary efficacy endpoints include:

- Major organ deterioration progression-free survival (MOD-PFS). This is a composite endpoint of clinically observable endpoints and will be defined from randomization to any one of the following events, whichever comes first:
  1. Death
  2. Clinical Manifestation of Cardiac Failure:

     Defined as development of dyspnea at rest (for at least 3 consecutive days) and due solely to amyloidosis cardiac deterioration, or need for cardiac transplant, left ventricular assist device (LVAD), or intra-aortic balloon pump (IABP)
  3. Clinical Manifestation of Renal Failure:

     Defined as the development of end-stage renal disease (need for hemodialysis or renal transplant)
  4. Development of hematologic PD as per consensus guidelines

     From CHR, abnormal free light chain ratio (light chain ratio must double) or from CHR/VGPR/PR, 50% increase in serum M-protein to >0.5 g/dL or 50% increase in urine M-protein to >200 mg/day (a visible peak must be present)

     Free light chain increase of 50% to >100 mg/L
- Organ response rate (OrRR) for kidney, heart, liver is defined as the proportion of baseline organ involved subjects who achieve confirmed organ response in each corresponding organ.
- Overall survival (OS) is measured from the date of randomization to the date of the subject's death. If the subject is alive or the vital status is unknown, then the subject's data will be censored at the date the subject was last known to be alive.
- CHR rate at 6 months is defined as the proportion of subjects who achieve a complete hematologic response at 6 months, according to the consensus guidelines for AL amyloidosis,[7] during or after the study treatment.

- Improvement in fatigue is defined as the change from baseline in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30 Fatigue scale score, improvement in mental functioning is defined as the change from baseline in the 36-Item Short Form Survey version 2 (SF-36v2) Mental Component Summary (MCS), and improvement in health-related quality of life is defined as change from baseline in the EORTC QLQ-C30 Global Health Status scale score.
- Time to next treatment (TNT) defined as the time from the date of randomization to the start date of subsequent AL amyloidosis (non-protocol) treatment. Death due to PD prior to subsequent therapy is considered as an event. Otherwise, TNT is censored at the date of death or the last date known to be alive.
- Hematologic VGPR or better rate is defined as the proportion of subjects who achieve hematologic CR or VGPR.
- Time to CHR (or VGPR or better) is defined as the time between the date of randomization and the first efficacy evaluation at which the subject has met all criteria for hematologic CR (or VGPR or better).
- Duration of CHR (or VGPR or better) is defined as the time between the date of initial documentation of CHR (or VGPR or better) to the date of first documented evidence of hematologic progressive disease. For subjects who have not progressed, data will be censored at the last disease assessment.
- Time to cardiac response, time to renal response, and time to liver response. Defined as the time between the date of randomization and the first efficacy evaluation at which the subject has each corresponding organ response.
- Duration of organ response is defined as the time between the date of initial documentation of each corresponding organ response to the date of first documented evidence of the corresponding organ progressive disease. For subjects who have not had organ progression, data will be censored at the last disease assessment.
- Time to cardiac progression, time to renal progression, and time to liver progression. Defined as the time from the date of randomization to the date of each corresponding organ progression per consensus guidelines.

Exploratory Endpoint

Exploratory endpoints are:

- Hematologic progression-free survival (HemPFS) is defined as the time from the date of randomization to the date of first documentation of hematologic disease progression, according to central laboratory results and judged by international consensus guidelines, or death due to any cause, whichever occurs first. For those subjects who are still alive and have not yet progressed, the subject's data will be censored at the last disease assessment.
- Evaluation of MRD status in subjects who achieve CHR based on next generation sequencing or similar technologies.
- Assessment of physical functioning, symptom improvement, functional improvement, and health utility as measured by the SF-36v2, EORTC QLQ-C30 with supplemental symptom items, and the European Quality of Life Five Dimensions Questionnaire (EQ-5D-5L).

- Assessment of diastolic heart dysfunction based on analysis of transthoracic echocardiograms.

2.3. Hypothesis

The primary hypothesis of this study is that daratumumab in combination with CyBorD will improve the overall CHR rate compared to CyBorD alone, in subjects with newly diagnosed AL amyloidosis.

3. STUDY DESIGN AND RATIONALE

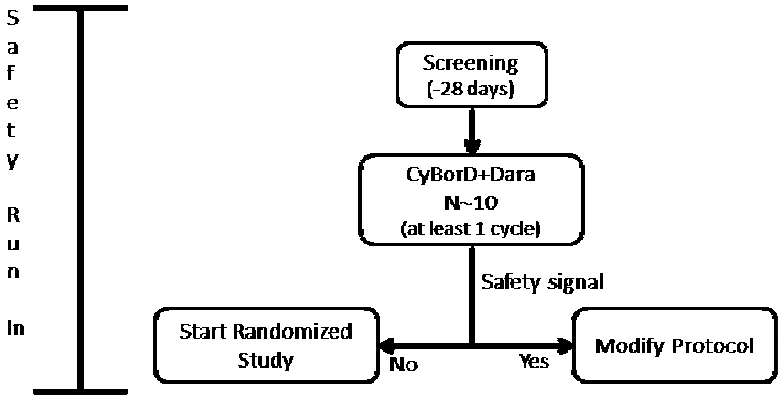
3.1. Overview of Study Design

This is a randomized, open-label, active-controlled, multicenter Phase 3 study in subjects with newly diagnosed amyloid light chain amyloidosis. Approximately 360 subjects will be stratified by cardiac stage based on the Mayo Clinical Cardiac Staging System (Dispenzieri 2014[11]; Palladini 2016)[11,36] (Stages I, II, and IIIa) (Attachment 14), countries that typically offer transplant for patients with AL amyloidosis (List A or List B), and renal function (creatinine clearance [CrCl] ≥60 mL/min or CrCl <60 mL/min) and then assigned to receive either CyBorD or CyBorD in combination with daratumumab. Subject participation will include a Screening Phase, a Treatment Phase, a Post-Treatment Observation Phase, and a Long-term Follow-up Phase.

Given the potential safety concern with regards to the use of IV daratumumab in the amyloidosis population (ie, volume overload), this study will utilize the daratumumab SC co-formulation with rHuPH20. Although the risk of volume overload is predicted to be lower with SC daratumumab than with IV infusion, patients with newly diagnosed AL amyloidosis may still develop AEs attributable to hypervolemia (for example, dyspnea, peripheral edema, etc) secondary to amyloid-induced cardiac or renal insufficiency. Additionally, daratumumab has not been co-administered with CyBorD. Therefore, prior to the start of the randomized portion of the study, a safety run-in will be conducted (Figure 1). Dosing of these subjects will be staggered so that no subject will receive their first dose sooner than 48 hours after the previously enrolled subject. Safety evaluation will be performed by the sponsor (and external academic hematologists) after at least 10 subjects have received at least 1 cycle of treatment. If no safety signal is observed, particularly in regard to volume overload, the randomized portion of the study will begin.

Subjects in the safety run-in will not be required to complete PRO assessments, but will undergo other scheduled assessments as specified in the Time and Events Schedule for Treatment Arm B (Table 1).

Figure 1: Schematic Overview of the Safety Run-In



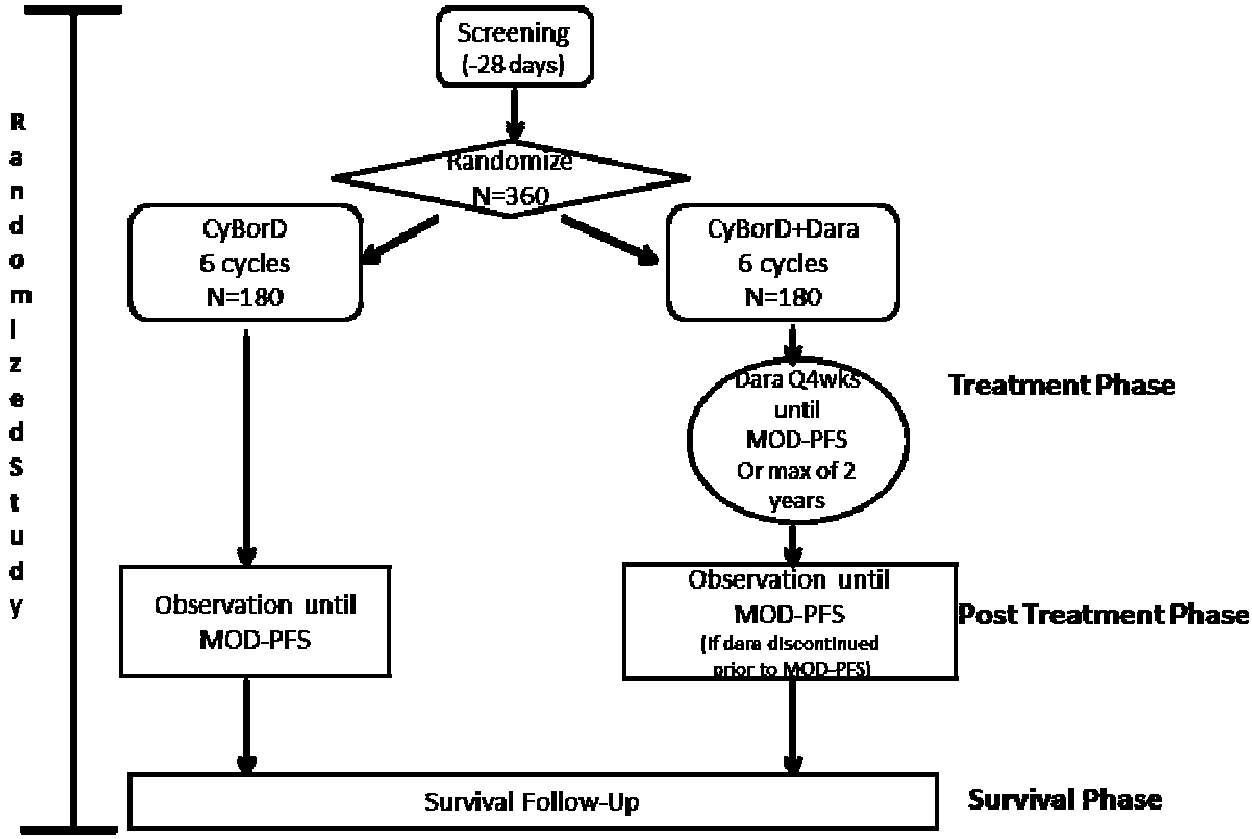
In the randomized portion of the study, subjects randomized to Treatment Arm A will receive study treatment with CyBorD (Figure 2). All treatment cycles are 4 weeks (28 days with a +/-5 day window) in length. CyBorD will be administered for a maximum of 6 cycles (24 weeks).

Subjects randomized to Treatment Arm B will receive CyBorD plus daratumumab at a fixed dose of 1800 mg. A maximum of 6 cycles (24 weeks) of CyBorD plus daratumumab will be administered. After Cycle 6, subjects may receive daratumumab monotherapy on Day 1 of subsequent 28-day cycles until disease progression, start of subsequent therapy, or a maximum of 24 cycles (~2 years) from the first dose of study treatment. Treatment with daratumumab after Cycle 6 is based on the approved daratumumab dosing regimen for multiple myeloma (weekly for the first 2 cycles [8 weeks] of treatment, followed by every 2 weeks for 4 cycles [16 weeks] and then every 4 weeks until a maximum of 24 cycles of therapy [~2 years]).

Once the randomized portion of the study begins, subjects in Treatment Arm B (CyBorD plus daratumumab) will be observed for at least 6 hours after the end of study drug administration during Cycle 1 Day 1 and, if deemed necessary by the investigator, after consecutive administrations.

Two interim analyses are planned for this study. The first interim analysis is a pre-specified safety analysis that will occur after the first 30 subjects complete at least 1 cycle of treatment. The second interim analysis will assess safety and efficacy, and will occur after 180 subjects have been treated for at least 6 cycles. Both interim analyses will be conducted by an Independent Data Monitoring Committee (IDMC). The primary endpoint of overall CHR and secondary efficacy endpoints will be adjudicated by an Independent Review Committee (IRC).

Figure 2: Schematic Overview of the Randomized Study



3.2. Study Design Rationale

3.2.1. Rationale for Dose and Subcutaneous Administration

Daratumumab monotherapy for subjects with multiple myeloma is approved for the treatment of patients with relapsed/refractory multiple myeloma in the United States, European Union, and other countries at a dose of 16 mg/kg (weekly for 8 weeks, then every 2 weeks for 16 weeks, then every 4 weeks thereafter) administered via IV infusion until disease progression, start of subsequent therapy, or unacceptable toxicity.

Study MMY1004 is an ongoing, open-label Phase 1b study of daratumumab-mix and deliver (Dara-MD), produced by mixing daratumumab 20 mg/mL with rHuPH20. The Dara-MD mixture, in a volume of 90 mL, is 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 daratumumab administration is feasible and has a substantially shortened SC-infusion time compared with standard IV administration. Furthermore, the data show that the incidence of IRRs is reduced with SC-administration compared with IV administration and that SC daratumumab at the 1800 mg dose has antitumor activity (ORR 38%) which is consistent with IV daratumumab in a similar patient population (Usmani 2016).[46] The median time to response was 4 weeks (range 4-8 weeks).

The PK profile in MMY1004 Part 1 is generally consistent with the approved IV dose regimen of 16 mg/kg, but the peak-and-trough fluctuation for daratumumab serum concentration is reduced and the maximum trough concentration (predose level prior to Cycle 3 Day 1) is comparable or higher compared to IV administration.

Daratumumab 1800 mg co-formulated with rHuPH20 2000 U/mL administered SC was well-tolerated, with clinically manageable side effects. The incidence of IRRs (24%) appeared to be substantially less when compared with the IV administration of daratumumab. Other TEAEs for SC-daratumumab appear to be similar to those reported in the 2 previous studies in which daratumumab was administered IV as a single agent (Lokhorst 2015, Lonial 2016).[24,25] After a median treatment duration of 3.4 months (range 0.7-8.6) for the 1800 mg cohort, the key safety findings are summarized below:

- The incidence of all-grade IRRs was 24% in the Dara MD 1800 mg cohort. By comparison, IRRs were reported in 48% of subjects in single-agent or combination therapy studies of Dara IV.
- IRRs were mostly Grade 1 or 2.
- All IRRs developed during or within 6 hours of the start of the first SC-administration and did not result in treatment discontinuation. No IRRs were reported on subsequent SC-administrations.
- The most frequently reported treatment-emergent adverse events (TEAEs) (≥20% of all subjects) with Dara MD were anemia (30%), pyrexia (23%), thrombocytopenia (21%), and fatigue (21%). These events were reported with similar incidences in single agent studies of Dara IV 16 mg/kg.
- Grade 3 or 4 TEAEs were reported in 40% of subjects in the 1800 mg cohort. By comparison, Grade 3 or 4 TEAEs were reported in 56% of subjects in single-agent studies of Dara IV 16 mg/kg.
- Serious adverse events (SAEs) were reported in 22% of subjects in the 1800 mg cohort. By comparison, SAEs were reported in 33% of subjects in single-agent studies of Dara IV 16 mg/kg.
- There were no treatment-related deaths.

The majority of patients with amyloidosis have cardiac and renal co-morbidities. The IV infusion of daratumumab (1000 mL for the first infusion and 500 mL for the subsequent infusions) could have resulted in signs or symptoms of volume overload, particularly for the patients with cardiac or renal insufficiency. 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 daratumumab and rHuPH20 is a single, pre-mixed vial with daratumumab at a higher concentration of 120 mg/mL and rHuPH20 at a concentration of 2000 U/mL. The co-formulated drug product will reduce the time for drug preparation, reduce the SC-infusion volume to approximately 15 mL, and can be administered in 5 minutes by manual SC push. Daratumumab co-formulated product contains 1800 mg of daratumumab and 30,000 U of rHuPH20.

3.2.2. Rationale for Study Treatment Regimen

Therapeutic options which form the basis of the systemic AL amyloidosis treatment paradigm are derived from experience in multiple myeloma, as both diseases originate from malignant plasma cells. Consequently, treatments include autologous stem cell transplantation, the combination of steroids and alkylating agents, immunomodulatory drugs, and various proteasome-inhibitor-based therapies. Treatment for amyloidosis is taken directly from the myeloma experience, with all anti-myeloma drugs used without modification of dose or schedule for treatment of amyloidosis. Daratumumab, with its novel, diverse mechanism of action, is highly efficacious in the treatment of patients with multiple myeloma and has a favorable safety profile. Thus, daratumumab may be a potential new treatment for the systemic AL amyloidosis patient population.

In addition to its use as a single agent, daratumumab has been successfully combined with standard anti-plasma cell directed treatment regimens. All combinations have been at the full dose for each regimen, and dose-finding preliminary studies have not been necessary. For example, with regard to the current study that will combine daratumumab with bortezomib, a Phase 3 study (MMY3004 known also as CASTOR) compared daratumumab, bortezomib, and dexamethasone (DVd) with bortezomib and dexamethasone (Vd) in patients with multiple myeloma who had received at least 1 prior therapy (DVd=243; Vd=237) (Palumbo 2016).[39] This study was a randomized, controlled, open-label study. All subjects received Vd (bortezomib 1.3 mg/m^2 on Days 1, 4, 8, 11 of a 21-day cycle, and dexamethasone 80 mg every week for 2 out of 3 weeks) for a maximum of 8 cycles, as recommended in the bortezomib prescribing information. Subjects randomized to the DVd group also received daratumumab 16 mg/kg every week for the first 9 weeks (Cycle 1 to Cycle 3), then on Day 1 of every 3-week cycle until the end of Vd (Cycle 4 to Cycle 8). Patients receiving DVd continued to receive daratumumab monotherapy beyond Cycle 8.

The addition of daratumumab to bortezomib and dexamethasone significantly improved clinical outcomes in subjects with relapsed or relapsed and refractory multiple myeloma, with a statistically significant 61% reduction in the risk of disease progression or death for the DVd group compared with the Vd group (HR=0.39; 95% CI: 0.28, 0.53; p <0.0001). As of the clinical cutoff date of 11 January 2016, median PFS was not reached for the DVd group and was 7.2 months for the Vd group at a median follow-up of 7.4 months. The estimated 12-month PFS rate was 61% (DVd group) versus 27% (Vd group). The PFS results were consistent for all preplanned sensitivity analyses and across all predefined subgroups. Results of secondary efficacy analyses support the improved benefit for the addition of daratumumab to the standard regimen of bortezomib and dexamethasone. This combination of daratumumab, bortezomib, and dexamethasone has been approved for myeloma patients with at least one prior therapy in the US and the EU.

In the DVd and Vd groups, the most common TEAEs (≥30% of subjects in either treatment group) were thrombocytopenia (DVd: 59%; Vd: 44%), peripheral sensory neuropathy (DVd: 47%; Vd: 38%), diarrhea (DVd: 32%; Vd: 22%), and anemia (DVd: 26%; Vd: 31%). Daratumumab may increase thrombocytopenia, known to be associated with bortezomib

treatment. However, in the DVd and Vd groups, bleeding events were low and the majority of events were minor. Grade 3 or 4 bleeding events were experienced by less than 1% of subjects. Discontinuation of treatment due to TEAEs and deaths due to TEAEs was low and balanced between treatment groups: DVd: 7%; Vd: 9%; DVd: 5%; Vd: 5%, respectively. Subgroup analyses based on age, sex, race, baseline renal function, baseline hepatic function, and geographic region did not identify any differences that were clinically meaningful.

Based on the assessment of TEAEs, deaths, and laboratory findings, the safety profile of daratumumab in combination with bortezomib/dexamethasone, was consistent with the known safety profiles of daratumumab and bortezomib/dexamethasone. With the exception of IRRs, the safety profile of this combination was similar to that of the background therapy.

AMY3001 is designed to evaluate the efficacy of daratumumab in combination with CyBorD compared with CyBorD alone. Based on clinical study data, CyBorD represents an emerging standard of care for subjects with newly diagnosed systemic AL amyloidosis (Palladini 2015, Jaccard 2014).[38,14] The use of CyBorD is recommended by the NCCN, British Society of Haematology, and consensus guidelines from academic institutions (Comenzo 2012, Anderson 2014; Mahmood 2014, Wechalekar 2008).[7,26,49]

Daratumumab has been administered successfully with several background regimens (including bortezomib, lenalidomide, pomalidomide, dexamethasone, melphalan, and prednisone) (Chari 2015, Dimopoulos 2016, Rajkumar 2016).[3,10,40] As described above, the combination of daratumumab with a bortezomib based regimen was synergistic and did not result in treatment terminating additive toxicity. Daratumumab has also already been combined with melphalan, an alkylating agent similar in toxicity profile to cyclophosphamide. It is therefore expected that daratumumab and CyBorD can be combined at the full dose of each regimen, and that the tolerability of the combination will be similar to the known safety profile of CyBorD, which would be added to the occurrence of IRRs due to daratumumab.

3.2.3. Rationale for Run-in Phase

As this is the first study of daratumumab in treatment-naïve amyloidosis, the study will start with a safety run-in of at least 10 subjects who will receive daratumumab plus CyBorD at the full dose for each regimen. As described above in Section 3.2.2, combinations of daratumumab with other standard treatment regimens have all been at full dose. Based on that prior experience, it is unlikely that dose reductions of either daratumumab or CyBorD will be needed when they are administered together. The safety run-in will confirm this is the case, and will also confirm the safety of the new co-formulated drug product. While not statistically driven, 10 subjects were considered appropriate for this initial phase of the study. Dosing of the subjects will be staggered to allow for assessment of both early or delayed IRRs. After at least 10 subjects have completed at least 1 cycle of treatment, there will be an analysis of safety by the sponsor (and external academic hematologists) before proceeding to randomization.

3.2.4. Rationale for Biomarker Collection

As this is the first study of daratumumab in treatment-naïve amyloidosis and additional information about CD38 expression on malignant plasma cells in amyloidosis is warranted to better understand the disease, CD38 will be assessed by immunohistochemistry (IHC) in a subset of patients. Minimal residual disease assessment of bone marrow allows deeper evaluation of clinical response beyond standard measures. MRD assessment has been shown to have prognostic significance in many hematological malignancies and may have utility in amyloidosis. Methodologies such as the Clonoseq next generation sequencing assay that quantitatively evaluate neoplastic plasma cell DNA from bone marrow aspirates may be used to evaluate MRD negativity. MRD may be assessed in patients who achieve CHR to evaluate depth of response in bone marrow. Immune populations such as immunosuppressive Treg and MDSC have not been well studied in amyloidosis. These cells have been shown to express CD38 and can be depleted by daratumumab in patients with multiple myeloma (Krejcik 2016)[18] and may play a role in daratumumab's mechanism of action in amyloidosis. Flow cytometry will be performed on peripheral blood to evaluate the effect of daratumumab treatment on these immunosuppressive cell populations in amyloidosis. The goal of the biomarker analysis is to evaluate the pharmacodynamics of daratumumab in amyloidosis and aid in evaluating the drug-clinical response relationship. Biomarker samples may be used to help address emerging issues and to enable the development of safer, more effective, and ultimately individualized therapies.

3.2.5. Rationale for Patient-Reported Outcome Measures

Patient-reported outcome (PRO) measures, including health-related quality of life (HRQOL) concepts, are included to complement clinical data and data collected by other methods. PRO data contributes to enhanced communication of treatment efficacy and value to patients, clinicians, regulators, and payers.

To collect PRO data, the study includes the EQ-5D-5L, SF-36v2, and EORTC QLQ-C30 with 3 supplemental questions from the EORTC item bank. The EQ-5D-5L is a preference-based measure included to obtain utility values from the study population to support cost-effectiveness modeling. The SF-36v2 is a generic PRO measure included based on the recommendation from the Amyloidosis Research Consortium. The EORTC QLQ-C30 is a generic PRO measure designed for use in cancer patient populations; included with 3 additional questions to capture core symptoms and concepts relevant to patients with amyloidosis.

4. SUBJECT POPULATION

Adult subjects age 18 and older with newly diagnosed AL amyloidosis are eligible for the study.

Screening for eligible subjects will be performed within 28 days before Cycle 1 Day 1. The inclusion and exclusion criteria for enrolling subjects in this study are described in the following subsections. If there is a question about the inclusion or exclusion criteria below, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a subject in the study. Waivers are not allowed.

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

All subjects will require approval from the sponsor before randomization into the study. If the sponsor agrees that the eligibility criteria have been met, then the investigator will receive confirmation that the subject may be randomized into the study. If the sponsor considers that the eligibility criteria have not been met, then the sponsor will contact the investigator to discuss.

4.1. Inclusion Criteria

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

1. 18 years of age (or the legal age of consent in the jurisdiction in which the study is taking place) or older.

2. Histopathological diagnosis of amyloidosis based on detection by IHC and polarizing light microscopy of green bi-refringent material in congo red-stained tissue specimens (in an organ other than bone marrow) or characteristic electron microscopy appearance (please refer to Section 9.1.2.1).

   Considerations for specific populations where other types of amyloidosis may be encountered:

   - For male subjects 70 years of age or older who have cardiac involvement only, and subjects of African descent (black subjects), mass spectrometry typing of AL amyloid in a tissue biopsy is recommended to rule out other types of amyloidosis such as age-related amyloidosis or hereditary amyloidosis (ATTR mutation)

3. Criterion modified per Amendment 2.

   3.1 Measurable disease of amyloid light chain amyloidosis as defined by at least ONE of the following:

   - serum M-protein ≥0.5 g/dL by protein electrophoresis (routine serum protein electrophoresis and immunofixation (IFE) performed at a central laboratory),
   - serum free light chain ≥50 mg/L with an abnormal kappa:lambda ratio or the difference between involved and uninvolved free light chains (dFLC) ≥50 mg/ L.

   Note: Measurable disease by urine Bence-Jones proteinuria is not sufficient for study enrollment.

4. One or more organs impacted by AL amyloidosis according to consensus guidelines (See Attachment 2).

5. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0, 1 or 2

(Attachment 1).

6. Pretreatment clinical laboratory values meeting the following criteria during the Screening Phase:

   a. Absolute neutrophil count $\geq 1.0 \times 10^9$/L;
   b. Hemoglobin level ≥8.0 g/dL (≥5 mmol/L); red blood cell transfusion allowed until 7 days before randomization
   c. Platelet count $\geq 50 \times 10^9$/L; Platelet transfusions are acceptable without restriction during the Screening period
   d. Alanine aminotransferase level (ALT) ≤2.5 times the ULN
   e. Aspartate aminotransferase (AST) ≤2.5 times the ULN
   f. Total bilirubin level ≤1.5 × ULN except for subjects with Gilbert syndrome, in which case direct bilirubin ≤2 × ULN
   g. Estimated glomerular filtration rate (eGFR) ≥20 mL/min/1.73 m^2. Please note the eGFR is measured by using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (see Attachment 5 for details)

7. Women of childbearing potential must commit to either abstain continuously from heterosexual sexual intercourse (if this is the preferred and usual lifestyle of the subject) or to use 2 methods of reliable birth control simultaneously. This includes one highly effective form of contraception (tubal ligation, intrauterine device, hormonal [birth control pills, injections, hormonal patches, vaginal rings or implants] or partner's vasectomy) and one additional effective contraceptive method (male latex or synthetic condom, diaphragm, or cervical cap). Contraception must begin 4 weeks prior to dosing and continue for 1 year after discontinuation of cyclophosphamide or 3 months after discontinuation of daratumumab, whichever is longer. Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy or bilateral oophorectomy.

8. During the study and for 1 year after stopping cyclophosphamide or 3 months after receiving the last dose of daratumumab, whichever is longer, a woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction.

9. Criterion modified per Amendment 1.

   9.1 A man who is sexually active with a woman of childbearing potential and has not had a vasectomy must agree to use a barrier method of birth control; eg, either condom with spermicidal foam/gel/film/cream/suppository or partner with occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository during and up to 6 months after discontinuation of cyclophosphamide or 3 months after discontinuation of daratumumab, whichever is longer. All men must also not donate sperm during the study and for 6 months after discontinuation of cyclophosphamide or

3 months after discontinuation of daratumumab, whichever is longer.

10. Criterion modified per Amendment 1.

10.1 A woman of childbearing potential must have a negative serum or urine pregnancy test (serum preferred) result within 14 days prior to randomization. For requirements during the Treatment Phase, please see the Time and Events Schedule (Table 1).

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

4.2. Exclusion Criteria

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

1. Prior therapy for AL amyloidosis or multiple myeloma including medications that target CD38, with the exception of 160 mg dexamethasone (or equivalent corticosteroid) maximum exposure prior to randomization

2. Previous or current diagnosis of symptomatic multiple myeloma, including the presence of lytic bone disease, plasmacytomas, ≥60% plasma cells in the bone marrow, or hypercalcemia

3. Evidence of significant cardiovascular conditions as specified below:

    a. NT-ProBNP >8500 ng/L

    b. New York Heart Association (NYHA) classification IIIB or IV heart failure (see Attachment 3)

    c. Heart failure that in the opinion of the investigator is on the basis of ischemic heart disease (eg prior myocardial infarction with documented history of cardiac enzyme elevation and ECG changes) or uncorrected valvular disease and not primarily due to AL amyloid cardiomyopathy

    d. Inpatient admission to a hospital for unstable angina or myocardial infarction within the last 6 months prior to first dose or percutaneous cardiac intervention with recent stent within 6 months or coronary artery bypass grafting within 6 months

    e. For subjects with congestive heart failure, cardiovascular-related hospitalizations within 4 weeks prior to randomization

    f. Subjects with a history of sustained ventricular tachycardia or aborted ventricular fibrillation or with a history of atrioventricular nodal or sinoatrial (SA) nodal dysfunction for which a pacemaker/ICD is indicated but not placed (Subjects who

do have a pacemaker/ICD are allowed on study)

g. Screening 12-lead ECG showing a baseline QT interval as corrected by Fridericia's formula (QTcF) >500 msec. Subjects who have a pacemaker may be included regardless of calculated QTc interval.

h. Supine systolic blood pressure <90 mm Hg, or symptomatic orthostatic hypotension, defined as a decrease in systolic blood pressure upon standing of >20 mmHg despite medical management (eg, midodrine, fludrocortisones) in the absence of volume depletion

4. Planned stem cell transplant during the first 6 cycles of protocol therapy are excluded. Stem cell collection during the first 6 cycles of protocol therapy is permitted

5. History of malignancy (other than AL amyloidosis) within 3 years before the date of randomization (exceptions are squamous and basal cell carcinomas of the skin, carcinoma in situ of the cervix or breast, or other non-invasive lesion that in the opinion of the investigator, with concurrence with the sponsor's medical monitor, is considered cured with minimal risk of recurrence within 3 years).

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

7. Moderate or severe persistent asthma within the past 2 years (see Attachment 6), 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).

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

9. Criterion modified per Amendment 1.

9.1 Criterion modified per Amendment 2.

9.2 Any of the following:

a. seropositive for hepatitis B (defined by a positive test for hepatitis B surface antigen [HBsAg]). 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.

b. 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).

10. Grade 2 sensory or Grade 1 painful peripheral neuropathy.

11. Criterion modified per Amendment 1.

11.1 Known hypersensitivity or contraindication to any of the study drugs including bortezomib, boron, mannitol, or cyclophosphamide or any of its metabolites.

12. Concurrent medical condition or disease (eg, active systemic infection) that is likely to interfere with study procedures or results, or that in the opinion of the investigator would constitute a hazard for participating in this study.

13. Any form of non-AL amyloidosis, including wild type or mutated (ATTR) amyloidosis.

14. Criterion modified per Amendment 1.

14.1 Known allergies, hypersensitivity, or intolerance to monoclonal antibodies, hyaluronidase, human proteins, or their excipients (refer to IB), or known sensitivity to mammalian-derived products.

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

16. Woman who is pregnant or breastfeeding or planning to become pregnant while enrolled in this study or within 1 year after discontinuation of cyclophosphamide or 3 months following discontinuation of daratumumab, whichever is longer

17. Received an investigational drug (including investigational vaccines) or used an invasive investigational medical device within 4 weeks before Cycle 1 Day 1.

18. Major surgery within 2 weeks before Cycle 1 Day 1, or will not have fully recovered from surgery, or has surgery planned during the time the subject is expected to participate in the study or within 2 weeks after the last dose of study treatment administration. Note: subjects with planned surgical procedures to be conducted under local anesthesia may participate.

19. Criterion modified per Amendment 2.

19.1 Subjects who are taking strong CYP3A4 inducers must discontinue their use at least 5 half-lives prior to the first dose of study treatment.

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 first dose of study treatment is given such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study. Section 17.4 describes the required documentation to support meeting the enrollment criteria. Subjects may be rescreened upon approval by the sponsor.

5. TREATMENT ALLOCATION AND BLINDING

Eligible subjects will be stratified by cardiac stage based on the Mayo Clinical Cardiac Staging System (Dispenzieri 2014[11]; Palladini 2016[36]) (Stages I, II, and IIIa) (Attachment 14), countries that typically offer transplant for patients with AL amyloidosis (List A or List B), and renal function (CrCl ≥60 mL/min or CrCl <60 mL/min). Country List A contains the countries that typically offer stem cell transplant while country List B contains the countries that do not offer stem cell transplant for patients with AL amyloidosis. Randomization will be in a 1:1 ratio to either Treatment Arm A (CyBorD alone) or Treatment Arm B (CyBorD plus daratumumab). The method of randomization is randomly permuted blocks. An interactive web-based randomization system (IWRS) will be used. Each subject will be assigned a unique subject number.

Blinding

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

6. DOSAGE AND ADMINISTRATION

In this protocol, the term “study drug” refers to daratumumab only, and “study treatment” refers to daratumumab, cyclophosphamide, VELCADE (bortezomib), and dexamethasone.

Treatment should be administered in the following order:

- Treatment Arm A (CyBorD alone): dexamethasone first, then cyclophosphamide, and finally bortezomib.
- Treatment Arm B (CyBorD plus daratumumab): premedication dexamethasone (refer to Section 6.5), followed by administration of daratumumab, then cyclophosphamide, bortezomib and the remaining dose of dexamethasone.

6.1. Treatment Cycles

All cycles are 28-day cycles. Cycle 1 should begin within 72 hours of randomization. Each following cycle should begin 28 days after Day 1 of the previous cycle, with a 5-day window permitted to accommodate holidays, weekends, or other site scheduling concerns. If Day 1 of a cycle is delayed for more than 5 days, then the entire cycle is delayed and the reason should be recorded in the eCRF. Whenever study treatment is administered for the first time in a cycle, that day will be considered Day 1.

Any delay in the start of a cycle by more than 28 days in Cycles 1 to 6 may be reason for permanent discontinuation in the study treatment, but should prompt discussion with the sponsor before withdrawing the subject from the protocol.

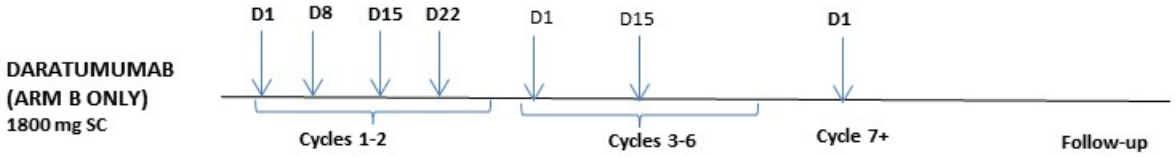
6.2. Daratumumab

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

6.2.1. Treatment Schedule and Administration

Daratumumab 1800 mg will be administered subcutaneously through a syringe by a manual push over approximately 5 minutes. Daratumumab will be administered weekly for the first 8 weeks (2 cycles), then every 2 weeks for 4 cycles (Cycles 3-6), and then every 4 weeks until progression of disease or subsequent therapy for a maximum of 24 cycles (~2 years) from the first dose of study treatment. Doses will be administered on alternating opposite (right/left) sides of the abdomen. Subjects will receive preinfusion and postinfusion medications as detailed in Section 6.2.3. A schematic of the daratumumab dosing schedule is provided in Figure 3. Information and details regarding preparation and SC-administration of daratumumab are provided in the IPPI.

Figure 3: Daratumumab Dosing Schedule



Subjects enrolled in the safety run-in phase of the study will be kept in the hospital for observation for at least 24 hours after the end of the Cycle 1 Day 1 SC-administration. Subjects enrolled in the randomized portion of the study and randomized to Treatment Arm B (CyBorD plus daratumumab) will be observed for at least 6 hours after the end of study drug administration during Cycle 1 Day 1 and, if deemed necessary by the investigator, after consecutive administrations.

Study drug administration will be performed as outpatient visits. Every effort should be made to keep subjects on the planned dosing schedule. However, within any given cycle, doses given within 3 days of the scheduled dose are permitted. The dose of daratumumab will remain constant throughout the study.

Additional details for SC-administration times and rates, as well as preinfusion medications, will be provided in the IPPI and Site Investigational Product Procedures Manual (SIPPM).

As noted in the Time and Events Schedule (Table 2), all subjects should have vital signs monitored before and at the end of all treatment administrations. If a subject experiences any significant medical event, then the investigator should assess whether the subject should stay overnight for observation. If the subject has not experienced a significant medical event but is hospitalized overnight only for observation, then the hospitalization should not be reported as an SAE.

6.2.2. Dose Delays and Dose Modification

6.2.2.1. Dose Modification

No daratumumab dose modification (increase or decrease) will be permitted in response to toxicity. Dose delay is the only method for managing daratumumab-related toxicities.

6.2.2.2. Toxicity Management

If any of the following criteria are met, then all study treatment must be held to allow for recovery from toxicity. The criteria for a hold in study treatment (applicable to both arms) are:

- Grade 4 hematologic toxicity (anemia, neutropenia or thrombocytopenia)
- Grade 3 or higher thrombocytopenia with bleeding
- Febrile neutropenia of any grade
- Neutropenia with infection, of any grade
- For other Grade 3 or 4 toxicities which, in the investigator's medical opinion, would cause excess risk to the patient, all study medications may be held until the toxicity has resolved to Grade 2 or less.

If daratumumab SC-administration does not commence within the prespecified window (Table 4) of the scheduled SC-administration date within an individual cycle, then the dose will be considered a missed dose. Subcutaneous administration may resume at the next planned dosing date. A missed dose will not be made up. Note: there should be at least 4 days between each daratumumab administration.

Table 4: Daratumumab-Related Toxicity Management

Cycles	Frequency	Dose Miss	Dosing Resumption*
1 -2	Weekly (Q1wk)	>3 days	next planned weekly dosing date
3-6	Every 2 weeks (Q2W)	>7 days	next planned every 2 weeks dosing date
7+	Every 4 weeks (Q4W)	>14 days	next planned every 4 weeks dosing date
*Dosing on Day 1 of a cycle must not be skipped.			

If a dose is delayed on Day 1 of a cycle, then the dates of all the subsequent doses should be adjusted. However, if a within-cycle dose is delayed, then the dates of the subsequent doses should not be adjusted. If dosing is delayed, then pharmacokinetic and pharmacodynamic assessments should be performed on the actual day of study drug administration, not on the original scheduled administration day. In addition, if D1 of a cycle has been delayed, disease evaluation schedule should not change but **will continue to be performed according to the original schedule** (every 28 days during Cycles 1 through 6 and every 8 weeks Cycle 7 and beyond). Please refer to Section 9.2.1 of the protocol.

Any AE deemed to be related to daratumumab that requires a dose hold of more than 28 days (Cycle 1 to Cycle 6) or more than 6 weeks (Cycle 7 and beyond) will result in permanent discontinuation of daratumumab.

If a dose of daratumumab is not given due to toxicity, or if daratumumab treatment is discontinued because of an SC daratumumab-related infusion reaction, doses of cyclophosphamide, bortezomib, and dexamethasone may continue, unless criteria exist to hold these medications as well (see subsequent sections).

6.2.2.3. 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, or a delay of more than 5 days before the start of a new cycle, 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 toxicity should be withdrawn from treatment, unless, upon consultation with the sponsor and the review of safety and efficacy, continuation is agreed upon.

6.2.3. Guidelines for Prevention and Management of Daratumumab Infusion-related Reactions

For the purpose of this protocol, infusion-related reactions (IRRs) are defined as systemic reactions related to the SC administration of the investigational agent.

6.2.3.1. Preinfusion Medication

In an effort to prevent infusion-related reactions, all subjects will receive the following medications 1 to 3 hours prior to each SC-daratumumab administration (1 hour prior to daratumumab administration is preferred):

Preinfusion medications include the following:

- Dexamethasone 20 mg IV or PO (an equivalent of long-acting corticosteroid may substitute [see Attachment 4 for conversion table])
- Antipyretic: Paracetamol (acetaminophen) 650 to 1000 mg PO or IV
- An antihistamine (diphenhydramine 25 to 50 mg, or equivalent) either given IV or PO. Avoid IV use of promethazine.
- Montelukast (leukotriene inhibitor): Predose administration of a leukotriene inhibitor (montelukast 10 mg PO or equivalent) is optional on Cycle 1 Day 1 and can be administered up to 24 hours before SC-infusion as per investigator discretion.

If necessary, oral preinfusion medications may be administered outside the clinic on the day of the daratumumab treatment, provided they are taken within 3 hours prior to the SC-administration of daratumumab infusion.

6.2.3.2. Postinfusion Medication

Consider administering low-dose oral methylprednisolone (≤20 mg) or equivalent, the day after the SC- infusion.

However, if a background regimen-specific corticosteroid (eg, dexamethasone) is administered the day after the SC-infusion, additional postinfusion steroids are not required, but may be considered by the investigator. Refer to Section 6.5.

Subjects who continue daratumumab monotherapy after completing 6 cycles in Treatment Arm B: in the absence of SC infusion-related AEs, postinfusion corticosteroids may be administered per investigator discretion. Note: Subjects will continue to receive 20 mg of dexamethasone, or equivalent, as pretreatment medication prior to each dose of daratumumab.

For subjects with a higher risk of respiratory complications (eg, subjects with mild asthma or subjects with COPD who have an FEV1 <80% at Screening or developed FEV1 <80% during the study without any medical history), the following postinfusion medications should be considered:

- Antihistamine (diphenhydramine or equivalent)
- Leukotriene inhibitor (montelukast or equivalent)
- Short-acting β2 adrenergic receptor agonist such as salbutamol aerosol
- Control medications for lung disease (eg, inhaled corticosteroids plus 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 SC administration. If subjects are hospitalized, then their FEV1 should be measured before discharge. If at-risk subjects are not hospitalized, then a follow-up telephone call should be made to monitor their condition within 48 hours. If the subject has not experienced a significant medical event but is hospitalized overnight only for observation, then the hospitalization should not be reported as an SAE. Investigators may prescribe bronchodilators, H1-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 postinfusion medications may be omitted after 4 doses at the investigator's discretion.

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

6.2.3.3. Management of Infusion-Related Reactions

Subjects should be observed during daratumumab SC-administration. 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. Attention to staffing should be considered when multiple subjects will be dosed at the same time.

If an IRR develops, then the administration of daratumumab should be temporarily interrupted (see IPPI for further details). Subjects who experience AEs during daratumumab SC administration must be treated for their symptoms. The following recommendations apply:

- 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.

6.2.3.3.1. Infusion-Related Reactions of Grade 1 or Grade 2

If the investigator assesses a Grade 1-2 IRR to be related to the daratumumab SC administration, then the administration of daratumumab 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.

6.2.3.3.2. Infusion-Related Reactions of Grade 3 or Higher

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

For IRR AEs that are Grade 4, the daratumumab SC-administration must be stopped and the subject withdrawn from daratumumab treatment.

6.2.3.3.3. Recurrent Infusion-Related Reactions

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

6.2.4. Guidelines for Management of Daratumumab Administration-related Reactions

For the purpose of this protocol, "administration-related reactions" are defined as localized reactions at the injection site (eg, erythema, local tenderness, swelling, etc).

In Study MMY1004 Part 1, 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.

6.3. Cyclophosphamide

Subjects will receive 300 mg/m^2 cyclophosphamide as an oral or IV weekly dose (NOTE: maximum absolute weekly dose of cyclophosphamide is 500 mg, irrespective of body surface area [BSA]) (Days 1, 8, 15, 22) in every 28-day cycle for a maximum of 6 cycles. The amount (in mg) of cyclophosphamide to be administered will be determined by body surface area, calculated according to a standard nomogram (Attachment 7). The dose can be rounded to the nearest pill size. For example, a dose of 310 mg can be rounded to 300 mg if 10 mg pills are not available. The exact dose of cyclophosphamide administered will be recorded in the eCRF.

Subjects may instead receive cyclophosphamide 300 mg/m^2 (maximum absolute weekly dose 500 mg, irrespective of BSA) via intravenous infusion at the discretion of the investigator. Mannitol can be used as a concomitant medication for subjects who receive IV cyclophosphamide to prevent cystitis per investigator's discretion. In the case of IV cyclophosphamide administration, the dose should be rounded to the nearest 1 mg.

For both IV and PO cyclophosphamide, subjects in Treatment Arm B should complete SC-administration of daratumumab prior to administration of cyclophosphamide. The dose of cyclophosphamide should be recalculated should the subject experience a weight change of more than 10% from baseline weight.

6.3.1. Dose Adjustments for Cyclophosphamide

Cyclophosphamide can cause myelosuppression (leukopenia, neutropenia, thrombocytopenia, or anemia), or bone marrow failure, or both. Monitoring of complete blood counts is essential during cyclophosphamide treatment so that the dose can be adjusted, if needed, according to Table 5.

Table 5: Cyclophosphamide Dose Adjustment

Neutrophil count/mm^3	Platelet count /µL	Dosage
>1500	>100,000	100% of the planned dose
1500 – 1000	50,000 – 100,000	50% of the planned dose[a]
<1000	<50,000	Dose should be held[b]

a. Cyclophosphamide dose should remain at 50% of planned dose if subject's neutrophil or platelet counts or both meet these values. If count increases to required levels for 100% of planned dose, then dose may be re-escalated to 100% of planned dose.
b. Cyclophosphamide dose should be held if subject's neutrophil or platelet counts or both meet this value. However, if counts increase to required levels for 50% of the planned dose or 100% of the planned dose, then dose may be re-escalated as appropriate.

G-CSF may be administered to reduce the risks of neutropenia complications associated with cyclophosphamide use. Primary and secondary prophylaxis with G-CSF should be considered in all subjects considered to be at increased risk for neutropenia complications.

6.3.2. Urinary Tract and Renal Toxicity

Hemorrhagic cystitis, pyelitis, ureteritis, and hematuria have been reported with cyclophosphamide therapy. Bladder ulceration/necrosis, fibrosis/contracture, and secondary cancer may develop. Before starting treatment, it is necessary to exclude or correct any urinary tract obstructions. Urinary sediment should be checked regularly for the presence of erythrocytes and other signs of uro/nephrotoxicity. Adequate treatment with Mesna or strong hydration to force diuresis can markedly reduce the frequency and severity of bladder toxicity. It is important to ensure that patients empty the bladder at regular intervals.

It is recommended to withhold cyclophosphamide if the subject has Grade 2 or higher urinary or bladder toxicity and resume when the toxicity resolves to Grade 1 or lower. The use of concomitant medications to treat urinary or bladder toxicity is at the discretion of the treating physician and allowed per protocol. Reference should also be made to the USPI, SmPC, or locally approved prescribing information for further discussion of cyclophosphamide reconstitution and dispensing guidelines and management of AEs.

6.4. Bortezomib

Subjects will receive 1.3 mg/m^2 bortezomib as an SC injection weekly (Days 1, 8, 15, 22) in every 28-day cycle for a maximum of 6 cycles. The amount (in mg) of bortezomib to be administered will be determined by BSA, calculated according to a standard nomogram (Attachment 7). The total calculated dose of bortezomib may be rounded to the nearest decimal point (eg, a calculated dose of 2.47 mg can be rounded to 2.5 mg). For subjects who experience injection site reactions, bortezomib may be administered by IV injection (see bortezomib locally approved prescribing information or SmPC). On daratumumab treatment days, subjects in Treatment Arm B should receive bortezomib after daratumumab and cyclophosphamide have been administered. The dose of bortezomib should be recalculated should the subject experience a weight change of more than 10% from baseline weight.

6.4.1. Dose Adjustments of Bortezomib

Dose adjustments should be based on the highest grade of toxicity that is ascribed to bortezomib. Bortezomib therapy should be withheld at the onset of any Grade 3 non-hematological or Grade 4 hematological toxicities excluding neuropathy as discussed in Table 6. Once the symptoms of the toxicity have resolved, bortezomib therapy may be reinitiated at a 25% reduced dose per approved labelling, as follows:

- Starting dose – 1.3 mg/m^2
- Dose level 1 – 1.0 mg/m^2
- Dose level 2 – 0.7 mg/m^2
- Dose level 3 – discontinue bortezomib.

For subjects whose bortezomib is discontinued because of a bortezomib-related toxicity (eg, peripheral neuropathy), doses of daratumumab, cyclophosphamide, and dexamethasone may continue unless criteria exist to hold these medications as well.

6.4.2. Neurologic Toxicity

If the subject experiences peripheral neuropathy, then dose adjustments should be made according to the recommendations in Table 6.

Table 6: Recommended Dose Modification for Bortezomib-related Neuropathic Pain or Peripheral Sensory or Motor Neuropathy

Severity of Peripheral Neuropathy Signs and Symptoms	Modification of Dose and Regimen
Grade 1 (asymptomatic; loss of deep tendon reflexes or paresthesia) without pain or loss of function	No action
Grade 1 with pain or Grade 2 (moderate symptoms; limiting instrumental ADL)	Reduce bortezomib by one dose level
Grade 2 with pain or Grade 3 (severe symptoms; limiting self-care ADL)	Withhold bortezomib treatment until symptoms of toxicity have resolved. When toxicity resolves, reinitiate with a reduced dose of bortezomib at 0.7 mg/m^2 once per week
Grade 4 (life-threatening consequences; urgent intervention indicated)	Discontinue bortezomib
Abbreviations: ADL, activities of daily living; Common Terminology Criteria for Adverse Events; NCI, National Cancer Institute. Grading based on NCI CTCAE v4.03 Instrumental ADL: refers to preparing meals, shopping for groceries or clothes, using telephone, managing money etc. Self-care ADL: refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.	

6.4.3. Other Grade 3 or 4 Adverse Events

For other Grade 3 or 4 toxicities judged by the investigator to be related to bortezomib alone, treatment with bortezomib should be interrupted and restarted at the next lower dose level once the toxicity has resolved to Grade 2 or less. For complete details on bortezomib, refer to the most current locally approved product prescribing information or SmPC.

6.5. Dexamethasone

Dexamethasone will be administered at a total dose of 40 mg weekly (ie, Days 1, 8, 15, 22). On days of daratumumab dosing, subjects in Treatment Arm B will receive 20 mg on the day of daratumumab dosing as premedication and 20 mg on the day after daratumumab dosing. On weeks that daratumumab is not administered, or for subjects randomized to Treatment Arm A, dexamethasone is to be given 40 mg weekly on a single day or divided into 2 days. An appropriate substitute for dexamethasone is allowed (as per local standards; see Attachment 4 for conversion table).

For subjects who are older than 70 years, underweight (BMI <18.5), have hypervolemia, poorly controlled diabetes mellitus, or prior intolerance/AE to steroid therapy, the dexamethasone dose may be administered at a dose of 20 mg weekly. For subjects receiving dexamethasone 20 mg weekly, on days of daratumumab treatment, it is recommended that dexamethasone 20 mg be administered as premedication.

For management of dexamethasone toxicity, see Table 7. This table represents suggested dose modifications of dexamethasone, but physician discretion and clinical judgment should prevail. For complete details on dexamethasone, refer to the most current locally approved product prescribing information.

Table 7: Dexamethasone Dose Modification Based on Toxicity

CTCAE Category	Toxicity	Dose Change
Gastrointestinal	Grade 1-2 dyspepsia, gastric, or duodenal ulcer, gastritis requiring medical management	Treat with histamine antagonists, sucralfate, or proton pump inhibitors such as omeprazole. If symptoms persist despite these measures, decrease dexamethasone dose by 50%.
	≥Grade 3 requiring hospitalization or surgery	Hold dexamethasone until symptoms are adequately controlled. Restart at 50% of current dose along with concurrent therapy with H2 blockers, sucralfate, or proton pump inhibitors. If symptoms persist despite these measures, discontinue dexamethasone and do not resume.
	Acute pancreatitis	Discontinue dexamethasone and do not resume.
Cardiovascular	≥Grade 3 edema limiting function and unresponsive to therapy or anasarca	Diuretics as needed and decrease dexamethasone dose by 25%. If edema persists despite these measures, decrease dose to 50% of initial dose. Discontinue dexamethasone and do not resume if symptoms persist despite 50% reduction.
Neurology/ Psychiatric	≥Grade 2 interfering with function but not interfering with activities of daily living	Hold dexamethasone until symptoms adequately controlled. Restart at 50% of current dose. If symptoms persist despite these measures, discontinue dexamethasone and do not resume.
Musculoskeletal	≥Grade 2 muscle weakness symptomatic and interfering with function but not interfering with activities of daily living	Decrease dexamethasone dose by 25%. If weakness persists despite these measures, decrease dose to 50% of initial dose. Discontinue dexamethasone and do not resume if symptoms persist despite 50% decrease.
Metabolic	≥Grade 3 hyperglycemia	Treat with insulin or oral hypoglycemic agents as needed. If uncontrolled despite these measures, decrease dose by 25% decrements until levels are satisfactory.

7. TREATMENT COMPLIANCE

Daratumumab and bortezomib will be administered by qualified site staff. Dexamethasone and cyclophosphamide will be administered by qualified site staff if given as an IV dose. The details of each administration will be recorded in the electronic case report form (eCRF). Subjects will be provided with a treatment diary which will be used to assess compliance with cyclophosphamide and dexamethasone treatment, when self-administered. Additional details are provided in the SIPPM or equivalent document.

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. Systemic use of the following concomitant medications will be collected in the eCRF and recorded in the source documents beginning with signing of the ICF and ending 30 days after the last dose of the last study treatment or until the start of subsequent anticancer treatment, if earlier: growth factors, transfusions, anti-infectives (antibacterials, antivirals, and antimycotics), steroids, anti-arrhythmics and other cardiac supportive therapy (including diuretics), anti-epileptics, centrally acting psychiatric medication, antihistamines and other medications targeting postinfusion systemic reactions, and any anti-amyloid therapy. The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

For subjects who may need stem cell transplant at a later time, stem cell harvest following mobilization with G-CSF or plerixafor or cyclophosphamide or any combination of the three is permitted while on study.

8.1. Recommended Therapies

8.1.1. Prophylaxis for *Pneumocystis carinii (jirovicii)*

Pneumocystis carinii (jirovicii) pneumonia prophylaxis is recommended, as per institutional guidelines.

8.1.2. Prophylaxis for Herpes Zoster Reactivation

Prophylaxis for herpes zoster reactivation as per local standard of care is recommended during the Treatment Phase. Acceptable antiviral therapy includes acyclovir (eg, 200 mg given orally 3 times a day, or 400 mg given orally 2 times a day or per institutional standards), famciclovir (eg, 125 mg given orally, twice a day or per institutional standards), or valacyclovir (eg, 500 mg given orally, once a day or per institutional standards), initiated within 1 week after the start of study drug.

8.1.3. Prophylaxis or Management of Hemorrhagic Cystitis

Medications used to treat hemorrhagic cystitis, including but not limited to mannitol, Mesna, normal saline hydration, are permitted during the study.

8.1.4. 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 9.9.

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

8.1.5. Management of Peripheral Edema, Pulmonary Edema, Congestive Heart Failure.

Patients with AL amyloidosis are prone to volume overload secondary to their underlying illness and secondary to the administration of dexamethasone, which may also cause peripheral edema. The subject will have weight assessments as described in the Time and Events Schedule (Table 1). Any weight gain should prompt evaluation and management of volume overload, if appropriate. Management of volume overload is at the discretion of the treating physician, but will likely include loop diuretics (furosemide, torsemide or equivalent), nitrate preparations, or positive ionotropic agents. Use of these medications is permissible during the study and should be recorded in the eCRF as concomitant medications. Dose reductions of dexamethasone are also recommended according to Section 6.5 of the protocol.

8.2. Permitted Therapies

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

- Antiviral, antibacterial, and antifungal medications
- Colony stimulating factors, erythropoietin, and transfusion of platelets and red cells
- G-CSF/plerixafor for mobilization of stem cells
- Single dose of cyclophosphamide for mobilization of stem cells

8.3. Prohibited Therapies <u>During the First 6 Cycles of Therapy</u>

Concomitant administration of any other therapy for the intention of treating AL Amyloidosis is prohibited including medications that target CD38.

Concurrent use of corticosteroids is prohibited, unless subjects are on chronic steroids (maximum dose 20 mg/day prednisone equivalent) if they are being given for disorders other than amyloidosis; ie, adrenal insufficiency, rheumatoid arthritis, etc.

Concomitant administration of investigational agents is prohibited. Concurrent use of NEOD-1 (currently under clinical investigation for amyloidosis) is prohibited. Use of chronic doxycycline (under clinical investigation for amyloidosis) is prohibited. Administration of commercially available agents with activity against or under investigation for AL amyloidosis, including systemic corticosteroids (>20 mg prednisone per day or equivalent) (other than those given for IRRs as described in Section 6.2.3) should be avoided. If steroids are given for other AEs (for example, asthma exacerbation), treatment duration greater than 14 days should be avoided.

Concomitant administration of strong CYP3A4 inducers is prohibited with the use of bortezomib. Administration of strong CYP3A4 inhibitors (eg, ketoconazole, ritonavir) should be avoided and is not recommended in patients receiving bortezomib. If a strong CYP3A4 inhibitor must be given in combination with bortezomib, monitor patients for signs of bortezomib toxicity and consider a bortezomib dose reduction. For a list of CYP3A4 inhibitors and inducers, see Attachment 15.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedule (Table 1) summarizes the frequency and timing of measurements applicable to this study. Study assessments will be performed only after written informed consent is obtained. It is acceptable to obtain informed consent before the first day of the Screening Phase. Every effort should be made to keep subjects on the planned study schedule. At each visit, study assessments should be completed before study treatment administration. All visit-specific PRO assessments should be completed before any tests, procedures, or other consultations for that visit to prevent influencing subject perceptions. If a patient has completed the PRO assessment and dosing is delayed, the PRO assessment does not need to be repeated if the assessment occurs ≤4 days before dosing. Medical resource utilization data will be collected (see Section 9.7).

Post-baseline disease evaluations may be conducted ±5 days from the scheduled visit date (based on Study Day 1, ie, the first day of dosing), if necessary. At the following study visit, the subject should return to the original planned schedule. Any missed study visits, tests not performed, or examinations that are not conducted must be reported as such on the eCRF. Additional serum or urine pregnancy tests (serum preferred) may be performed, as determined necessary by the investigator, to establish the absence of pregnancy at any time during the subject's participation in the study.

The total blood volume to be collected is approximately 25 mL during Screening, 280 mL during the first 6 cycles, 20 mL at each subsequent cycle (daratumumab monotherapy and observation phase), with an additional 10 mL at Cycle 7 Day 1 and Cycle 12 Day 1 and 15 mL at the End-of-Treatment visit. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1.1.1. Bone Marrow Biopsy/Aspirate Considerations

Three unstained formalin fixed paraffin embedded (FFPE) slides from the bone marrow biopsy or 2 unstained slides and 1 hematoxylin and eosin (H&E)-stained slide should be sent to the central laboratory to assess CD38 expression on the plasma cells. These slides may be from samples collected at any time, although it is preferable that the samples were collected within 56 days before randomization. In addition to the bone marrow biopsy slides, a fresh bone marrow aspirate (3 mL) should be collected and sent to the central laboratory for baseline MRD clone analysis. If a fresh bone marrow aspirate will not be performed at Screening because a sample is available within 56 days prior to Cycle 1 Day 1, then non-decalcified diagnostic tissue (3 non-decalcified bone marrow aspirate slides, touch-prep from biopsy (rolled biopsy) slides, or clot specimen slides) is requested.

Bone Marrow Aspirate to be Obtained at Complete Hematologic Response

For this study, subjects will be asked for a repeat bone marrow aspirate collection, if feasible, at the time CHR is assessed. All subjects, regardless of treatment assignment, are highly encouraged to provide this additional sample for research purposes. If a repeat sample is obtained at CHR, 3 mL of bone marrow aspirate should be sent to the central laboratory for biomarker analysis.

9.1.2. Screening Phase

The signed ICF must be obtained before any study-specific procedures are performed. Routine procedures performed as standard of care can be used for the study and do not need to be repeated if performed within the specified screening window. The Screening Phase begins when the first screening procedure is conducted (that was not performed as part of the subject's standard of care). During the Screening Phase, eligibility criteria will be reviewed and a complete clinical evaluation will be performed as specified in the Time and Events Schedule (Table 1). Screening procedures will normally be performed within 28 days before Cycle 1 Day 1. For subjects requiring mass spectrometry typing, the screening period is extended to 42 days. During Screening, a pregnancy test (serum preferred), for women of childbearing potential only, must be performed within 14 days prior to randomization. Blood type assessment and IAT testing must be done before the Cycle 1 Day 1 SC-administration of daratumumab (Arm B only). Results from skeletal surveys obtained within 42 days before Cycle 1 Day 1 and bone marrow aspirate/biopsy obtained within a maximum of 56 days before Cycle 1 Day 1 may be used without these tests being repeated. If laboratory tests are performed within 7 days before Cycle 1 Day 1, it is not mandatory to collect these samples again at the Cycle 1 Day 1 visit before administration of study treatment. Retesting of abnormal screening values that lead to exclusion are allowed only once during the screening period (to reassess eligibility). The last result known prior to Cycle 1 Day 1 will be used to determine eligibility. If approved by the sponsor, subjects who are screen failures may be rescreened once if their condition changes.

9.1.2.1. Histopathological Diagnosis of Amyloidosis

Tissue Specimens: based on detection of homogenous amorphous, eosinophilic, hyaline-like, extracellular (subepithelial) material by light microscopy of a hematoxylin and eosin stained biopsy (4-6µ thick sections) and concomitant congo red staining (organophilic/eosinophilic under bright light; apple green birefringence under polarized light (4-6µ thick sections) followed by immunohistochemical confirmation.

Electron microscopy appearance: unbranched 10 nm thick fibrils

Immunohistochemistry: Suggested antibodies for IHC evaluation include:

- Kappa light chain (monoclonal/ in situ hybridization or IHC)
- Lambda light chain (monoclonal/ in situ hybridization or IHC)
- Amyloid A (monoclonal)
- Transthyretin (polyclonal) should be negative in AL Amyloidosis

- Amyloid P component (polyclonal)
- Antihuman β amyloid (polyclonal)
- Anti-human β2 microglobulin (polyclonal)
- Fibrinogen (polyclonal)
- Lysozyme (polyclonal)

Mass Spectrometry Typing of AL Amyloid (Liquid Chromatography-Tandem Mass Spectrometry [LC-MS/MS]):

For male subjects over 70 years of age who have cardiac involvement only, and subjects of African descent (black subjects), a mass spectrometry typing of AL amyloid in a tissue biopsy is recommended to rule out age-related amyloid or hereditary amyloid (ATTR mutation). Mass spectrometry typing may be performed locally. However, if local mass spectrometry typing is not feasible, central testing is available. If using central testing, paraffin-embedded tissue biopsy specimens should be sent to the central laboratory to identify the amyloid protein as AL. Processes for collection and transmission to the central vendor can be found in the central laboratory manual. Of note, mass spectrometry will not be available in China.

9.1.2.2. Factor X Deficiency

Subjects with AL amyloidosis may develop acquired factor X deficiency (Choufani 2001).[5] Testing coagulation parameters and factor X levels for all subjects is recommended if a subject will have an invasive procedure, but not required. Any clinically significant bleeding should prompt testing for acquired factor X level and supportive therapy including factor replacement if needed.

9.1.3. Treatment Phase

Details of the procedures performed during the Treatment Phase are outlined in the Time and Events Schedule (Table 1). Subjects should start study treatment within 72 hours after randomization. Subjects will be closely monitored for AEs, laboratory abnormalities, and clinical response. Clinical evaluations and laboratory assessments may be repeated more frequently, if clinically indicated.

9.1.3.1. Safety Run-In

Subjects in the safety run-in will receive daratumumab plus CyBorD, with dosing staggered by at least 48 hours between subjects. After at least 10 subjects in the run-in have had at least 1 cycle of study treatment, an analysis of safety will be conducted by the sponsor and external academic hematologists. Subjects in the safety run-in will not be required to complete PRO assessments, but will follow all other scheduled assessments as specified in the Time and Events Schedule for Treatment Arm B including pharmacokinetic and immunogenicity blood sampling (Table 1). Data from these subjects will contribute to the overall safety evaluation but will not contribute to the efficacy evaluation.

9.1.3.2. Randomized Study

For subjects in Treatment Arm A, treatment will be from Cycle 1 to Cycle 6. Thirty days after the end of Cycle 6, subjects will have an End-of-Treatment visit and then enter the Post-Treatment Observation Phase.

For subjects in Treatment Arm B, combination treatment will be from Cycle 1 to Cycle 6. From Cycle 7, subjects may receive daratumumab SC as monotherapy for up to 24 cycles (~2 years) from the first dose of study treatment. Subjects will then have an End-of-Treatment visit and enter the Post-Treatment Observation Phase.

Before subjects discontinue study treatment due to disease progression as defined by the MOD-PFS composite endpoint, sites will document disease progression by completing a disease progression form and sending the completed form by facsimile (fax) to the sponsor's medical monitor within 24 hours of disease progression assessment. Patients who meet disease progression criteria based only on biomarker progression will continue study therapy until criteria for the MOD-PFS endpoint are met. If continued treatment is desired after MOD-PFS is met, a discussion between the investigator and medical monitor should occur about whether further study treatment would benefit a subject, without safety concerns. If disease progression is confirmed by the sponsor and no benefit is expected from further treatment, the subject will discontinue study treatment, complete the End-of-Treatment visit, and enter the Long-Term Follow-up Phase.

9.1.3.3. Autologous Stem Cell Collection Considerations

Stem cell collection is permitted during the study. Granulocyte colony-stimulating factor or plerixafor may be used as mobilization agents. Additional cyclophosphamide may also be used for mobilization. Investigators will record details of the stem cell yield (number of days of collection, number of failed collections, and total CD34+ cells per kg). A cycle delay of 4 weeks is permissible to accomplish stem cell mobilization and harvesting. Thereafter, the subject should continue treatment with study medications. Subcutaneous administration of daratumumab will not be extended beyond 24 cycles (~2 years) if treatment was delayed for stem cell collection.

Subjects for whom stem cell transplantation is planned within the first 6 cycles of study treatment are excluded from the study (see exclusion criterion 4). After 6 cycles of study treatment and evaluation of the primary endpoint of CHR have been completed, subjects may electively undergo stem cell transplantation. If they were in Treatment Arm B, these subjects will discontinue treatment with daratumumab. The reason for discontinuation should be recorded in the eCRF. However, these subjects will continue in the study for follow-up assessments. Disease assessments should continue for the first 2 years after transplantation or until progression of disease. Investigators will record time from transplant to engraftment. Engraftment will be defined as the day on which absolute neutrophil count is ≥1000 and platelet count is ≥50,000. Adverse events that are attributable to study treatment should be recorded for 30 days after the last dose of study treatment.

9.1.4. End-of-Treatment

The end-of-treatment is defined as any of the following:

- Completion of 6 cycles of CyBorD in Treatment Arm A
- Completion of 24 cycles (~2 years) of daratumumab treatment in Treatment Arm B
- Meeting any criterion in the MOD-PFS endpoint at any time (see Section 2.2 for definition of MOD-PFS)

Reasons for premature discontinuation of treatment are listed in Section 10.2. Subsequent therapy may be started after the end-of-treatment. Please refer to Section 9.1.4.1 for further considerations.

9.1.4.1. Subsequent Therapy

If a subject starts subsequent therapy prior to meeting the MOD-PFS endpoint, disease assessments should continue as scheduled until disease progression per the MOD-PFS endpoint has been recorded. In addition, collection of PRO data will occur when subsequent therapy is started and continue at a frequency of every 6 months until the MOD-PFS endpoint is met.

Prior to completion of 6 cycles in either Treatment Arm A or Treatment Arm B, subjects should not receive any non-protocol therapy for the treatment of AL amyloidosis unless the subject develops MOD-PFS. However, certain patients who have not responded after 3 cycles of treatment have a poor prognosis and may benefit from a switch to second line therapy (Wechalekar 2012).[48] While the goal is for all subjects to complete 6 cycles of treatment if possible, any subject who has achieved a best response of PR but has worsening organ function on Cycle 4 Day 1 may discontinue protocol therapy to switch to a second line therapy. For subjects who do not meet this criterion but for whom subsequent therapy might be optimal, please contact the sponsor's medical monitor to discuss continued treatment.

After completion of 6 cycles in either Treatment Arm A or Arm B and the post-treatment or Cycle 7 disease assessment, subsequent anti-amyloidosis therapy may be started. Subjects in Treatment Arm B who start subsequent therapy must discontinue daratumumab. Subsequent therapy may be started if the subject has had an insufficient response to initial therapy (eg, PR or stable disease) or if there has been cardiac or renal deterioration. Autologous stem cell transplant would also be considered subsequent therapy (see Section 9.1.3.3). For Treatment Arm A subjects who continue CyBorD post 6-cycles, the continued CyBorD treatment will be considered subsequent therapy.

Please refer to Table 8 for recommendations regarding subsequent therapy. Sites will document subsequent therapy by completing a subsequent therapy form and sending the completed form by fax to the sponsor's medical monitor prior to the start of salvage therapy.

Note: Isolated changes in cardiac biomarkers (Troponin and NT-proBNP) should not prompt any subsequent therapy unless accompanied by objective signs/symptoms of progressive cardiac dysfunction.

Table 8: Recommendations for Subsequent Therapy After Cycle 6

Response after 6 cycles of initial therapy	Action taken
Hematologic Response (PR or better) with improved major organ function	Observation or daratumumab monotherapy until disease progression
Hematologic Response (PR or better) with stable or worsening major organ function	Subsequent therapy may be considered
Hematologic Non-Response or disease progression with stable/improved organ function	Subsequent therapy may be considered
Hematologic Non-Response or disease progression with worsening organ function	Subsequent therapy recommended

9.1.4.2. End-of-Treatment Visits

Unless a subject withdraws consent for study participation or is lost to follow-up, an End-of-Treatment visit is to occur 30 days (±3 days) after the last dose of study treatment, or as soon as possible before the start of subsequent therapy. Every effort should be made to conduct the End-of-Treatment visit before the subject starts subsequent treatment. If a subject is unable to return to the study site for the End-of-Treatment visit, then the subject should be contacted to collect information on AEs that occur up to 30 days after the last dose of study treatment. Additional information on reporting of AEs is presented in Section 12.

9.1.5. Post-Treatment Observation Phase and Long-Term Follow-up

For subjects who discontinue study treatment before disease progression has been observed, disease evaluations should continue to be performed in the Post-Treatment Observation Phase as specified in the Time and Events Schedule (Table 1). Subjects will be instructed that study drug will not be made available to them after they have completed/discontinued study treatment and that they should return to their primary physician to determine standard of care.

Subjects with confirmed disease progression according to MOD-PFS will enter the Long-term Follow-up Phase.

After the clinical cutoff, currently defined as 200 MOD-PFS events, all subjects in the post-treatment observation phase of the study will enter Long-Term Follow-up. Subsequent anticancer treatment, response to subsequent treatment, and date of progression will be recorded and survival status will be obtained every 16 weeks. Information on secondary malignancies will also be collected. Information may be obtained via telephone contact, in which case 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 on the eCRF.

9.2. Efficacy Evaluations

Disease response and progression will be based on assessments for hematologic response as defined in Section 9.2.1. A blinded IRC consisting of 3 experts in AL amyloidosis will evaluate and adjudicate responses. The investigator should also continue to evaluate responses locally and document in the eCRF.

Daratumumab detection on serum IFE (S-IFE) has been demonstrated in subjects treated with 16 mg/kg, and may interfere with the traditional criteria of negative S-IFE for hematological complete response (McCudden 2015)[29]. To mitigate this interference, the sponsor has developed a reflex assay that utilizes anti-idiotype antibody to bind daratumumab and confirm its interference on IFE. For all subjects on Arm B (daratumumab plus CyBorD) with VGPR, and a negative M-protein by SPEP, reflex IFE testing may be performed by the central laboratory to confirm daratumumab interference on IFE.

9.2.1. Hematologic Response Categories

Disease evaluations must be performed on the scheduled assessment day (±5 days) every 4 weeks during Cycles 1 through 6 and every 8 weeks at Cycle 7 and beyond (including during the Post-Treatment observation phase) until MOD-PFS is observed. If study treatment has been delayed for any reason, disease evaluations will continue to be performed according to the original schedule, regardless of any changes to the dosing regimen.

Disease evaluations will be performed by a central laboratory (unless otherwise specified) according to the Time and Events Schedules (Table 1) until disease progression as defined by the MOD-PFS endpoint is documented, death, withdrawal of consent for study participation, or the end of study, whichever occurs first. Disease evaluations scheduled for study treatment days should be collected before study treatment is administered. For free light chain assessment, M-protein, and IFE measurements in serum and 24-hour urine, the investigator will use results provided by the central laboratory. This study will use the consensus recommendations for AL amyloidosis treatment response criteria (Comenzo 2012)[7] presented in Table 9. Subjects with positive S-IFE and confirmed daratumumab IFE interference, that meet all other clinical criteria for CHR, will be considered CHR.

Table 9: International Amyloidosis Consensus Criteria

Hematologic response and progression criteria	
Response Category	*Criteria*
Complete	Normalization of free light chain levels and ratio, negative serum and urine IFE[a]
Very Good Partial	Baseline[b] dFLC ≥50 mg/L: Reduction in the dFLC <40 mg/L Baseline[b] dFLC < 50 mg/L: ≥ 90% reduction in serum M-protein plus urine M-protein <100 mg/24 hours
Partial	Baseline[b] dFLC ≥50 mg/L: A greater than 50% reduction in the dFLC Baseline[b] dFLC < 50 mg/L: ≥50% reduction in serum M-protein plus reduction in 24-hr urine M-protein by ≥90% or to <200 mg/24 hours.
No response	Less than a PR
Progression	From CHR, abnormal free light chain ratio (involved light chain must double), Or From CHR/VGPR/PR, 50% increase in serum M-protein to >0.5 g/dL or 50% increase in urine M-protein to >200 mg/day (a visible peak must be present) Involved Free light chain increase of 50% to >100 mg/L

Abbreviations: CHR=Complete hematologic response; dFLC=difference between iFLC and uninvolved FLC; FLC=free light chain; IFE=immunofixation; PR=partial response.

a. If iFLC <ULN and serum and urine IFE are negative, then neither a normal uFLC level nor a normal FLC ratio are required for complete response (CR).[6,27,31]

b. Baseline measurement is defined as the closest non-missing measurement taken on or prior to the first study treatment administration.

Hematologic response/disease progression must be documented consistently across clinical study sites using the criteria shown in Table 9. It is important that instances of suspected disease progression be reported to the sponsor as soon as possible. Laboratory values can fluctuate for a variety of reasons. Therefore, it is strongly recommended that hematologic disease progression be confirmed in a subsequent disease evaluation visit via central laboratory values prior to determining MOD-PFS.

Diagnosis and documentation of disease progression will be faxed within 24 hours to the sponsor. The medical monitor will review the form to confirm that the criteria for disease progression have been met. If the medical monitor agrees that disease progression has occurred, then a confirmation fax or e-mail will be returned to the investigator, and the subject will be withdrawn from study treatment. If the medical monitor considers that the criteria for disease progression have not been met, then the medical monitor will contact the investigator to discuss the subject.

For continuation of study treatment, response will be determined on an ongoing basis by the investigator. Primary analysis will be based on IRC determination. For additional data analysis, the sponsor will use a modification of a computer algorithm validated for multiple myeloma that has been shown to provide consistent review of the data necessary to determine disease progression and response according to the response criteria. For CHR, the response criteria require subjects to have a negative serum and urine IFE as well as normalization of FLC levels and ratio.

9.2.2. Monoclonal Protein (M-protein) Measurements in Serum and Urine

Blood and 24-hour urine samples for M-protein measurements will be sent to and analyzed by a central laboratory. Only 1 serum and one 24-hour urine sample per time point are required by the central laboratory to perform the following tests. If the 24-hour urine collection (for UPEP and U-IFE) began before informed consent was obtained as part of routine patient care, the sample can be used in this study as long as it was sent to the central laboratory for analyses after the informed consent was obtained.

- Serum M-protein quantitation by electrophoresis (SPEP) and serum immunofixation (S-IFE)
- If daratumumab interference is suspected based on SPEP and IFE results, additional reflex IFE testing will be performed
- Serum free light chain assay
- 24-hour urine M-protein quantitation by electrophoresis (UPEP) and U-IFE

Blood and 24-hour urine samples will be collected as specified in Table 1. S-IFE and U-IFE test and serum free light chain assay will be performed at Screening and Day 1 of every cycle. For subjects with VGPR or better and suspected daratumumab interference on serum IFE, a second reflex assay using the anti-idiotype monoclonal antibody may be used to confirm daratumumab migration on the IFE. Subjects that meet all other response criteria for CHR, and whose positive IFE is confirmed to be daratumumab, will be considered complete responders.

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

9.2.3. Determination of Organ Response

Organ disease that is considered to be quantifiable for response evaluated by the central laboratory includes cardiac disease (NT-proBNP, troponin T, and high sensitivity troponin T), renal disease (proteinuria, eGFR), and hepatic disease (alkaline phosphatase). Cardiac and liver organ response must be monitored by the International Amyloidosis Consensus Criteria (Comenzo 2012)[7]. Renal organ response must be monitored by Palladini criteria (Palladini 2014)[35]. Refer to Table 10.

The cardiac biomarker NT-proBNP will be used to monitor cardiac response. Response is defined as a decrease of >30% in NT-proBNP levels and >300 ng/L (NOTE: subjects with NT-proBNP <650 ng/L are not assessable for a cardiac NT-proBNP response) compared to baseline levels or NYHA class response (>2 class decrease in subjects with NYHA class of 3 or 4). The cardiac biomarkers (NT-proBNP, troponin T and high sensitivity [HS] troponin T) will be evaluated by the central laboratory. Of note, only HS Troponin T will be sent to central laboratory in China.

For kidney response, the recent Palladini criteria response is defined as a decrease in proteinuria by ≥30% or below 0.5 g/24 hours without renal progression; renal progression is defined as a ≥25% eGFR decrease (Palladini 2014)[35].

For liver response, alkaline phosphatase will be monitored. For hepatic response, a 50% decrease in abnormal alkaline phosphatase value is required.

Table 10: Organ Response and Progression Criteria[a]

Organ	Response[d]	Progression[d]
Heart[a]	NT-ProBNP response (>30% and >300 ng/L decrease in subjects with baseline NT-proBNP ≥650 ng/L) or NYHA class response (≥2 class decrease in subjects with baseline NYHA class 3 or 4)	NT-proBNP progression (>30% and >300 ng/L increase[c]) or cTn progression (≥33% increase) or ejection fraction progression (≥10% decrease)
Kidney[b]	≥30% decrease in proteinuria or drop in proteinuria below 0.5 g/24 hours in the absence of renal progression.	≥25% decrease in eGFR
Liver[a]	50% decrease in abnormal alkaline phosphatase value	50% increase of alkaline phosphatase above the lowest value

Abbreviations: eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; cTn, cardiac troponin; NYHA, New York Heart Association.

a. Based on Comenzo 2012 consensus criteria (Comenzo 2012)[7]
b. Based on Palladini 2014 criteria (Palladini 2014)[35]
c. Subjects with progressive worsening renal function cannot be scored for NT-proBNP progression.
d. Baseline measurement is defined as the closest non-missing measurement taken on or prior to the first study treatment administration.

9.2.4. Bone Marrow Assessment

Bone marrow biopsy slides will be assessed by IHC for CD38 expression on the plasma cells and bone marrow aspirate slides will be used to identify an index clone(s) for baseline MRD assessment. MRD assessment has been shown to have prognostic significance in many hematological malignancies and may have utility in amyloidosis. In the present study, MRD will be assessed in bone marrow aspirates, when feasible, from subjects who achieve CHR.

9.3. Pharmacokinetics and Immunogenicity

9.3.1. Evaluations

Samples to assess both the serum concentration (pharmacokinetics) of daratumumab and the generation of anti-daratumumab antibodies (immunogenicity) will be obtained from all subjects in the safety run-in and in Treatment Arm B according to the Time and Events Schedule (Table 1 and Table 2). At specified time points, venous blood samples (5 mL per sample) will be collected to determine serum concentration of daratumumab and the serum will be divided into 3 aliquots (1 aliquot for pharmacokinetic analysis, 1 aliquot for antibodies to daratumumab analysis [when appropriate], and 1 aliquot as a backup).

Samples will also be collected from all subjects in the safety run-in and in Treatment Arm B to evaluate the immunogenicity of rHuPH20 according to the Time and Events Schedule. At specified time points, venous blood samples (5 mL per sample) will be collected and the plasma will be divided into 5 aliquots to accommodate immunogenicity screening, confirmatory, and titer assays and neutralizing antibody analysis (when appropriate) as well as volume for backup.

The exact dates and times of blood sampling must be documented. Refer to the central 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

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

For the 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 Treatment Arm B. The pharmacokinetic parameters are defined as:

- Sample collected on Day 4 will be nominally classified as Cmax: Maximum observed serum concentration
- Predose samples will be reported as Ctrough: Trough concentrations

To further describe the PK of daratumumab in amyloidosis, population pharmacokinetic analysis of serum concentration-time data of daratumumab may be performed using nonlinear mixed-effects modeling and may include data from other clinical studies. Details will be provided in a population pharmacokinetic 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 safety run-in and Treatment Arm B 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 safety run-in and Treatment Arm B and assessed for antibodies to rHuPH20.

When an IRR occurs associated with the second daratumumab SC-administration or beyond, 2 separate blood samples should be obtained, if possible, for determination of antibodies to daratumumab and antibodies to rHuPH20. No unscheduled samples need to be collected for SC-infusion reactions associated with the first SC-infusion of daratumumab. Daratumumab serum concentration will also be determined from the daratumumab SC-infusion reaction sample for the purpose of interpreting immunogenicity data. These samples will be stored and evaluated if deemed necessary. If the SC-infusion reaction results in treatment discontinuation, then subjects 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.

9.4. Pharmacokinetic/Pharmacodynamic Evaluations

Data permitting, pharmacokinetic/pharmacodynamic modeling may be performed, to assess the relationship between serum concentrations of daratumumab and endpoints of clinical efficacy or safety. If these analyses are performed, then the details and results will be presented in a separate report.

9.5. Biomarkers

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. All biomarker assessments will be performed in a central laboratory. Samples for biomarker evaluations will be collected as specified in Table 1.

Biomarker evaluations will focus on the evaluation of CD38 expression by IHC on the malignant plasma cells from core diagnostic biopsies to determine if CD38 expression correlates with response to daratumumab. Bone marrow aspirate will also be obtained to evaluate MRD. MRD negativity may be a potential surrogate for HemPFS and OS. Minimal residual disease may be monitored in subjects who achieve CHR using next generation sequencing (NGS) or similar technologies that utilize malignant plasma cell DNA from bone marrow aspirates. Flow cytometry will be performed on peripheral blood to confirm daratumumab mechanism of actions in amyloidosis.

Whole blood samples and their derivatives will be obtained for evaluation including but not limited to biomarkers related to AL amyloidosis or immune biology. The initial values of these parameters and relative changes during therapy may be correlated with the quality and duration of clinical response. Biomarker assessments may monitor changes in immune cell subpopulations including the determination of frequency and activity of regulatory T cells and MDSC as these cells express CD38 and may be involved in immune-regulatory mechanisms of daratumumab activity (Krejcik 2016).[18] Samples will also be processed to obtain plasma and may be analyzed for exploratory biomarkers predictive of response or resistance to therapy.

9.6. Sample Collection and Handling

The actual dates and times of local sample collection must be recorded in the eCRF or laboratory requisition form. If blood samples are collected via an indwelling cannula, then an appropriate amount (1 mL) of serosanguineous fluid slightly greater than the dead space volume of the lock will be removed from the cannula and discarded before each blood sample is taken. Refer to the Time and Events Schedule (Table 1 and Table 2) for the timing and frequency of all sample collections.

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

9.7. Medical Resource Utilization

Medical resource utilization data, associated with protocol-driven medical encounters and safety monitoring, will be collected in the eCRF by the investigator and study-site personnel for all

subjects throughout the study. Specifically, the investigator will document all hospitalizations and indicate whether the hospitalization was for a primary cardiac or non-cardiac indication. In addition, use of hemodialysis, cardiac assist devices (IABP or LVAD), and solid organ transplantation of the kidney or heart will be documented in the eCRF. The use of hemodialysis will also be documented in the eCRF.

The Medical Encounters Summary (yes/no) question in the eCRF should be answered at each disease assessment (Cycles 1-6 every 28 days, Cycle 7+ and during the post-treatment observation phase every 8 weeks), and every 16 weeks during the long-term follow-up phase of the study. If the subject has required any additional encounters other than those mandated per protocol since the last disease evaluation visit, a Medical Encounters eCRF page must be completed.

9.8. Patient-Reported Outcomes

On the days that PROs are scheduled (see Table 1), the PROs should be administered before any other study procedures. If a subject has completed the PRO assessments and dosing is delayed, the PRO assessment does not need to be repeated if the assessment occurs ≤4 days before dosing. PROs will be administered electronically and collected to understand what trends occur over time.

To our knowledge, no validated, disease-specific questionnaires for amyloidosis exist to evaluate symptoms and disease-specific HRQOL. Symptoms experienced by patients with amyloidosis can vary widely (Lin 2015).[23] The EORTC QLQ-C30 (Attachment 8 and Attachment 9) is a cancer-specific PRO measure that captures most of the symptoms reported by patients with amyloidosis. It includes 30 items resulting in 5 functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), 1 Global Health Status scale, 3 symptom scales (fatigue, nausea and vomiting, and pain), and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Also, 3 additional items will be used from the EORTC Item Bank (MY20, V28, and PR25) to assess symptoms (upper and lower body swelling and neuropathy) reported by patients with amyloidosis (Attachment 9, Lin 2015; EORTC website).[23] The recall period is 1 week (the past week). Administration time for the questionnaire is approximately 15 minutes. The EORTC QLQ-C30 has been widely used among cancer patients. Scores are transformed to a 0 to 100 scale. A high score for the global health status represents high quality of life, a high score for a functional scale represents high level of functioning, and a high score for a symptom scale/items represent a high level of symptomatology/problems. Reliability, validity, and clinically meaningful change of the EORTC QLQ-C30 has been demonstrated in multiple myeloma patients (Wisløff 1996, Wisløff 1997).[52,51]

The EQ-5D-5L (Attachment 10) is a generic measure of health status. For the purposes of this study, the EQ-5D-5L will be used to generate utility scores for use in cost-effectiveness analyses. The EQ-5D-5L is a 5-item questionnaire that assesses 5 domains including mobility, self-care, usual activities, pain/discomfort and anxiety/depression plus a visual analog scale rating “health today” with anchors ranging from 0 (worst imaginable health state) to 100 (best imaginable

health state) (Herdman 2011).[13] The scores for the 5 separate questions are categorical and cannot be analyzed as cardinal numbers. However, the scores for the 5 dimensions are used to compute a single utility score ranging from zero (0.0) to 1 (1.0) with higher values representing better general health status of the individual. Administration time for the questionnaire is up to approximately 10 minutes.

The SF-36v2 Health Survey (Attachment 11) is a generic measure of health status. The SF-36v2 consists of 36 questions that yield an 8-scale profile of functional health and well-being, as well as 2 physical and mental health summary measures and a preference-based health utility index. The physical component summary, the MCS, and the 8 domain scores range from zero (0) to 100, with higher scores representing higher level of functioning. Administration time for the questionnaire is approximately 10 minutes.

9.9. Safety Evaluations

Safety will be assessed by AEs, laboratory test results, ECGs, echocardiograms, vital sign measurements, physical examination findings, and ECOG performance status.

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.

Adverse Events

Adverse events (with the exception of progression of AL amyloidosis) will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) from the time a signed and dated informed consent is obtained until 30 days following the last dose of study treatment. Adverse events will be followed by the investigator as specified in Section 12, Adverse Event Reporting. Expected progression of disease should not be considered an AE (or SAE). However, if determined by the investigator to be more likely related to the study treatment than the underlying disease, the clinical signs or symptoms of progression and the possibility that the study treatment is enhancing disease progression, should be reported per the usual reporting requirements (see Section 12).

Clinical Laboratory Tests

Blood samples for serum chemistry and hematology will be collected. 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.

The following tests will be performed by the local laboratory:

Hematology Panel

-hemoglobin
-white blood cell (WBC) count with absolute neutrophils and lymphocytes
-platelet count
- Optional: coagulation studies (PTT, PT)
- Optional: Factor X levels (recommended if a subject will have an invasive procedure or experiences a clinically significant bleeding event)

Serum Chemistry Panel

-sodium
-potassium
-aspartate aminotransferase (AST)
-alanine aminotransferase (ALT)
-Thyroid-stimulating hormone (TSH) and T4 (at Screening only and subsequently if clinically indicated)
-total bilirubin
-direct bilirubin if history of Gilbert's syndrome
-alkaline phosphatase
-creatinine

Serum or urine pregnancy testing (serum preferred): 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 who are within 6 months of starting study treatment when Protocol Amendment 2 is implemented will be required to have HBV serology performed locally upon signing the updated ICF. If the Hepatitis B serologic status of a subject in the daratumumab plus CyBorD arm is unknown, HBsAg, Anti-HBs, and Anti-HBc testing is recommended if the subject is still receiving daratumumab or is within 6 months of the last dose.

HBV serology is not required at Screening or for subjects ongoing in the Treatment Phase 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.

Hepatitis B Virus (HBV) DNA Tests

Subjects who tested positive for Anti-HBc or Anti-HBs or both 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 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.

At Screening: calcium and eGFR calculated using CKD-EPI equation.

FEV1 Test: Subjects with known or suspected COPD or asthma must have an FEV1 test during Screening.

The following tests will be performed by the central laboratory and results made available to the site study staff:

- NT-proBNP
- Troponin and high sensitivity troponin
- SPEP, S-IFE
- UPEP, U-IFE
- Serum free light chains
- Serum creatinine (to derive creatinine clearance)
- 24-hour urine protein
- eGFR

Electrocardiogram (ECG)

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

Transthoracic Echocardiogram (TTE) or Alternative Assessment:

Transthoracic echocardiogram (TTE) will be performed as specified in the Time and Events Schedule to assess left ventricular ejection fraction (LVEF) and diastolic dysfunction. Repeat TTE may be done during the study if clinically indicated.

Adverse events identified on TTE imaging (decrease in LVEF, for example) should be reported in the eCRF. Alternative cardiac assessments including multigated acquisition scan, cardiac magnetic resonance imaging (MRI), and cardiac catherization are acceptable methods of evaluating LVEF if TTE is not used.

To assess diastolic function, several attributes of the echocardiogram (with units) will be captured in the eCRF. These assessments include the following parameters, if available locally:

- Left Ventricular Internal Diameter in diastole (LVIDd): (mm)
- Left Ventricular Intra-ventricular Septal Thickness: (mm)
- Left Ventricular Posterior wall thickness: (mm)
- Mitral Valve Inflow E-wave velocity (E): (cm/second)

- Mitral annular Velocity of Lateral wall (Ea): (cm/second)
- E/Ea ratio
- Ejection fraction

Vital Signs

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

Weight assessment should be performed at every visit as per the Time and Events Schedule to monitor volume overload. Any weight gain should prompt evaluation and if needed, management of volume overload.

Physical Examination and ECOG Performance Status

Physical examinations will be performed and ECOG performance status will be assessed as specified in Attachment 1. Any clinically significant abnormalities identified during the study upon physical examination should be reported as an AE. ECOG performance status will be used to evaluate the impact of the disease status on the activities of daily living.

Blood Type, Rh, and Indirect Antiglobulin Testing (IAT)

Blood type, Rh, and IAT should be done before the first dose of daratumumab for subjects in the safety run-in and in Treatment Arm B. Subject RBC phenotyping (standard or extended) is an alternative option to the IAT test, if locally required. Either method must be completed prior to first daratumumab SC-administration.

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 SC-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 (Chapuy 2015).[2]

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

a) Providing ABO/RhD compatible, phenotypically (standard or extended phenotyping) or genotypically matched units

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

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

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

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

10.1. Completion

A subject will be considered to have completed the study if he or she has died before the end of the study, has not been lost to follow-up, or has not withdrawn consent for study participation before the end of the study (end of study defined in Section 17.9.1).

10.2. Discontinuation of Study Treatment/Withdrawal from the Study

Discontinuation of Study Treatment

A subject will not be automatically withdrawn from the study if they must discontinue treatment before the end of the treatment regimen. The End-of-Treatment visit and Post-Treatment visit assessments should continue as specified in the Time and Events Schedule.

A subject's study treatment must be discontinued if:

1. The investigator believes that for safety reasons or tolerability reasons (eg, AE), it is in the best interest of the subject to discontinue study treatment.
2. The subject becomes pregnant.
3. The subject (or the subject's legally acceptable representative) withdraws consent for administration of study treatment.
4. The subject initiates treatment with a prohibited medication.
5. The subject receives concurrent (non-protocol) treatment for AL amyloidosis (subsequent therapy).
6. The subject experiences unacceptable toxicity, including daratumumab IRRs as described in Section 6.2.3. For subjects whose daratumumab treatment is discontinued because of a daratumumab-related SC-infusion reaction, they may continue to receive cyclophosphamide/bortezomib/dexamethasone. For subjects whose bortezomib is discontinued because of a bortezomib-related toxicity (eg, peripheral neuropathy), they may continue to receive daratumumab, cyclophosphamide, and dexamethasone.
7. The subject's dose is held for more than 28 days in Cycles 1 to 6 (or more than 6 weeks from Cycle 7) due to toxicity, or if 3 consecutive planned doses are missed for reasons other than toxicity (unless agreed upon by the investigator and sponsor to continue).

8. The subject meets criteria for MOD-PFS endpoint (See Section 2.2), provided no benefit is expected from continuing treatment (see Section 9.1.3.2).
9. The subject receives autologous stem cell transplant.
10. A subject who experiences a second primary malignancy that cannot be treated by surgery or radiotherapy alone must be withdrawn from the study. However, a subject who develops a malignancy that can be cured surgically or by radiation therapy may continue to receive the assigned study treatment and should continue to be followed for subsequent progression of AL amyloidosis.

The primary reason for discontinuation of study treatment is to be recorded in the eCRF. For subjects who discontinue study treatment due to meeting MOD-PFS criteria, sites will complete a disease progression form and fax the completed form to the sponsor's medical monitor. If study treatment is discontinued for a reason other than disease progression, then disease evaluations will continue to be performed as specified in the Time and Events Schedule (Table 1).

Withdrawal From the Study

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

1. Lost to follow-up.
2. Withdrawal of consent for any type of follow-up, including overall survival.
3. Death.
4. Sponsor terminates the study.

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 with the subject 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 from the study will not be replaced.

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 primary analysis population will be the intent-to-treat (ITT) population, which will include all randomized subjects. Safety will be evaluated for the population of all treated subjects. The per protocol population is a subset of the ITT population defined as those subjects who have no major protocol violations related to inclusion and exclusion criteria. The pharmacokinetic analyses will be performed on the pharmacokinetic-evaluable population. Continuous variables will be summarized using descriptive statistics such as mean, standard deviation, median, and range. Categorical variables will be summarized using frequency and percentage. For time-to-event variables, the Kaplan-Meier method will be used for descriptive summaries.

11.2. Sample Size Determination

The sample size for this study is based on the alternative hypothesis of a 15% improvement in overall CHR. Taking an overall CHR rate estimated to be 25% for the CyBorD arm (Palladini 2015),[38] adding a 15% improvement translates to an overall CHR rate of 40% for the CyBorD plus daratumumab arm. Approximately 360 subjects (180 subjects per arm) would provide more than 85% power to detect a 15% improvement in overall CHR using a likelihood ratio test with a 2-sided alpha of 0.05.

The Post-Treatment phase will continue until 200 MOD-PFS events have been observed. Therefore, this study will achieve approximately 80% power to detect a 33% reduction in the risk of hematologic progression, MOD or death (hazard ratio [CyBorD plus daratumumab vs CyborD] of 0.67) with a log-rank test (2-sided alpha=0.05).

11.3. Efficacy Analyses

The primary comparison of the 2 randomized treatments will be made with respect to overall CHR based on IRC assessment using the Cochran-Mantel-Haenszel (CMH) chi square test in the ITT population stratified by cardiac risk (Dispenzieri 2014; Palladini 2016)[11,36] (Stages I, II, and IIIa), countries that typically offer transplant for patients with AL amyloidosis (List A or List B), and renal function (CrCl ≥60 mL/min or CrCl <60 mL/min). A Mantel-Haenszel odds ratio, along with its 2-sided 95% confidence interval, will be calculated. All binary secondary endpoints will be analyzed using the CMH chi-square test. Analysis of CHR rate at 6 months will be performed similarly to the primary endpoint CHR rate.

For time-to-event endpoints (eg, MOD-PFS, HemPFS, OS, etc.), Kaplan-Meier estimates will be presented, along with a log-rank test stratified by cardiac risk (Dispenzieri 2014[11]; Palladini 2016[36]) (Stages I, II, and IIIa), countries that typically offer transplant for patients with AL amyloidosis (List A or List B), and renal function (CrCl ≥60 mL/min or CrCl <60 mL/min) comparing the 2 treatment arms. Median along with corresponding 95% CIs will be obtained from the Kaplan-Meier estimates. Cox's regression will be applied to obtain the hazard ratio estimate and the corresponding 95% CI.

Organ response/progression analysis will be performed separately for each organ involved at baseline, specifically for heart, kidney, and liver. A transient increase in NT-proBNP, troponin T, 24-hour proteinuria, and alkaline phosphatase, or a transient decrease in eGFR meeting organ

progression criteria are not considered for organ progression if it persisted less than 6 months, and levels returned to baseline level or better. Descriptive statistics will be provided to summarize organ response/progression at 6 months, time to organ response, and time to organ progression.

11.4. Pharmacokinetic Analyses

Pharmacokinetic data will be listed by visit for the pharmacokinetic-evaluable population, defined as subjects assigned to Treatment Arm B (CyBorD plus daratumumab) who have received at least 1 dose of daratumumab and have at least 1 pharmacokinetic sample concentration value after the first SC-administration of daratumumab.

All serum concentrations below the lowest quantifiable concentration in a sample or missing data will be labeled as such in the concentration database. Concentrations below the lowest quantifiable concentration in a sample will be treated as zero in the summary statistics. All subjects and samples excluded from the analysis will be clearly documented in the clinical study report.

Serum concentration data collected within specified windows in Treatment Arm B will be summarized using descriptive statistics, by visit. All predose samples will be described as Ctrough, whereas Cycle 1 Day 4 and Cycle 3 Day 4 serum concentrations will be described as Cmax.

To further describe the PK of daratumumab in amyloidosis population and to identify covariates affecting the PK, pooled population pharmacokinetic analysis may be performed using nonlinear mixed-effects modeling and may include data from other studies. If the population pharmacokinetic analysis is conducted, then details will be given in a population pharmacokinetic analysis plan and the results of the analysis will be presented in a separate report.

11.5. Immunogenicity Analyses

The incidence of antibodies to daratumumab and antibodies to rHuPH20 will be summarized for all subjects assigned to Treatment Arm B (CyBorD plus daratumumab) who receive at least 1 dose of daratumumab and have appropriate samples for detection of antibodies to daratumumab or rHuPH20 after their first daratumumab SC-administration. The maximum titers of antibodies to daratumumab and rHuPH20 will be summarized for subjects who are positive for antibodies to daratumumab and rHuPH20.

11.6. Pharmacokinetic/Pharmacodynamic Analyses

To understand the relationship between serum concentrations of daratumumab and biomarkers or endpoints of clinical efficacy or safety, additional pharmacokinetic/pharmacodynamic modeling may be performed, which will be summarized in a separate report.

11.7. Biomarker Analyses

Any biomarker measurements will be listed, tabulated, and where appropriate, plotted. As this is an open-label study with an active control treatment, statistical analyses will be done to aid in the understanding of 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.

11.8. Patient-Reported Outcomes

EORTC QLQ-C30 scale and single-item scores, EQ-5D-5L visual analog scale and utility values, and SF-36v2 component summary and domain scores will be summarized at each time point. Treatment effect will be assessed by change from baseline at each time point summarized descriptively by treatment group.

11.9. Safety Analyses

Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events are AEs with onset during the Treatment Phase or that are a consequence of a pre-existing condition that has worsened since baseline. All reported AEs will be included in the analysis. For each AE, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment arm. In addition, comparisons between treatment arms 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 AE, or who experience a severe or an SAE.

Clinical Laboratory Tests

Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point. Changes from baseline results will be presented in pre- versus post-treatment cross-tabulations (with classes for below, within, and above normal ranges). Worst toxicity grade during treatment will be presented, according to the National Cancer Institute's Common Terminology for Adverse Events (NCI-CTCAE) (version 4.03). 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.

Electrocardiogram (ECG)

The number and percentage of subjects with normal or abnormal (clinically significant or clinically insignificant) 12-lead ECG results will be summarized by treatment arm.

Transthoracic Echocardiogram (TTE) or Other Assessment of Cardiac Function

Any changes from baseline TTE measurements (specifically, changes in LVEF and changes in diastolic function) will be summarized by treatment arm. Descriptive statistics will be calculated for observed values at baseline and change from baseline at each scheduled time point. Frequency tabulations of the abnormalities will be made.

Vital Signs

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

Physical Examination and ECOG

Descriptive statistics of baseline values and change from baseline will be summarized at each scheduled time point.

11.10. Interim Analysis

Two interim analyses are planned for the randomized study. The first interim will occur after the first 30 subjects are treated for at least 1 cycle (CyBorD and CyBorD plus daratumumab). The purpose of the first interim analysis is to have a comprehensive evaluation of safety. The second interim analysis will occur after at least 180 subjects in total are treated for at least 6 cycles. The purpose of the second interim analysis is to evaluate cumulative interim safety and efficacy data. Both futility and efficacy stopping rules are built in this interim analysis. The study may be stopped due to futility if the overall CHR rate in Treatment Arm B (CyBorD plus daratumumab) is the same or worse than Treatment Arm A (CyBorD). The study may be stopped due to efficacy if the significance level at this interim analysis to establish the superiority of CyBorD plus daratumumab over CyBorD is ≤0.0001 (2-sided). The primary analysis will occur after all subjects are treated for at least 6 cycles and the alpha to be spent is 0.04999 (2-sided).

An IDMC, consisting of 2 clinicians and 1 statistician, will be established to review the interim results at the planned interim analyses in the randomized study. After the interim review, they will make recommendations regarding any required modification and provide guidance in the continuation of the study. The details will be provided in a separate IDMC charter.

12. ADVERSE EVENT REPORTING

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

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

An AE is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Council for 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 AEs starting with the signing of the ICF (refer to Section 12.3.1, All Adverse Events, for time of last AE recording).

Serious Adverse Event

An SAE based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

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

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

If a serious and unexpected AE 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 AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For daratumumab, the expectedness of an AE will be determined by whether or not it is listed in the IB. For bortezomib, cyclophosphamide, and dexamethasone, please refer to the appropriate product label or SmPC for the expectedness of an AE.

Adverse Event Associated With the Use of the Drug

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

12.1.2. Attribution Definitions

Not Related

An AE that is not related to the use of the drug.

Doubtful

An AE 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 AE 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 AE 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 AE 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 AE or SAE should be completed using the NCI-CTCAE version 4.03. Any AE or SAE not listed in the NCI-CTCAE version 4.03 will be graded according to investigator clinical judgment by using the standard grades as follows:

Grade 1 (Mild): asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 (Moderate): minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.

Grade 3 (Severe or medically significant): not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.

Grade 4: Life-threatening consequences; urgent intervention indicated.

Grade 5: Death related to the AE

Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

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
- Inadvertent or 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)

Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of an SAE should be recorded on the Serious Adverse Event page of the eCRF.

12.3. Procedures

12.3.1. All Adverse Events

All AE and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until 30 days after the last dose of study treatment (cyclophosphamide, bortezomib, dexamethasone or daratumumab), until the subject withdraws consent for study participation, or until the subject starts subsequent therapy, whichever occurs first. The only exception is for subjects who have withdrawn informed consent for study participation or for subjects who have received additional treatment with therapeutic intent for AL amyloidosis within 30 days after the last study treatment administration. For subjects who

have received additional treatment with therapeutic intent for AL amyloidosis during the AE reporting period, only AEs that are considered to be possibly, probably, or very likely related to study drug must be reported (unless the subject has been withdrawn from the study).

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

Anticipated events will be recorded and reported as described in Attachment 12 in countries where required.

Expected progression of disease should not be considered an AE (or SAE). However, if determined by the investigator to be more likely related to the study treatment than the underlying disease, the clinical signs or symptoms of progression and the possibility that the study treatment is enhancing disease progression, should be reported per the usual reporting requirements (see Section 12). Death should not be recorded as an AE or SAE, but as the outcome of an AE. The AE that resulted in the death should be reported as an SAE. All events that meet the definition of an SAE will be reported as SAEs, regardless of whether they are protocol-specific assessments.

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

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

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

- Subject number
- Site number
- Study number
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number
- Blood type and IAT results (safety run-in and Treatment Arm B only)
- Statement, in the local language(s), that the subject is participating in a clinical study

12.3.2. Serious Adverse Events

All SAEs 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 SAEs 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 an SAE should be made by fax.

All SAEs 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 treatment 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 an SAE. 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 an SAE, except hospitalizations for the following:

- If the subject has not experienced a significant medical event but is hospitalized overnight only for observation following SC-administration of daratumumab, then the hospitalization should not be reported as an SAE.
- Hospitalizations not intended to treat an acute illness or AE (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 SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.

12.3.3. Pregnancy

All initial reports of pregnancy 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, stillbirth, and congenital anomaly) are considered SAEs and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must promptly discontinue further study treatment. The subject should be referred to a physician experienced in teratology for evaluation and advice. 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 an SAE, the study-site personnel must report the PQC to the sponsor according to the SAE reporting timelines (refer to Section 12.3.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2. Contacting Sponsor Regarding Product Quality

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

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drug(s)

The daratumumab SC supplied for this study is a colorless to yellow liquid and sterile concentrate of 120 mg/mL as a liquid vial. The study agent should be essentially free of visible particulate matter at the time of syringe preparation and drug product administration. Each vial of co-formulated daratumumab contains nominal 15 mL (16 mL including overfill to account for hold-up volume losses), 10 mM histidine, 300 mM sorbitol, 1 mg/mL methionine, 0.04 % PS20, and 2000 U/mL of rHuPH20 at pH 5.6. It will be manufactured and provided under the responsibility of the sponsor.

14.2. Packaging

Daratumumab SC 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 SC product 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 utilized after the expiry date printed on the label. Daratumumab SC product must be protected from light and must not be frozen. Daratumumab SC does not contain preservatives; therefore, any unused portion remaining in the vial must be discarded.

Refer to the IPPI for additional guidance on daratumumab SC preparation, handling, and storage.

14.5. Bortezomib, Cyclophosphamide, and Dexamethasone

Bortezomib may be provided in 3.5 mg single-use vials as a lyophilized powder or as prescribed by the investigator. Cyclophosphamide may be provided in 50 mg oral tablets or as prescribed by the treating physician. Dexamethasone may be provided in 4 mg oral tablets or as prescribed by the treating physician. Bortezomib, cyclophosphamide, and dexamethasone labels will contain information to meet the applicable regulatory requirements.

Bortezomib must be prepared in an aseptic manner according to local standards. Refer to the bortezomib, cyclophosphamide, and dexamethasone local prescribing information or the SIPPM for further instructions on preparation, handling, and storage.

14.6. 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:

- Study Protocol and Amendments
- IB for daratumumab and rHuPH20
- Site Investigation Product Procedures Manual (SIPPM)
- Investigational Product Preparation Instructions (IPPI)
- Laboratory Manual
- IWRS Manual
- eCRF Completion Guidelines
- Sample Informed Consent Form
- PRO Questionnaires and PRO Completion Guidelines
- Subject diaries, as needed
- Subject wallet card indicating blood type and IAT
- Other manuals and guidance documents, as needed

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

The primary safety profile of daratumumab is consistent with IRRs. Based on the mechanism of action of daratumumab, a potential risk could be infection; therefore, the protocol requires the review of hematological laboratory results prior to daratumumab SC-administration. CD38 is distributed in erythrocytes and platelets. A significant reduction of platelets was reported in an animal study. In a human clinical study of subjects with relapsed or refractory multiple myeloma (Study GEN501), thrombocytopenia was also reported. However, safety laboratory monitoring did not show a clinically meaningful reduction of platelets, and no bleeding events were observed. Safety data from a Phase 3 clinical study (MMY3004) in subjects with relapsed or refractory multiple myeloma comparing DVd versus Vd, showed daratumumab may increase thrombocytopenia associated with bortezomib-based regimens. However, bleeding events were low and the majority of events were minor (<1% of subjects experienced Grade 3 or 4 bleeding events). Anemia was also reported in Study GEN501. Free hemoglobin was mildly elevated, but other parameters did not support hemolysis. Anemia, all grades and Grade 3 or 4 in the MMY3004 study, were similar among the 2 treatment groups. Routine safety laboratory measurement of hemoglobin and platelets will be closely monitored in this study.

In the current study with SC-administration, a lower risk of IRRs is expected due to a more gradual absorption of daratumumab and encouraging data presented by Usmani and colleagues from study MMY1004 (Usmani 2016).[46] However, IRRs may still occur and may develop at a later time point than previously observed with IV administration (where most IRRs occur within 24 hours after administration). Therefore, as an extra safety precaution for the safety run-in, a staggered enrollment approach will be applied. Furthermore, inpatient observation for at least 24 hours after the first dose will be implemented for the safety run-in phase. Inpatient observation after SC delivery during the randomization phase may be implemented based on safety observations collected during the safety run-in. Apart from IRRs, a similar toxicity profile is anticipated with SC versus IV administration for anemia, thrombocytopenia, and other toxicities based on projected exposures being lower at equivalent doses of SC versus IV daratumumab. In this study, local tolerability at the SC-administration 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 AEs of the study, and provide their consent voluntarily will be enrolled.

The blood volume to be collected for the study is estimated at approximately 25 mL at Screening, 280 mL during Cycle 1 through Cycle 6, approximately 20 mL every 8 weeks during monotherapy treatment (Cycle 7+) and observation phase with an additional 10 mL at Cycle 7 Day 1 and Cycle 12 Day 1 and approximately 15 mL at End-of-Treatment visit. The volume of blood to be

drawn is considered to be acceptable for subjects participating in a cancer clinical study and also reasonable over the time frame of the study.

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

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

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

16.2.2. Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor 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)
- IB (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 IB and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of AEs that are serious, unlisted/unexpected, and associated with the study treatment
- 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 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 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.

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

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

16.2.4. Privacy of Personal Data

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

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

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

The subject has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps

will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Exploratory DNA, pharmacodynamics, 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 from last patient out (or according to local regulations) for additional research. Samples will only be used to understand daratumumab, to understand amyloidosis, to understand differential drug responders, and to develop tests/assays related to daratumumab and amyloidosis. 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).

16.2.6. Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product 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 Food and Drug Administration [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 randomized into the study, the date seen and date of birth (as allowed by local regulations) will be used.

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

17.4. Source Documentation

At a minimum, source 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 AEs and follow-up of AEs; concomitant medication; drug receipt/dispensing/return records; study treatment administration information; and date of study completion and reason for early discontinuation of study treatment or withdrawal from the study, if applicable.

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).

Subject- and investigator-completed scales and assessments designated by the sponsor (EORTC QLQ-C30, EQ-5D-5L, SF-36v2 Health Survey) will be recorded directly into an electronic device or other tool and will be considered source data.

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

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

- Discharge summaries

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

An eSource system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If eSource is utilized, references made to the eCRF in the protocol include the eSource system but information collected through eSource 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

Electronic data capture (eDC) will be used for this study. Electronic case report forms are provided for each subject in electronic format. Study-site personnel must log in eDC via a secure manner - personal password. The individual password must keep confidential for personal use.

The study data will be transcribed by study-site personnel from the source documents onto an eCRF according to eCRF completion guideline provided by the sponsor. Data must be entered into the eCRFs in English. Study-site personnel must complete the eCRF as soon as possible after a subject visit. The eCRFs should be available for review at the next scheduled monitoring visit. Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the subject's source documentation.

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

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

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

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

17.6. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, 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 perform remote monitoring during the safety run-in and randomization phases, and 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 data recorded in the eCRF are consistent with the original source data. Findings from this review of eCRFs and source documents will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source 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 end of the study is defined to be 5 years after the last subject is randomized. The final data from the study sites will be sent to the sponsor (or designee) after completion of the final subject visit 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 pharmacogenomics or 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. Results of pharmacogenomics or exploratory biomarker analyses performed after the clinical study report has been issued will be reported in a separate report and will not require a revision of the clinical study report. Study subject identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors (ICMJE) guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has

the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after study end date, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work, and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

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

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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 et al 1982

ATTACHMENT 2: DEFINITION OF ORGAN INVOLVEMENT BASED ON AMYLOIDOSIS CONSENSUS CRITERIA

Heart	Echo: mean wall thickness >12mm, no other cardiac cause or an elevated NT-ProBNP (>332 ng/L) in the absence of renal failure or atrial fibrillation
Kidney	24-hour urine protein>0.5 g/day, predominantly albumin
Liver	Total liver span >15 cm in the absence of heart failure or alkaline phosphatase >1.5 times institutional upper limit of normal
Nerve	Peripheral: clinical, symmetric lower extremity sensorimotor peripheral neuropathy Autonomic: gastric-emptying disorder, pseudo-obstruction, voiding dysfunction not related to direct organ infiltration
Gastrointestinal Tract	Direct biopsy verification with symptoms
Lung	Direct biopsy verification with symptoms Interstitial radiographic pattern
Soft Tissue	Tongue enlargement, clinical Arthropathy Claudication, presumed vascular amyloid Skin Myopathy by biopsy or pseudohypertrophy Lymph node (may be localized) Carpal tunnel syndrome

(adapted from NCCN Guidelines Version 1.2016)

ATTACHMENT 3: NYHA CLASSIFICATION

Class	Functional Capacity by Class	Objective Assessment*
I	No limitation in physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No evidence of cardiovascular disease.
II	Slight limitation of physical activity. Patient is comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of **minimal** cardiovascular disease.
IIIA	Comfortable at rest. Less than ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of **moderately severe** cardiovascular disease.
IIIB	Comfortable at rest. Shortness of breath with performance of activities of daily living (dressing, toileting, showering etc).	Objective evidence of **severe** cardiovascular disease.
IV	Shortness of breath at rest. Unable to carry on any physical activity without discomfort. Signs /Symptoms of heart failure or anginal syndrome may be present **at rest**. If any physical activity is undertaken, discomfort is increased.	Objective evidence of very **severe** cardiovascular disease.

** Measures such as EKG, stress test, x-ray, echocardiogram, or radiologic images.*

ATTACHMENT 4: CONVERSION TABLE FOR GLUCOCORTICOID DOSE

CONVERSION TABLE FOR GLUCOCORTICOSTEROID DOSE FOR METHYLPREDNISOLONE OR EQUIVALENT		
Generic Name	**Oral or Intravenous Dose (mg)**	**Half-life (Biologic) hours**
Short-Acting		
Hydrocortisone	100	8-12
Intermediate-Acting		
Methylprednisolone	20	18-36
Prednisolone	25	18-36
Prednisone	25	18-36
Long-Acting		
Dexamethasone	3.75	36-54
Betamethasone	3	36-54

CONVERSION TABLE FOR GLUCOCORTICOSTEROID DOSE FOR DEXAMETHASONE OR EQUIVALENT			
Generic Name	**Oral or Intravenous Dose (mg)**	**Oral or Intravenous Dose (mg)**	**Half-life (Biologic) hours**
Long-Acting			
Dexamethasone	20	40	36-54
Betamethasone	16	32	36-54

ATTACHMENT 5: CALCULATED CREATININE CLEARANCE AND ESTIMATED GLOMERULAR FILTRATION RATE

Cockcroft-Gault formula:

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

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

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

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

Chronic Kidney Disease Epidemiology Collaboration

Glomerular filtration rate will be calculated according to the CKD-EPI (Levey et al 2009).

For online calculators, please go to https://www.kidney.org/professionals/KDOQI/gfr_calculator .

ATTACHMENT 6: GUIDELINE FOR ASTHMA ELIGIBILITY CRITERIA

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

ATTACHMENT 7: BODY SURFACE AREA NOMOGRAM

Body surface area should be calculated using the standard calculation given below. However, the DuBois Formula can be used as an alternative to calculate BSA. If a site uses another formula other than the standard calculation given below or the DuBois Formula, they must receive approval from the Sponsor to use another BSA formula.

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

or

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

ATTACHMENT 8: EORTC QLQ-C30

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Today's date (Day, Month, Year): 31 ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
16. Have you been constipated?	1	2	3	4
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

ATTACHMENT 9: SUPPLEMENTAL ITEMS TO EORTC QLQ-C30 (FROM EORTC ITEM BANK)

During the past week:

Module, Item #		Not at all	A Little	Quite a Bit	Very Much
PR25, Item #46	Have you had swelling in your legs or ankles?	1	2	3	4
OV28, Item #32	Did you have a bloated feeling in your abdomen/stomach?	1	2	3	4
MY-20, Item #43	Did you have tingling hands or feet?	1	2	3	4

ATTACHMENT 10: EQ-5D-5L

(English version for the UK)

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

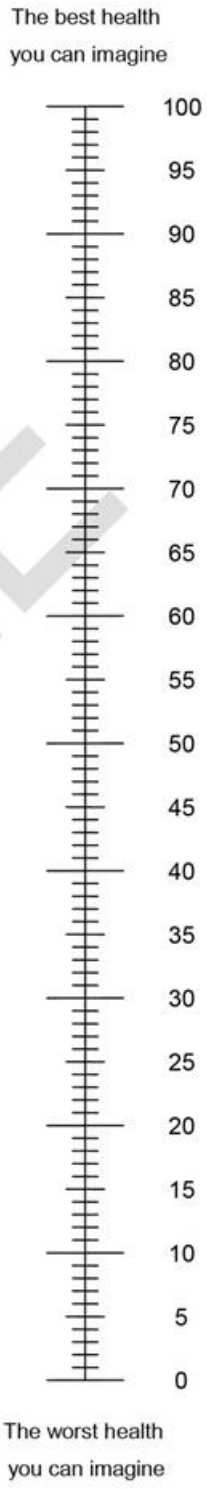
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



ATTACHMENT 11: SF-36V2

Your Health in General

Please answer every question. Some questions may look like others, but each one is different. Please take the time to read and answer each question carefully, and mark an ☒ in the one box that best describes your answer. ***Thank you for completing this survey!***

Please enter Today's Date: _____

Please fill out this questionnaire as though it were one week PRIOR to your accident/injury. Thank you!

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐1	☐2	☐3	☐4	☐5

2. Compared to one year ago, how would you rate your health in general now?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐1	☐2	☐3	☐4	☐5

Baseline Version

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c. Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d. Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e. Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f. Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g. Walking more than a mile	☐ 1	☐ 2	☐ 3
h. Walking several hundred yards	☐ 1	☐ 2	☐ 3
i. Walking one hundred yards	☐ 1	☐ 2	☐ 3
j. Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐1	☐2	☐3	☐4	☐5
b. Accomplished less than you would like	☐1	☐2	☐3	☐4	☐5
c. Were limited in the kind of work or other activities	☐1	☐2	☐3	☐4	☐5
d. Had difficulty performing the work or other activities (for example, it took extra effort)	☐1	☐2	☐3	☐4	☐5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐1	☐2	☐3	☐4	☐5
b. Accomplished less than you would like	☐1	☐2	☐3	☐4	☐5
c. Did work or other activities less carefully than usual	☐1	☐2	☐3	☐4	☐5

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐1	☐2	☐3	☐4	☐5

7. How much bodily pain have you had during the past 4 weeks?

None	Very mild	Mild	Moderate	Severe	Very Severe
☐1	☐2	☐3	☐4	☐5	☐6

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐1	☐2	☐3	☐4	☐5

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of life?	☐1	☐2	☐3	☐4	☐5
b. Have you been very nervous?	☐1	☐2	☐3	☐4	☐5
c. Have you felt so down in the dumps that nothing could cheer you up?	☐1	☐2	☐3	☐4	☐5
d. Have you felt calm and peaceful?	☐1	☐2	☐3	☐4	☐5
e. Did you have a lot of energy?	☐1	☐2	☐3	☐4	☐5
f. Have you felt downhearted and depressed?	☐1	☐2	☐3	☐4	☐5
g. Did you feel worn out?	☐1	☐2	☐3	☐4	☐5
h. Have you been happy?	☐1	☐2	☐3	☐4	☐5
i. Did you feel tired?	☐1	☐2	☐3	☐4	☐5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐1	☐2	☐3	☐4	☐5

11. How TRUE or FALSE is each of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	☐1	☐2	☐3	☐4	☐5
b. I am as healthy as anybody I know	☐1	☐2	☐3	☐4	☐5
c. I expect my health to get worse	☐1	☐2	☐3	☐4	☐5
d. My health is excellent	☐1	☐2	☐3	☐4	☐5

THANK YOU FOR COMPLETING THESE QUESTIONS!

ATTACHMENT 12: ANTICIPATED EVENTS

Anticipated Event

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

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

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

Reporting of Anticipated Events

All AEs will be recorded in the eCRF regardless of whether considered to be anticipated events and will be reported to the sponsor as described in Section 12.3.1. Any anticipated event that meets serious criteria will be reported to the sponsor as described in Section 12.3.2.

Each anticipated event will be assessed by the investigator at the individual case level and if considered to be drug-related will undergo expedited reporting (if appropriate) as per applicable clinical trial legislation to Health Authorities and IRB/ECs. If an anticipated event is considered disease-related or not related to study drug the event will be exempt from expedited reporting.

To meet US regulatory clinical trial legislation, the sponsor will perform aggregate review of anticipated events as outlined below, and if determined to be drug-related will implement expedited reporting of these events to Health Authorities and IRBs/ECs. If an interim analysis of trial results leads to an unblinded, aggregate review of safety data by the study team, the sponsor may terminate the review of pre-specified anticipated events outlined above.

Safety Assessment Committee (SAC)

A Safety Assessment Committee (SAC) will be established to perform reviews of pre-specified anticipated events at an aggregate level. The SAC is a safety committee within the sponsor's organization that is independent of the sponsor's study team. The SAC will meet to aid in the recommendation to the sponsor's study team as to whether there is a reasonable possibility that an anticipated event is related to the study intervention based on a review of the aggregate data by arm.

Statistical Analysis

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

ATTACHMENT 13: PROTOCOL 54767414AMY3001 STUDY RISK/BENEFIT ASSESSMENT

Janssen Research & Development

Benefit Risk Assessment

Protocol 54767414AMY3001

JNJ-54767414 (daratumumab)

Status:	Approved
Date:	28 September 2017
Prepared by:	Janssen Research & Development, LLC
EDMS No.	EDMS-ERI-125792704

TABLE OF CONTENTS

TABLE OF CONTENTS **2**

LIST OF ABBREVIATIONS **3**

1. INTRODUCTION **4**

2. BACKGROUND ON DISEASE AND EXISTING TREATMENT OPTIONS **4**
2.1. Rationale for the Use of CyBorD as a Backbone Regimen 4
2.2. Rationale for the Use of Daratumumab in AL Amyloidosis 4
2.3. Rationale for the Combination of Daratumumab with CyBorD 5

3. STUDY 54767414AMY3001 DESIGN **5**

4. RATIONALE FOR DOSE AND SUBCUTANEOUS ADMINISTRATION OF DARATUMUMAB **7**
4.1. Potential Benefits for Subcutaneous Administration 7
4.2. Study 54767414MMY1004 8
4.2.1. Preliminary Data from Study MMY1004 Part 1 8
4.2.2. Preliminary Data from Study MMY1004 Part 2 9

5. POTENTIAL RISKS **10**
5.1. Daratumumab 11
5.2. CyBorD 11

6. CONCLUSION: OVERALL BENEFIT RISK ASSESSMENT **12**

REFERENCES **14**

LIST OF IN-TEXT FIGURES

Figure 1 Schematic Overview of the Safety Run-In 6
Figure 2 Schematic Overview of the Randomized Study 7

LIST OF ABBREVIATIONS

Abbreviation	Description of abbreviated term
AL	light chain
C3D1	Cycle 3 Day 1
CR	complete response
CTA	Clinical trial application
CyBorD	cyclophosphamide, bortezomib, dexamethasone
Dara-IV	daratumumab intravenous formulation
Dara-MD	daratumumab-mix and deliver
Dara SC	daratumumab administered subcutaneously
EU	European Union
IAT	indirect antiglobulin test
IDMC	Independent Data Monitoring Committee
IRC	Independent Review Committee
IRR	infusion-related reaction
IV	intravenous
MM	multiple myeloma
NCCN	National Comprehensive Cancer Network
ORR	overall response rate
PR	partial response
Rd	lenalidomide and dexamethasone
rHuPH20	recombinant human Hyaluronidase
SC	subcutaneous
TEAE	treatment-emergent adverse event
Tregs	regulatory T-cells
Vd	bortezomib and dexamethasone
VGPR	very good partial response

1. INTRODUCTION

This benefit risk assessment document is being submitted to support the clinical trial application (CTA) for Study 54767414AMY3001 (hereafter referred to as Study AMY3001), titled "A Randomized Phase 3 Study to Evaluate the Efficacy and Safety of Daratumumab in Combination with Cyclophosphamide, Bortezomib and Dexamethasone (CyBorD) Compared with CyBorD Alone in Newly Diagnosed Systemic AL Amyloidosis."

The European Commission issued a conditional marketing authorization for daratumumab (Darzalex®) on 20 May 2016 for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor (PI) and an immunomodulatory drug (IMiD) and who demonstrated disease progression on the last therapy. On 28 April 2017, Darzalex was approved in combination with lenalidomide and dexamethasone (Rd) or bortezomib and dexamethasone (Vd) for the treatment of adult patients with multiple myeloma who have received at least 1 prior therapy, and the license was transitioned to a standard authorization.

There are currently no approved therapies to treat or prevent systemic amyloid light chain (AL) amyloidosis and there is, therefore, a high unmet medical need. Although there are no approved therapies, based on clinical study data, the combination regimen of cyclophosphamide, bortezomib, and dexamethasone (CyBorD) is recommended by the National Comprehensive Cancer Network (NCCN), the British Society of Haematology, and consensus guidelines from academic institutions (Comenzo 2012, Mahmood 2014, Anderson -NCCN, Wechalekar 2008)

2. BACKGROUND ON DISEASE AND EXISTING TREATMENT OPTIONS

Refer to protocol 54767414AMY3001 Section 1.1 for background information regarding amyloidosis and available treatment options.

2.1. Rationale for the Use of CyBorD as a Backbone Regimen

Refer to protocol 54767414AMY3001 Section 1.1.1 and Section 1.1.2 for information regarding the bortezomib-based treatment options for amyloidosis, and the use of bortezomib in combination with cyclophosphamide and dexamethasone in the CyBorD regimen in amyloidosis, respectively.

2.2. Rationale for the Use of Daratumumab in AL Amyloidosis

Refer to protocol 54767414AMY3001 Section 1.2 for information regarding the use of daratumumab in amyloidosis. In addition to the information provided in the protocol, further information to support the use of daratumumab in AL amyloidosis is provided in a recently published retrospective experience that described the use of daratumumab in 25 patients (median age 66 years) with biopsy-proven AL amyloidosis who had received a median of 3 prior treatments (including either bortezomib or carfilzomib). Daratumumab intravenous (IV) was administered at 16 mg/kg weekly for 8 weeks, followed by every other week treatments for 8 doses and then every 4 weeks. Daratumumab was administered over 8 hours with 500 mL of IV fluid except for the first dose which was split in half and given on 2 consecutive days. All subjects received acetaminophen, diphenhydramine and dexamethasone as pre-medication. A median of 12 (range 3 to 35) infusions

of daratumumab were administered. All subjects were evaluable for safety and 24 patients were evaluable for hematologic response (Kaufman 2017).

Hematologic response was observed in 19 subjects (76%), with complete response (CR) in 9 (36%), very good partial response (VGPR) in 6 (24%), and partial response (PR) in 4 (16%). Among the 11 subjects who had failed to achieve VGPR with prior therapy, treatment with daratumumab resulted in 3 CRs and 5 VGPRs. The median time to deepest hematologic response was 1 month (range 7-188 days). Tolerability of daratumumab was similar to that reported in studies of multiple myeloma with Grade 1-2 infusion-related reactions (IRRs) reported in 15 subjects (60%). There were no Grade ≥3 IRRs. The 18 subjectss with cardiac AL involvement at baseline tolerated daratumumab without need for adjustment in diuretic dosing or decompensated heart failure related to drug infusion. Hematologic toxicity was limited to 1 subject with baseline anemia and chronic renal insufficiency who required red blood cell (RBC) transfusion. Grade 3-4 clinical events resulted in hospitalization for spontaneous pneumothorax (n=1 subject), decompensated heart failure (n=1 subject) and infection (n=2 subjects). Although daratumumab was discontinued following these events, all subjects involved had received 8 to 17 infusions and achieved VGPR or CR. At the time of the report 14 subjects (56%) were continuing therapy with daratumumab. Eleven subjects (44%) had discontinued therapy: (n=7 subjects; 28%) from a lack of response or plateau of response at PR, progression after PR, or personal preference. After a median follow-up of 7 months from the start of daratumumab, neither the median duration or response nor the median progression-free survival had been reached (Kaufman 2017).

2.3. Rationale for the Combination of Daratumumab with CyBorD

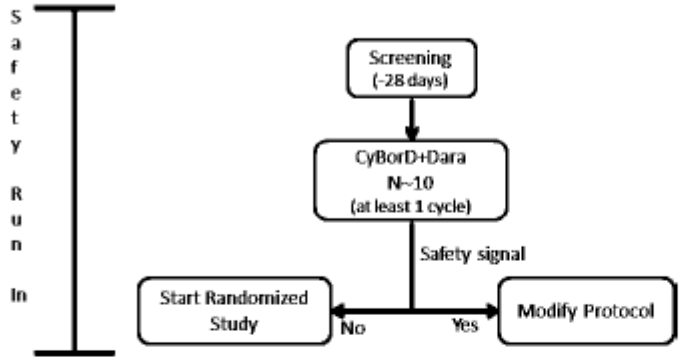
Refer to protocol 54767414AMY3001 Section 1.2.1 and Section 3.2.2 for the rationale supporting the use of daratumumab in combination with bortezomib and dexamethasone in patients with multiple myeloma. Based on the assessment of treatment-emergent adverse events (TEAEs), deaths and laboratory findings, the safety profile of daratumumab in combination with bortezomib/dexamethasone was consistent with the safety profiles of daratumumab and of bortezomib/dexamethasone. With the exception of IRRs, the safety of the combination was similar to that of background therapy. The combination of daratumumab with a bortezomib-based regimen was synergistic in patients with multiple myeloma and did not result in treatment terminating additive toxicity. It is anticipated that daratumumab and CyBorD can be combined at full dose of each regimen, and that the tolerability of the combination will be similar to the known safety profile of CyBorD, with the potential for the occurrence of injection site reactions due to daratumumab.

3. STUDY 54767414AMY3001 DESIGN

As this is the first study of daratumumab in amyloidosis, the study will start with a safety run-in of at least 10 subjects who will receive daratumumab plus CyBorD at the full dose for each regimen (Figure 1). The combination of daratumumab with other treatment regimens has been at full dose. Based on that prior experience, it is unlikely that the dose reductions of either daratumumab or CyBorD will be needed when they are administered together. The safety run-in will confirm this and the safety of the co-formulated subcutaneous (SC) daratumumab drug product that will be used in this study. While not statistically driven, 10 subjects were considered appropriate for this

initial phase of the study. Dosing of the subjects will be staggered to allow for assessment of both early and delayed IRRs. After at least 10 subjects have completed at least 1 cycle of treatment, there will be an analysis of safety by the sponsor and external academic hematologists before proceeding to randomization.

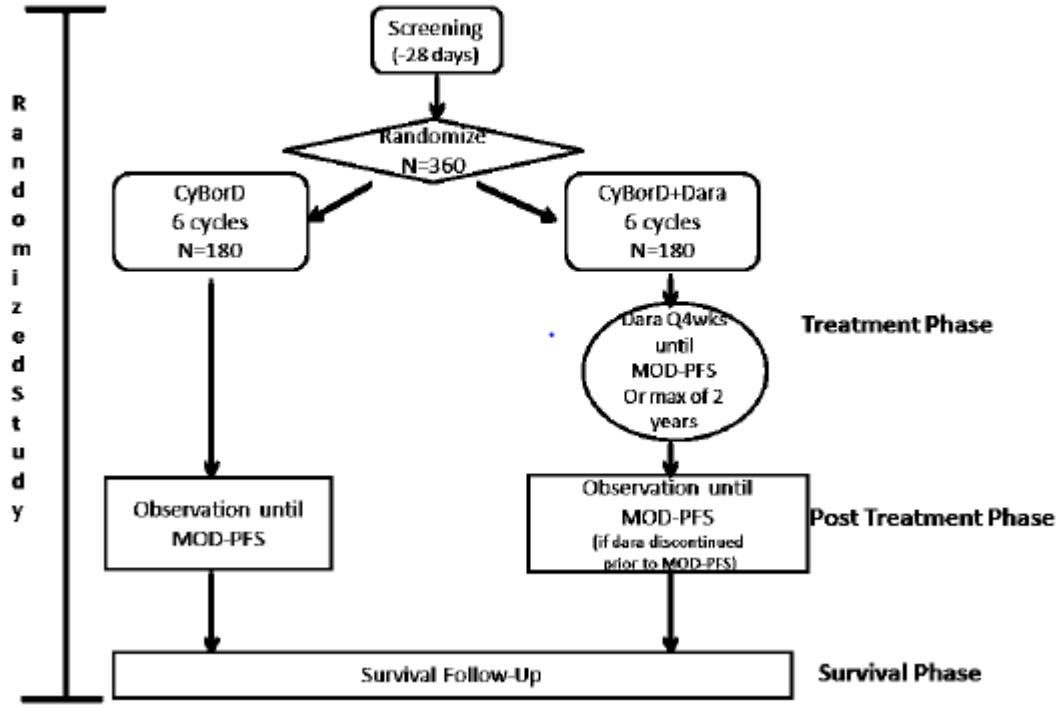
Figure 1 Schematic Overview of the Safety Run-In



In the randomized portion of the study, subjects randomized to Treatment Arm A will receive study treatment with CyBorD (Figure 2). All treatment cycles are 4 weeks (28 days) in length. CyBorD will be administered for a maximum of 6 cycles (24 weeks). Subjects randomized to Treatment Arm B will receive CyBorD plus co-formulated SC daratumumab at a fixed dose of 1800 mg.

Two interim analyses are planned for this study. The first interim analysis is a pre-specified safety analysis that will occur after the first 30 subjects complete at least 1 cycle of treatment. The second interim analysis will assess safety and efficacy, and will occur after 180 subjects have been treated for at least 6 cycles. Both interim analyses will be conducted by an Independent Data Monitoring Committee (IDMC). The primary endpoint of overall complete hematologic response (CHR) and secondary efficacy endpoints will be adjudicated by an Independent Review Committee (IRC).

Figure 2 **Schematic Overview of the Randomized Study**



Refer to protocol 54767414AMY3001 Section 3.1 for a complete description of the study design.

4. RATIONALE FOR DOSE AND SUBCUTANEOUS ADMINISTRATION OF DARATUMUMAB

Daratumumab monotherapy for subjects with multiple myeloma is approved at 16 mg/kg (weekly for 8 weeks, then every 2 weeks for 16 weeks, then every 4 weeks thereafter) administered via intravenous (IV) infusion until disease progression, start of subsequent therapy, or unacceptable toxicity.

In contrast to the approved IV formulation, Study AMY3001 will use co-formulated SC daratumumab (Dara-SC). This is a co-formulated drug product intended for a fixed-dose administration, containing recombinant human Hyaluronidase (rHuPH20) and daratumumab in a single vial. Daratumumab 1800 mg will be administered SC through a syringe by a manual push over approximately 5 minutes. Doses will be administered at alternating locations on the abdomen.

4.1. Potential Benefits for Subcutaneous Administration

Daratumumab IV (Dara-IV) has been approved as monotherapy or in combination with standard of care to treat relapsed refractory multiple myeloma in more than 50 countries, including the EU. As monotherapy, Dara-IV, is generally well tolerated, as demonstrated by a low number of subjects who discontinued treatment due to a TEAE, a low number of deaths due to TEAEs, and infrequent use of hematopoietic growth factors (eg, granulocyte-colony stimulating factor). However, one of the most common side effects associated with IV administration of daratumumab is IRRs, which

were experienced by approximately half of the subjects receiving daratumumab-based regimens (Darzalex® SmPC 2017). The vast majority of IRRs (>90%) occurred during the first infusion. Due to the risk of IRRs, 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.

The potential benefit of Dara-SC therefore lies in the shortened time of administration and decreased incidence of IRRs. In addition, as demonstrated in subsequent sections of this document, apart from a lower rate of IRRs, Dara-SC has a similar toxicity profile compared with Dara-IV administration for anemia, thrombocytopenia, and other toxicities.

4.2. Study 54767414MMY1004

The IV infusion of biologics is cumbersome for health care providers and patients. Recent efforts have led to the successful development of SC formulations for monoclonal antibodies based on the use of rhuPH20. Approval has been granted in Europe and the US for PH20-based formulation of the CD20-directed monoclonal antibody Rituximab. Janssen is developing a SC formulation of daratumumab which will be used in this study.

Study 54767414MMY1004 (hereafter referred to as Study MMY1004) is an ongoing, open-label, 2-part Phase 1b study to assess the safety and pharmacokinetics of SC daratumumab in subjects with relapsed or refractory multiple myeloma who have received ≥2 prior lines of therapy including a PI and an IMiD. In Part 1, subjects (n=53) received daratumumab-mix and deliver (Dara-MD); and in Part 2, subjects (n=25) are receiving Dara-SC. Enrollment in both parts of the study has been completed.

4.2.1. Preliminary Data from Study MMY1004 Part 1

Dara-MD is an "intermediate formulation" that is a solution that requires mixing of the daratumumab drug product with rHuPH20 prior to delivery. In Part 1 of Study MMY1004, Dara-MD was administered SC according to the same schedule as the approved IV daratumumab regimen, ie, once weekly in Cycles 1 and 2, every 2 weeks in Cycles 3 to 6, and then every 4 weeks in subsequent cycles until disease progression or unacceptable toxicity. Subjects were enrolled in sequential cohorts at 1200 mg (n=8 subjects) and 1800 mg (n=45 subjects).

After a median treatment duration of 2.6 months for the 1200 mg cohort and 5.4 months for the 1800 mg cohort (clinical cutoff 03 Aug 2017), the key safety findings were:

- The incidence of all-grade IRRs was 13% and 24% in the 1200 mg and 1800 mg Dara-MD cohorts, respectively. In comparison, among subjects treated in single-agent or combination studies with IV daratumumab, IRRs were reported in 47% of subjects.
  - Across both cohorts, all but 1 IRR were mostly Grade 1 or 2. One subject in the 1200 mg Dara-MD cohort developed a Grade 3 IRR of dyspnea.
  - All IRRs developed within 6 hours of the start of the Dara-MD infusion and did not result in treatment discontinuation.

- The most frequently reported TEAEs (≥20% of all subjects) were upper respiratory tract infection, thrombocytopenia and insomnia (38% each) and pyrexia, fatigue, anemia, diarrhea, vomiting, headache, and cough (25% each) for the 1200 mg cohort. For the 1800 mg cohort TEAEs were anemia (33%), diarrhea, upper respiratory tract infection (22% each), pyrexia (27%), fatigue and asthenia (20% each).
- Grade 3 or 4 TEAEs were reported in 63% and 49% of subjects in the 1200 mg and 1800 mg cohorts, respectively. Comparatively, in earlier studies of IV daratumumab, Grade 3 or 4 TEAEs were reported in 56% of subjects.
- Serious TEAEs were reported in 50% and 31% of subjects in the 1200 mg and 1800 mg cohorts, respectively.
- One subject in the 1800 mg cohort died due to a TEAE of depressed level of consciousness; this event occurred 20 days after last dose of Dara-MD and was considered by the investigator to be unrelated to study drug and related to progression of disease.

At the time of the clinical cutoff (03 Aug 2017), 53 subjects (8 subjects in the 1200 mg Dara-MD cohort and 45 subjects in the 1800 mg Dara-MD cohort) were evaluable for efficacy, which was defined as having Cycle 3 Day 1 (C3D1) disease evaluation or demonstrated disease progression. In the 1200 mg Dara-MD cohort, the overall response rate (ORR) was 25% (95% confidence interval: 3%-65%) and 2 subjects achieved PRs: one 8 weeks and the other 20 weeks after initiation of treatment. In the Dara-MD 1800 mg cohort, the ORR was 42%. The rates of greater than or equal to VGPR and CR were 20% and 9%, respectively. The median time to first response in the 1200 mg and 1800 mg cohorts was 3.4 months (range 1.8-4.9 months) and 1 month (range 0.9-10.2 months), respectively.

Preliminary Pharmacokinetic Data

Preliminary PK data following Dara-MD administration show a slower absorption with a later T_{max} (approximately 72 hours post-infusion) compared with IV administration. Preliminary analyses indicate the bioavailability of Dara-MD is approximately 77% when administered SC.

4.2.2. Preliminary Data from Study MMY1004 Part 2

The final SC daratumumab formulation, Dara-SC, which will be used in Study AMY3001 is a co-formulated drug product intended for a fixed-dose administration, containing rHuPH20 and daratumumab in a single vial. Part 2 of Study MMY1004 is a Phase 1b, nonrandomized, open-label study to evaluate Dara-SC (referred to in the MMY1004 protocol as Dara-CF) administered SC to subjects with multiple myeloma who have received at least 2 prior lines of therapy, including a PI and an IMiD, and have measurable disease. Based on the results from Part 1 of the study, the 1800 mg dose was selected for Part 2.

After a median treatment duration of 2.3 months (clinical cutoff date of 03 Aug 2017), key safety findings for the 25 subjects who have received at least 1 dose of 1800 mg Dara SC are as follows:

- IRRs (all grades) was reported in 8% of subjects. All IRRs (chills, dyspnea, and allergic rhinitis) were Grade 1 or 2.

- Injection site reactions were reported in 2 subjects: 1 subject had a Grade 1 injection site discoloration/injection site induration (although no measurable induration was reported in this subject), and 1 subject had a Grade 1 erythema. A Grade 1 hematoma was reported for a third subject after the clinical cutoff.
- The most frequently reported TEAEs (≥3 [12%] subjects) were lymphopenia (32%); thrombocytopenia, pyrexia, fatigue, asthenia, back pain, nausea, headache, insomnia (16% each); and leukopenia, anemia, chills, and diarrhea (12% each).
- Grade 3 or 4 TEAEs were reported in 36% of subjects.
- Serious TEAEs were reported in 2 subjects (8%). The serious TEAEs were pyrexia, asthenia, fatigue, hyponatremia, febrile neutropenia, leukopenia, and thrombocytopenia; and all were Grade 3 or 4 except for pyrexia.
- No subject discontinued treatment due to a TEAE.
- No subject died due to a TEAE.

Preliminary Pharmacokinetic Data

As of the clinical cutoff date, 20 subjects had reached Cycle 3 Day 1 (C3D1). Of those, 18 subjects had received all scheduled doses of study drug in cycles 1 and 2 and had provided a pre-dose PK sample on C3D1 and were therefore considered evaluable for the PK endpoint.

The primary PK endpoint of C3D1 C_{trough} mean value was 904.42 µg/mL for the Dara-SC cohort (n=18) compared with 754.62 µg/mL for the 1800 mg Dara-MD cohorts (n=38), 617.17 µg/mL in Study GEN501 Part 2 (n=27), and 573.49 µg/mL in Study MMY2002 (n=73). The median C3D1 C_{trough} values for Dara-SC are similar to the 1800 mg Dara-MD formulations (798.9 and 795.5 µg/mL, respectively) and slightly higher than the 16 mg/kg IV median values from Studies MMY2002 and GEN501 (559.6 and 713.9 µg/mL, respectively). The range of C3D1 C_{trough} observations for the SC cohort is within the range observed following 16 mg/kg IV dosing and the variability appeared to be similar for the Dara-SC and 16 mg/kg IV cohorts.

The observed mean C_{max} values following the last (8^{th}) weekly dose for the Dara-SC cohort was 1012.4 µg/mL, similar to the mean C_{max} of 914.9 µg/mL observed after the C3D1 (9^{th}) dose for Dara-IV in Study MMY2002. The C3D1 C_{max} was selected for this comparison as the C_{max} was not captured following the last weekly (8^{th}) dose in Study MMY2002. The observed C_{max} values from the Dara-SC cohort is within the range observed for Dara-MD and daratumumab 16 mg/kg IV.

5. POTENTIAL RISKS

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, electrocardiogram monitoring, clinical laboratory parameter (hematology and chemistry) monitoring, pulmonary function testing, and Eastern Cooperative Oncology Group 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 Independent Monitoring Committee will also review the safety and efficacy in preplanned analyses per Section 11.10 of the protocol. The initial run-in phase of the study in 10 patients will confirm whether any dose reductions of either daratumumab or CyBorD will be needed when they are administered together. Dosing of the subjects will be staggered to allow for assessment of both early and delayed IRRs. After at least 10 subjects have completed at least 1 cycle of treatment, there will be an analysis of safety by the sponsor (and external academic hematologists) before proceeding to randomization. Therefore, the Company believes the benefit/risk profile is favorable to support further evaluation of efficacy and safety of Dara-SC in combination with CyBorD in patients with AL amyloidosis in Study AMY3001."

5.1. Daratumumab

Apart from a lower rate of IRRs, Dara SC has a similar toxicity profile compared with Dara-IV administration for anemia, thrombocytopenia, and other toxicities. The potential risks of daratumumab will be mitigated by comprehensive and careful medical monitoring during the conduct of the study, as described in the protocol. Subjects will receive predose and post-dose medications to prevent and manage IRRs as specified in protocol Section 6.2.3. An IDMC will be established to review interim data as described in Section 3. IRRs and injection site reactions will be managed as specified in Sections 6.2.3.3 and 6.2.4 of the protocol, respectively. All subjects will be closely monitored for possible toxicity.

5.2. CyBorD

Refer to protocol 54767414AMY3001 Section 1.1.1 and Section 1.1.2 for background information regarding bortezomib-based treatment options and the use of bortezomib in combination with cyclophosphamide and dexamethasone in the CyBorD regimen, respectively.

Two published studies documented clinical experience with CyBorD in patients with AL amyloidosis (Mikhael 2012, Venner 2012). A retrospective analysis of 17 patients who received 2 to 6 cycles (median 3 cycles) of CyBorD reported that 2 patients experienced Grade 1 or 2 peripheral neuropathy (no reports of Grade 3 or 4). Hematologic toxicity was minimal without the need for blood or platelet transfusions. Infections requiring hospitalization were reported in 2 patients (1 *Clostridium difficile* colitis and 1 pneumonia) and 1 patient developed herpes zoster (Mikhael 2012). A second retrospective cohort study of 43 patients with AL amyloidosis who received mean 5 cycles (range 2 to 8) of CyBorD reported a 30% incidence of neuropathy which resulted in discontinuation of therapy in 14%. Two additional patients discontinued therapy due to possible treatment toxicity (1 with fluid overload and 1 with cardiac decompensation; each after having received 3 cycles of treatment). There were no discontinuations due to cytopenia or other nonhematologic toxicity. There were 2 deaths, however causality was not reported nor was assessment of possible relation to study drug (Venner 2012).

6. CONCLUSION: OVERALL BENEFIT RISK ASSESSMENT

AL amyloidosis is a rare disease with a poor prognosis. The median survival of untreated patients is 13 months from diagnosis (Sanchorawala 2007, Chaulagain 2013). Therapy for AL amyloidosis should include eradication of plasma cells that produce toxic protein deposits leading to organ failure. These plasma cells express CD38 (Matsuda 2003, Shimojima 2005) and could be targeted by antibodies such as daratumumab that binds and eliminates CD38 expressing cells.

Safety data is available from the ongoing single agent daratumumab studies (GEN501 and MMY2002), from the combination study of daratumumab and bortezomib-containing regimens (MMY1001 and MMY3004), and from the SmPC for bortezomib. The safety profile of daratumumab, which predominantly involves IRRs, is not expected to result in additional toxicity to the known adverse effects of the CyBorD regimen. The combination of daratumumab and CyBorD is therefore expected to be a safe combination. In addition, the safety run-in portion of this study will further validate the safety assumptions and provide information on the safety of daratumumab in combination with CyBorD in the AL amyloidosis patient population.

In contrast to the authorised IV formulation, daratumumab will be administered SC for Study AMY3001 and the preliminary safety and PK data from Study MMY1004 supports the 1800 mg Dara-SC dose selection for this study. The PK data indicate that an 1800 mg dose of Dara-SC administered SC would be anticipated to result in a similar or greater Cycle 3 Day 1 trough concentration (C3D1 C_{trough}) compared to 16 mg/kg IV administration. Study MMY1004 also showed that Dara-SC can be administered SC by manual injection with a median of 5 minutes (ranging from 2 to 11 minutes) and it is associated with a low incidence of IRRs (overall incidence of 8% without Grade 3 or 4 events). The overall safety profile for the Dara-SC cohort is similar to prior experience with daratumumab IV administration and SC administration with Dara-MD. There are no new safety signals with the Dara-SC administration. Preliminary efficacy data are also very promising to support a positive benefit/risk using Dara-SC in Study AMY3001.

In summary, there is a strong rationale for evaluating SC daratumumab in combination with CyBorD for AL amyloidosis:

- There is no approved standard of care in the frontline or relapsed setting for AL Amyloidosis. There is, therefore, an unmet medical need for new treatments, given the high morbidity and mortality in this patient population.
- Flow cytometric data suggest that malignant plasma cells in AL express CD38 and therefore can be targeted by daratumumab.
- Previous experience with CyBorD has shown efficacy for AL amyloidosis with a tolerable safety profile (Mikhael 2012; Venner 2012; Palladini 2015) and is, therefore, considered to be a suitable comparator.
- The addition of daratumumab to bortezomib-containing regimens have shown efficacy in multiple myeloma and does not add significantly to the toxicity of the backbone therapy.

- Co-formulated Dara-SC will be used given the potential advantages of SC administration of daratumumab (e.g. small volume; fewer IRRs). The safety and tolerability of SC daratumumab has been demonstrated in Study MMY1004 Part 1 & 2.
- The potential risks will be mitigated by comprehensive and careful medical monitoring during the conduct of the study, as described in the protocol. An IDMC will be established to review interim data and a safety run-in will be conducted with 10 patients. Dosing of these subjects will be staggered so that no subject will receive their first dose sooner than 48 hours after the previously enrolled subject. Safety evaluation will be performed by the sponsor (and external academic hematologists) after at least 10 subjects have received at least 1 cycle of treatment.

In conclusion, the combination of CyBorD with SC daratumumab is therefore anticipated to have a positive benefit/risk for the treatment of patients with Newly Diagnosed Systemic AL Amyloidosis and supports the investigation of this combination in Study AMY3001.

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ATTACHMENT 14: MAYO CLINICAL CARDIAC STAGING SYSTEM

AMY3001 Clinical Cardiac Stage will be based on 2 biomarker Risk Factors; NT-proBNP and high sensitivity cardiac troponin T (hs-cTnT). Central lab NT-proBNP and hs-cTnT should be used to determine Clinical Cardiac Stage.

Risk Factors:

- NT-proBNP: >332 ng/L
- hs-cTnT: >54 ng/L

Stage definition:

- Stage 1: no risk factors (Both NT-proBNP and hs-cTnT do not meet above risk factors)
- Stage 2: one risk factor (NT-proBNP OR hs-cTnT meet above risk factors)
- Stage 3: 2 risk factors (Both NT-proBNP and hs-cTnT meet above risk factors)

References: Dispenzieri 2014; Palladini 2016

ATTACHMENT 15: LIST OF CYP3A INDUCERS AND INHIBITORS

CYP3A Inducers

Strong Inducers ≥80% decrease in AUC	Moderate Inducers 50-80% decrease in AUC	Weak Inducers 20-50% decrease in AUC
Avasimibe, carbamazepine, phenytoin, rifampin, St. John's wort	Bosentan, efavirenz, etravirine, modafinil, nafcillin	Amprenavir, aprepitant, armodafinil, clobazam, echinacea, pioglitazone, prednisone, rufinamide, vemurafenib

Source: Department of Health and Human Services (DHHS) 2012

CYP3A Inhibitors

Strong Inhibitors ≥5-fold increase in AUC or >80% decrease in CL	Moderate Inhibitors ≥2 but <5-fold increase in AUC or 50-80% decrease in CL	Weak Inhibitors ≥1.25 but <2-fold increase in AUC or 20-50% decrease in CL
Boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole	Amprenavir, aprepitant, atazanavir; ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, imatinib, verapamil	Alprazolam, amiodarone, amlodipine, atorvastatin, bicalutamide, cilostazol, cimetidine, cyclosporine, fluoxetine, fluvoxamine, ginkgo, goldenseal, isoniazid, lapatinib, nilotinib, oral contraceptives, pazopanib, ranitidine, ranolazine, tipranavir/ritonavir, ticagrelor, zileuton

Source: Department of Health and Human Services (DHHS) 2012

INVESTIGATOR AGREEMENT

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

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

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Jessica Vermeulen; MD, PhD

Institution: Janssen Research & Development

Signature: PPD PPD Date: 10 Oct 2019
(Day Month Year)

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

150

Approved, Date: 10 October 2019