Phase 2 study of daratumumab monotherapy in previously untreated patients with stage 3B light chain (AL) amyloidosis

Protocol Identifying Number: EMN22/54767414AMY2005

Protocol Version Number: 6.0

EudraCT Number: 2018-004333-33

Sponsor:
European Myeloma Network (EMN)
Erasmus MC
Wytemaweg 80
Rotterdam, The Netherlands
Sponsor representative: Prof. Pieter Sonneveld

Co-ordinating Investigator:
Prof. Efstathios Kastritis
Department of Clinical Therapeutics, National and Kapodistrian University of Athens School of Medicine, Athens - Greece

Scientific Co-ordinating Investigator:
Prof. Meletios Athanasios Dimopoulos
Department of Clinical Therapeutics, National and Kapodistrian University of Athens School of Medicine, Athens - Greece

Dated: 31 March 2023

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PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	01 February 2019
Amendment 1	16 September 2019
Amendment 2	30 June 2021
Amendment 3	20 April 2022
Amendment 4	31 March 2023

Amendments below are listed beginning with the most recent amendment.

Amendment 4 (31 March 2023)

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

The overall reason for the amendment: To update the protocol based on the annual safety findings associated with Daratumumab and to extend the overall study duration.

Applicable Sections	Description of Changes
Rationale: To update the background information of Daratumumab based on the new Ed.19 Investigator's Brochure JNJ-54767414.	
• Section 1.2: Daratumumab	Updates regarding the annual safety findings were performed for alignment with the newest data from the Ed.19 Daratumumab (JNJ-54767414) Investigator's Brochure.
Rationale: To update the overall study duration.	
• Section 17.9.1: Study completion/end of study	Study duration was updated from 60 months and 8 days to 64 months and 5 days.
Rationale: To perform minor amendments in the 'Adverse Event Reporting' section for clarity.	
• Section 12.1.1: Adverse Event Definitions and Classifications	To clarify that for bortezomib the expectedness of an adverse event will be determined by whether or not it is listed in the SPC.
• Section 12.1.2: Attribution Definitions	Sub-headings were rephrased for clarity and alignment with study documents.
• Section 12.3: Special Reporting Situations	Text regarding the maximum tolerated dose of Daratumumab IV was removed and replaced with Daratumumab SC.
• Section 12.4.1: All Adverse Events	Minor rephrasing was performed as per below: The phrase "the study investigational medicinal products" was added to clarify that the investigational medicinal products within the follow-up phase should also be reported in the Serious Adverse Event Form. The term "wallet (study) card" was rephrased to "patient (study) card" for clarity and alignment with study documents.
• Section 12.4.2: Serious Adverse Events	The phrase "the principal investigator or the sub-investigator" was added to clarify that the Serious Adverse Event Form should be completed and signed by the principal investigator or the sub-investigator and not a "physician". Clarification was made to indicate that the initial and follow-up reports of a serious adverse event should be downloaded from the eCRF. Hospitalization was "defined as an overnight hospital stay".

Amendment 3 (20 April 2022)

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

The overall reason for the amendment: To update the protocol on the extension of the overall study duration.

Applicable Sections	Description of Changes
Rationale: To update the overall study duration.	
• Section 17.9.1: Study completion/end of study	Study duration has been updated from 51 months to 60 months & 8 days.

Amendment 2 (30 June 2021)

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

The overall reason for the amendment: To update the protocol on the extension of the overall study duration.

Applicable Sections	Description of Changes
Rationale: To update the overall study duration.	
• Section 17.9.1: Study completion/end of study	Study duration has been updated from 48 to 51 months.
Rationale: To correct the minimal hemoglobin concentration accepted for eligibility.	
• Synopsis: Overview of study design • Section 4.1: Inclusion criteria	The threshold value for hemoglobin concentration has been corrected from 10.0 to 8.0 g/dL, in order to be consistent with the 5 mmol/L concentration that is also stated in the inclusion criterion 6b.
Rationale: To provide more information on the median overall survival of AL amyloidosis patients according to the literature.	
• Section 1.3: Overall rationale for the study	A paragraph was added to provide information on the overall survival of AL amyloidosis patients at stage 3B.
Rationale: To provide more information on the rationale for the transition to daratumumab subcutaneous.	
• Section 3.2.1: Rationale for daratumumab subcutaneous dose selection	A paragraph was added to provide information on the mean trough concentrations and safety profile of daratumumab subcutaneous compared to daratumumab intravenous.

Amendment 1 (16 September 2019)

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

The overall reason for the amendment: To update the protocol on the transition from intravenous daratumumab administration to subcutaneous.

Applicable Sections	Description of Changes
Rationale: To expand the study design to include the subcutaneous administration of daratumumab; to establish the definition of daratumumab IV and daratumumab SC terms.	
• Synopsis: Overview of study design • Section 3.1: Overview of Study Design • Figures 1 and 2	The text was revised to indicate that all new subjects will be dosed subcutaneously with daratumumab and subjects who have already begun treatment with daratumumab IV must switch to daratumumab SC on their next scheduled drug administration date. Daratumumab IV and daratumumab SC are defined
Rationale: To provide more details about the Safety run-in phase	
• Synopsis: Overview of study design • Section 3.1: Overview of study design	The paragraph was updated to indicate that the evaluation of the safety run-in will not include patients who will not have completed the first cycle for reasons unrelated to study treatment. More specifically, this would refer to patients who die, withdraw from the study, or discontinue study treatment for reasons other than toxicity
Rationale: To provide more information on the rationale for daratumumab	
• Section 1.3: Overall rationale for the study • References: 41–44	The text was updated with information based on the relevant literature, and with additional references
Rationale: To provide information on the reactivation risk of Hepatitis B virus	
• Table 1: Time and events schedule • Section 4.2: Exclusion criteria • Section 8.1.1: Management of HBV reactivation • Section 9.6: Safety evaluations	Clarifications were made according to the latest information on the risk of HBV reactivation
Rationale: To provide the dose of daratumumab SC, the rationale for dose selection, and benefits associated with the used of daratumumab SC	
Section 3.2.1: Rationale for dose: • Benefits for SC • Rationale for daratumumab SC dose selection	Text was added to provide rationale for the dose and benefits of SC administration
Rationale: Text was added to clarify the administration schedule of daratumumab SC	
• Synopsis: Dosage and administration • Table 2: Time and events schedule: study drug dosing • Section 6.2.1: Treatment schedule and administration • Figure 3	Text was added to provide information with respect to daratumumab SC administration
Rationale: To provide details on injection site reactions and infusion related reactions related to daratumumab SC administration	

• Section 6.2.3.1: Pre-infusion medications • Section 6.2.3.2: Post-infusion medications • Section 6.2.3.3: Management of Infusion Related Reactions: o Local injection site reactions o Infusion Related Reactions for daratumumab SC	Text was added to clarify that pre-infusion and post-infusion medications refer to daratumumab SC as well; to provide information on the management of Infusion Related Reactions and Injection Site Reactions associated with subcutaneous administration of daratumumab
Rationale: To update the statistical methods regarding the Patient-Reported Outcomes with respect to the switch to daratumumab SC	
Section 11.5 Patient-Reported Outcomes	To specify that results from the EORTC-QLQ-C30 questionnaires will be presented in two groups, for patients who received daratumumab IV and patients who received daratumumab SC
Rationale: To provide information regarding physical description and packaging of daratumumab SC	
Section 14.1: Physical description of study drug Section 14.2: Packaging	Text was updated accordingly
Rationale: To clarify that for hematologic response categories two consecutive assessments are required	
Section 2.1: Objectives and endpoints Section 9.2.5: Endpoints	Text was added to specify the hematologic disease progression criteria for MOD-PFS
Section 9.2.1: Hematologic response categories	Text was added to specify that all response categories require two consecutive measurements from independent samples
Rationale: To clarify that a disease progression form will be completed within 24 hours from the disease progression assessment	
Section 9.1.3: Treatment phase	Text was corrected from 48 to 24 hours
Rationale: To clarify that all biological material will be destroyed at the end of the study	
Section 9.7: Sample collection and handling	The paragraph was updated in order to clarify that all collected biological samples will not be retained, and they will be destroyed at the end of the study
Rationale: To include information regarding Adverse Events of Special Interest (AESI) and information on the reporting of Special Reporting Situations that meet the criteria for Serious Adverse Events	
Section 12.2: Adverse Events of Special Interest	A paragraph was added to provide information about the categories of Adverse Events of Special Interest and guidelines for their reporting
Section 12.3: Special Reporting Situations	Additional information was provided to clarify the timelines for any Special Reporting Situation that meet the criteria for Serious Adverse Event
Rationale: Minor corrections	
Throughout the protocol	To perform minor corrections and updates throughout the protocol

SYNOPSIS

Phase 2 study of daratumumab monotherapy in previously untreated patients with stage 3B light chain (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 multiple myeloma and AL amyloidosis. This target is distinct from those of other approved agents for multiple myeloma therapy.

Daratumumab has shown high efficacy in multiple myeloma, even as a monotherapy, with a uniquely safe toxicity profile. Daratumumab in combination with CyBorD (or otherwise known as VCD) is under investigation for the primary therapy of patients with light chain (AL) amyloidosis with stage 1 to 3A disease, according to cardiac biomarkers. The current study aims to investigate daratumumab as a monotherapy in patients with stage 3B AL amyloidosis who have not received prior therapy.

OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

Primary Objective

The primary objective is to evaluate the overall survival (OS) rate at 6 months following treatment with daratumumab in frontline AL patients with stage 3B disease.

Secondary Objectives

The secondary objectives are:

- To evaluate the overall (ORR), very good partial (VGPR) and complete (CR) hematologic response rates at 3 and 6 months
- To evaluate the Major Organ Deterioration Progression-Free Survival (MOD-PFS). This is a composite endpoint of clinically observable endpoints and will be defined from the start of study treatment (Cycle 1 Day 1) until any one of the following events (whichever occurs first)
  - Death
  - Clinical manifestation of cardiac failure:
    - Defined as development of dyspnea at rest (for at least 3 consecutive days and solely due to amyloidosis cardiac deterioration) that requires hospitalization for management, or need for cardiac transplant, or left ventricular assist device (LVAD), or intra-aortic balloon pump (IABP).
  - Clinical manifestation of renal failure:
    - Defined as the development of end stage renal disease (need for hemodialysis or renal transplant)

  - Development of hematologic progression of disease (PD) as per consensus guidelines (two consecutive assessments are required, see section 9.2.1)
    - From CHR, abnormal free light chain ratio (light chain ratio must double).
    - 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

- To evaluate PFS based on all-cause mortality and progression of disease (PD; including hematologic PD and organ (heart and kidney) PD according to consensus guidelines)
- To evaluate the organ response rate (OrRR)
    - Heart
    - Kidney
    - Liver
- To evaluate treatment effects on patient-reported outcomes (PROs) such as the Short Form-36 Health Survey (SF-36), European Quality of Life-5 Dimensions Questionnaire (EQ-5D-5L) and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30)
- To characterize time to and duration of response
- To assess the safety and tolerability of daratumumab in patients with stage 3B AL amyloidosis
- To describe the proportion of subjects who received additional treatment with bortezomib and low dose dexamethasone (at the investigator's discretion).

Exploratory Objectives

The exploratory objectives are:

- To evaluate CD 38 expression and its correlation with response to daratumumab
- To explore minimal residual disease status in amyloidosis patients as a surrogate for PFS and OS or as a biomarker for relapse
- To evaluate diastolic function following treatment with daratumumab based on analysis of transthoracic echocardiograms

Refer to Section 9 for evaluations related to endpoints.

Hypothesis

The primary hypothesis of this study is that the 6-month OS rate of patients with newly diagnosed stage 3B AL amyloidosis will exceed 50% after primary therapy with daratumumab.

OVERVIEW OF STUDY DESIGN

This is an open-label, multicenter, Phase 2 study in subjects with newly diagnosed stage 3B light chain (AL) amyloidosis. Approximately 40 subjects will receive primary therapy with daratumumab. Subject participation will include a Screening Phase, a Treatment Phase, a Post-Treatment Observation Phase, and a Long-term Follow-up Phase.

A safety run-in will be conducted in 6 subjects treated with daratumumab for at least 1 cycle to establish safety of daratumumab in patients with stage 3B AL amyloidosis (Figure 1). Dosing of these 6 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 a Data Safety Monitoring Board (DSMB) after at least 1 cycle is completed for all 6 subjects. The evaluation of the safety run-in will not include patients who will not have completed the first cycle for reasons unrelated to study treatment. More specifically, this would refer to patients who die, withdraw from the study, or discontinue study treatment for reasons other than toxicity, i.e., disease progression, patient choice, patient lost to follow-up. If no safety signal is observed, the enrollment of the rest of the patients will begin.

The original design of this study was to treat patients with intravenous daratumumab infusion (daratumumab IV). However, as of Protocol Amendment 1, all new subjects will be dosed subcutaneously with daratumumab co-formulated with recombinant human hyaluronidase rHuPH20 (daratumumab SC). Subjects who already began treatment with daratumumab IV (i.e., prior to Amendment 1) must switch to daratumumab SC, on the next administration date according to the protocol schedule. Subjects will receive daratumumab IV at a dose of 16 mg/kg and daratumumab SC at a fixed dose of 1800 mg according to the dosing schedule referred in Section 6.2 and in Figure 2 and Figure 3. All treatment cycles are 4 weeks (28 days) in length. Subjects will receive daratumumab until disease progression (according to MOD-PFS), start of subsequent therapy, or a maximum of 2 years in total (Section 2.1).

SUBJECT POPULATION

Adult subjects aged 18 years or older with newly diagnosed amyloid light chain amyloidosis are eligible for the study. Key inclusion and exclusion criteria are as follows:

KEY INCLUSION CRITERIA

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

1. Men or women 18 years of age or older.
2. Diagnosis of amyloidosis, AL type, based on:
    a. Histopathological diagnosis of amyloidosis based on detection by immunohistochemistry and polarizing light microscopy of green bi-refringent

material in Congo Red stained tissue specimens (excluding 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 over 70 years of age who have cardiac involvement only, and subjects of African descent (black subjects), mass spectrometry, immunoelectron microscopy, or other immunohistochemistry-based typing of AL amyloid in a tissue biopsy or a negative bone scintigraphy with Tc99m-PYP or –DPD is recommended to rule out other types of amyloidosis such as age related amyloidosis and/or hereditary amyloidosis (ATTR mutation)

AND

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

- serum monoclonal protein ≥0.5 g/dL by protein electrophoresis (routine serum protein electrophoresis and immunofixation performed at local lab),
- serum free light chain (FLC) ≥2.0 mg/dL (20 mg/L) with an abnormal kappa:lambda ratio or the difference between involved and uninvolved free light chains (dFLC) ≥2mg/dL (20 mg/L). Serum free light chains (FLCs) will be measured using the Freelite assay at a central laboratory
- Note: Measurable disease by Urine Bence-Jones Proteinuria is not sufficient for study enrolment.

AND

c. Cardiac involvement by AL amyloidosis according to consensus guidelines (See ATTACHMENT 3)

3. Mayo Stage 3B disease, defined as both A. increased cardiac troponin (hsTnT > 54 pg/ml) AND B. increased NT-proBNP ≥ 8500 pg/ml

4. For subjects with congestive heart failure, symptoms should be optimally managed and clinically stable with no cardiovascular-related hospitalizations within 2 weeks prior to Cycle 1 Day 1, as assessed by the Principal Investigator. [See also exclusion criteria 3]

5. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0, 1, 2 or 3 (See ATTACHMENT 1)

6. Subject must have pre-treatment clinical laboratory values meeting the following criteria during the Screening Phase:

a. Absolute neutrophil count ≥1.0 × 10^9/L;

b. Hemoglobin level ≥8.0 g/dL (≥5 mmol/L)

c. Platelet count ≥75 × 10^9/L; platelet transfusions are NOT acceptable

d. Alanine aminotransferase level (ALT) ≤2.5 x the upper limit of normal (ULN);

e. Aspartate aminotransferase (AST) ≤2.5 x ULN

f. Total bilirubin level ≤1.5 × ULN, except for subjects with history of Gilbert Syndrome, in which case direct bilirubin ≤ 2 × ULN

g. Estimated Glomerular Filtration Rate (eGFR) ≥20 mL/min; Please note that the eGFR is measured using the CKD-EPI equation (see ATTACHMENT 6 for details)

7. Women of childbearing potential[a] 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 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 3 months after receiving the last dose of daratumumab, female subjects must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction.

9. 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, e.g. 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 3 months after discontinuation of daratumumab. All men must not donate sperm during the study and for 3 months after discontinuation of daratumumab.

10. Female subjects of childbearing potential must have a negative serum or urine pregnancy test within 14 days prior to Cycle 1 Day 1. For requirements during the Treatment Phase, please see the Time and Events Schedule.

11. Each subject must sign an informed consent form (ICF) indicating that he or she understands the purpose of the 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.

[a] Females are not of reproductive potential if they have been in natural menopause for at least 24 consecutive months, or have had a hysterectomy and/or bilateral oophorectomy

KEY 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 with the exception of 160 mg dexamethasone (or equivalent steroid) prior to Cycle 1 Day 1

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

3. Evidence of significant cardiovascular conditions as specified below:

    a. New York Heart Association (NYHA) classification of heart failure, stages IIIB or IV (see ATTACHMENT 4)

    b. 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 electrocardiogram (ECG) changes) or uncorrected valvular disease, and not due to AL amyloid cardiomyopathy

    c. Hospitalization for unstable angina or myocardial infarction, or percutaneous cardiac intervention with recent stent, or coronary artery bypass grafting, all within 6 months prior to first dose

    d. Subjects with a history of sustained ventricular tachycardia or aborted ventricular fibrillation or with a history of atrioventricular (AV) nodal or sinoatrial (SA) nodal dysfunction for which a pacemaker/ICD is indicated but will not be placed (subjects who do have a pacemaker/ ICD are allowed in the study)

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

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

4. Subjects planning to undergo a 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. Diagnosed or treated for malignancy other than AL, except:

    a. Malignancy treated with curative intent and with no known active disease present for ≥24 months before Cycle 1 Day 1

b. Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease

c. Adequately treated carcinoma in situ (e.g. cervical, breast) with no evidence of disease

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

7. Subject has known moderate or severe persistent asthma within the past 2 years (see ATTACHMENT 7), 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. Subject is known to be seropositive for human immunodeficiency virus (HIV). HIV positive subjects who are stable on highly active antiretroviral therapy (HAART) with no opportunistic infections within the last 6 months are eligible.

9. Subjects known to be:

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

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

12. Subject has known allergies, hypersensitivity or intolerance to monoclonal antibodies or human proteins, or their excipients (refer to Investigator Brochure), or known sensitivity to mammalian-derived products.

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

14. Subject is a female who is pregnant or breast-feeding or planning to become pregnant while enrolled in this study or within 3 months following discontinuation of daratumumab.

15. Subject has received an investigational drug (including investigational vaccines) or used an invasive investigational medical device within 4 weeks prior to Cycle 1, Day 1.

16. Subject has had major surgery within 2 weeks prior to 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 drug administration. Note: subjects with planned surgical procedures to be conducted under local anesthesia may participate.

    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 drug 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.

DOSAGE AND ADMINISTRATION

The original design of this study was to treat patients with daratumumab intravenous (dara IV) infusion, however as of Protocol Amendment 1, all enrolled patients will switch from IV to subcutaneous (dara SC) administration, and all new patients will initiate treatment directly with SC, whenever daratumumab SC supplies become available at the Sites. It should be noted that throughout this document, text was added to highlight any differences between daratumumab IV and daratumumab SC dosing; and where there is no clarification, it is implied that the descriptions are the same for both IV and SC.

Daratumumab will be administered at a dose of 16 mg/kg as an IV infusion or 1800 mg subcutaneously weekly for the first 8 weeks (Cycles 1 and 2) of treatment and then every 2 weeks

for 4 cycles (Cycles 3 to 6) and then every 4 weeks until progression of disease (according to MOD-PFS), unacceptable toxicity or subsequent therapy, for a maximum of 2 years in total.

For IV infusions, each subject's dose will be calculated based on the subject's weight rounded to the nearest kilogram. The dose does not need to be recalculated for weight changes that are < 10% from baseline. The weight will be used to determine the required volume of daratumumab from the vials needed for each subject. All infusions may be performed as outpatient visits. Subjects will receive pre-infusion and post-infusion medications as detailed in the protocol

Dexamethasone will be administered as premedication at a maximum total dose of 20 mg weekly (ie, Days 1, 8, 15, 22 during the first two cycles) on days of daratumumab dosing. On weeks that daratumumab is not administered, dexamethasone will not be given.

Subjects who do not achieve either a hematologic VGPR or better, OR a hematologic PR with a major organ response by Cycle 4 Day 1 (see Table 8 in main Protocol for more details), may receive, in addition to daratumumab, bortezomib (for a maximum of 6 cycles) and low dose dexamethasone (total maximum weekly dose of 20mg).

EFFICACY EVALUATIONS

Disease evaluations must be performed every 28 days on the scheduled assessment day (±5 days). For free light chain assessment, the investigator will use results provided by the central laboratory. Organ disease that is considered to be quantifiable for response includes cardiac disease (central laboratory evaluation of NT-proBNP and high sensitivity troponin T), renal disease (proteinuria, creatinine clearance), hepatic disease (alkaline phosphatase).

BIOMARKER EVALUATIONS

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 PFS and OS. Minimal residual disease may be monitored in subjects who achieve hematologic CR. Methodologies such as the Clonoseq NGS assay that quantitatively evaluate neoplastic plasma cell DNA from bone marrow aspirates, or NGF based on the EuroFlow protocol may be used to evaluate MRD negativity.

SAFETY EVALUATIONS

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

STATISTICAL METHODS

For the primary endpoint analysis, the Kaplan Meier estimate of the 6-month OS rate will be presented, along with the respective 95% confidence interval (CI).

Moreover, time-to-event analysis will be conducted and the Kaplan-Meier estimates of the median (e.g. OS, PFS, MOD-PFS, TTP etc.) along with the respective 95% CIs will be presented.

TIME AND EVENTS SCHEDULES

Table 1. Time and Events Schedule

			Treatment Phase		Post-Treatment Phase		Long-Term Follow-Up
		Screening Phase	**Cycles 1-6**	**C7+**	**EOT**		
	Notes	-28 days before C1D1	D1 of each cycle	D1	Post-treatment Week 4 (±3 days)	Post-treatment Week 8 (±3 days)	
Study treatment should be initiated within 72 hours after sponsor's approval of eligibility. Cycles are approximately 28 days in duration. The start of each cycle may occur ±5 days of the scheduled day.							
Procedures							
Informed consent	ICF must be signed before any study-related procedure is performed.						
Eligibility criteria		X					
Demography/ Medical History		X					
Issue Subject Study ID Card		X					
Height		X					
Assessment of lytic disease	To exclude multiple myeloma; skeletal survey or other imaging modality	-42 days					
FEV1 test	Subjects with known or suspected COPD or asthma, FEV1 must be measured	X					
ECOG	See appendix 1	X	X		X		
LVEF assessment	Echocardiogram preferred, other cardiac evaluation of LVEF also acceptable	X		C7D1 and when clinically indicated	X		
12-lead ECG		X			X		
Physical exam	Including neurological exam. Clinically significant abnormalities should be reported as AEs	X	Symptom and disease directed exam as clinically indicated				
Vital signs, Weight		X	Please see Table 2				

			Treatment Phase		Post-Treatment Phase		Long-Term Follow-Up
	Notes	Screening Phase -28 days before C1D1	Cycles 1-6 D1 of each cycle	C7+ D1	EOT Post-treatment Week 4 (±3 days)	 Post-treatment Week 8 (±3 days)	
Patient-Reported Outcome (PRO)	Paper PRO (EORTC QLQ-C30, EQ-5D-5L and SF-36) before any other study procedures. Window is 4 days prior to dosing.		X	Every 8 weeks	X		
Blood type, Rh and IAT	Obtain sample before first dose of daratumumab.		C1D1				
Study Drug Administration							
Daratumumab			See Table 2	See Table 2			
Laboratory Assessments							
Pregnancy test	For women of childbearing potential only, within 14 days prior to Cycle 1 Day 1. Pregnancy testing will not be captured in the eCRF but will be archived in the subject's source documentation.	X	Weekly during Cycle 1 and then monthly in women with regular menstrual cycles or every 2 weeks in women with irregular menstrual cycles				
Hematology		X	See Table 2		X		
Serum chemistry	Including TSH and T4 at screening and subsequently if clinically indicated	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 9.6	X					
HBV DNA testing[1]	For subjects with serologic evidence of resolved HBV infection (i.e., positive Anti-HBs or positive Anti-HBc) at Screening, HBV DNA testing by PCR must be performed locally. Refer to Section 9.6.	X	Every 12 weeks (window ±7 days)		X	Every 12 weeks for up to 6 months after the last dose of study treatment	
Disease Assessments							
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	X	Every 8 weeks until disease progression			
NYHA Functional Classification	See ATTACHMENT 4	X	X	Every 8 weeks until disease progression			
Serum disease evaluations (SPEP)	Not required on C1D1 if screening labs were within 14 days of C1D1	X	X	Every 8 weeks until disease progression			
Urine disease evaluations (UPEP)	Not required on C1D1 if screening labs were within 14 days of C1D1	X	X	Every 8 weeks until disease progression			

			Treatment Phase		Post-Treatment Phase		Long-Term Follow-Up
	Notes	**Screening Phase** -28 days before C1D1	**Cycles 1-6** D1 of each cycle	**C7+** D1	**EOT** Post-treatment Week 4 (±3 days)	Post-treatment Week 8 (±3 days)	
Serum FLC	Sample to be sent to the central laboratory	X	**X Cycle1 weekly; D1, D8, D15, D22. Cycle 2-6; 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			
HS Troponin T	Sample to be sent to central laboratory	X	X	Every 8 weeks until disease progression			
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 as concomitant medications and stem cell yield (number of CD34+ cells per kg and time to engraftment. See protocol				
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				
Biomarkers							
Bone Marrow Biopsy/Aspirate	Morphology, immunohistochemistry, karyotype and/or FISH required by local lab as per standard practice [del17p, t(4;14), t(11;14), amp1q21 etc]	X (-56 days)					
Bone Marrow Biopsy/Aspirate (CD38, MRD)	CD38: 3 unstained FFPE or biopsy slides, or 2 unstained and 1 H&E slide, local laboratory	X (-56 days)					
	MRD: 3 non decalcified aspirate slides (smears or clots), OR 3mL aspirate sample in EDTA, local laboratory	X (-56 days) (only for local laboratories where MRD is detected via Next Generation Sequencing)	When clinically feasible, bone marrow aspirate will be collected at CHR				
Ongoing Subject Review							

			Treatment Phase		Post-Treatment Phase		Long-Term Follow-Up
		Screening Phase	**Cycles 1-6**	**C7+**	**EOT**		
	Notes	-28 days before C1D1	D1 of each cycle	D1	Post-treatment Week 4 (±3 days)	Post-treatment Week 8 (±3 days)	
Adverse Events	See Section 12 for detailed instructions.	Continuous from the time of signing of ICF until 30 days after last dose of last study drug. Subsequently, only AEs considered possibly, probably, or definitely 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 drug					

Abbreviations: AE=adverse event; AntiHBc=hepatitis B core antibody; AntiHBs=hepatitis B surface antigen; C=cycle; CHR=complete hematologic response; COPD=chronic obstructive pulmonary disease;; D=day; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT= End-of-Treatment; EORTC QLQ-C30= European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D-5L=European Quality of Life Five Dimensions Questionnaire; FEV= Forced Expiratory Volume (in 1 second); FFPE=formalin fixed paraffin embedded; FISH=fluoresence in situ hybridization; FLC=free light chain; HBV=Hepatitis B Virus; HS=high sensitivity; IAT=indirect antiglobulin testing; ICF=informed consent form; LVEF=Left Ventricular Ejection Fraction; MRD=minimal residual disease; H&E= hematoxylin and eosin; NT-ProBNP=N-terminal pro-brain natriuretic peptide; PRO= patient reported outcome; SAE= serious adverse event; SF-36= Short Form-36 Health Survey; T4=thyroxine; TSH=thyroid stimulating hormone; SPEP=serum M-protein quantitation by electrophoresis; UPEP=urine M-protein quantitation by electrophoresis;

[1] In patients who develop reactivation of HBV while on treatment, study treatment (daratumumab and velcade/dexamethasone [if applicable]) should be interrupted and appropriate treatment should be instituted as per Investigator's discretion and current clinical guidelines (See Appendix 13). Resumption of study treatment in patients whose HBV reactivation is adequately controlled should be discussed with physicians with expertise in managing HBV.

Table 2. Time and Events Schedule: Study Drug Dosing

	Notes	Cycle 1-2				Cycle 3-6		Cycle 7+	EOT
		D1	D8	D15	D22	D1	D15	D1	Post-treatment Week 4 (±3 days)
Hematology	For Cycle 1 Day 1, no need to repeat tests if they have been performed within the past 5 days. Testing may be performed up to 2 days before other study treatment days. Results of hematology tests must be evaluated before each study drug administration. Perform at additional time points, as clinically indicated. To be done by local lab.	X		X		X	X	X	X
Clinical Chemistry		X		X		X	X	X	X
Vital Signs	Vital signs (blood pressure, temperature) measured in sitting position. Vital signs will be measured immediately before infusion start and after infusion 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 drug doses.	X	X	X	X	X	X	X	X
Pre-infusion Medications for Daratumumab									
Antihistamine	Diphenhydramine 25-50 mg or equivalent. paracetamol or acetaminophen 650-1000 mg. May be given up to 3 hours before the dose of daratumumab. See section 6.2.3 for more details.	X	X	X	X	X	X	X	
Paracetamol		X	X	X	X	X	X	X	
Montelukast	Montelukast 10mg PO recommended before Cycle 1 Day 1, optional for all other doses	X							
Dexamethasone (premedication)	Dexamethasone 20mg. May be given up to 3 hours before the dose of daratumumab. See section 6.2.3 for more details.	X	X	X	X	X	X	X	
Study Drug									
Study Drug Accountability	Accountability/exposure check	X	X	X	X	X	X	X	X
Study Drug Administration									
Daratumumab	Maximum 2 yr. Refer to SIPPM for preparation and administration of daratumumab	X	X	X	X	X	X	X	
Additional Study Treatment									
		Cycle 4+							
		D1	D8	D15	D22				
Bortezomib SC/IV	After Cycle 3 only for subjects that have not achieved EITHER a hematologic PR with improved major organ function (i.e cardiac or renal response per updated response criteria) OR a VGPR or better **(FOR A MAXIMUM of 6 CYCLES)**	X	X	X	X				
Dexamethasone PO	After Cycle 3 only for subjects that have not achieved EITHER a hematologic PR with improved major organ function (i.e cardiac or renal response per updated response criteria) OR a VGPR or better (do not exceed total weekly dose of 20mg)	X	X	X	X				

Abbreviations: D=day; EOT= End-of-Treatment; hr=hour; IV-intravenous; PO=oral; SC=subcutaneous; IV, intravenous; SIPPM=site investigational product procedures manual.

ABBREVIATIONS

ADCC	Antibody-dependent cell-mediated cytotoxicity
ADL	Activities of Daily Living
AE	Adverse events
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
AV	Atrioventricular
BMDex	melphalan and dexamethasone with bortezomib
BSA	Body surface area
CA	Competent authority
CDC	Complement-dependent cytotoxicity
CHR	Complete Hematologic Response
COPD	Chronic obstructive pulmonary disease
CR	Complete response
CRF	Case report forms
CTCAE	Common Terminology Criteria for Adverse Events
CTD	Cyclophosphamide, thalidomide, dexamethasone
CyBorD	Cytoxan, bortezomib, and dexamethasone
dFLC	Difference between involved and uninvolved free light chains
DSMB	Data Safety Monitoring Board
DVd	daratumumab + bortezomib-dexamethasone
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report forms
eDC	Electronic data capture
eGFR	Estimated Glomerular Filtration Rate
ECG	Electrocardiogram
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EOT	End-of-Treatment
EQ-5D-5L	European Quality of Life-5 Dimensions Questionnaire
FEV1	Forced Expiratory Volume in 1 second
FISH	Fluorescence in situ hybridization
FLC	Free light chain
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GEP	Gene expression profiling
HAART	Highly active antiretroviral therapy
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B Virus
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 Conference on Harmonisation
IHC	Immunohistochemistry
IRR	Infusion-related reactions
ITT	Intent-to-treat
IV	Intravenous
LC-MS/MS	Liquid Chromatography-Tandem Mass Spectrometry
LVAD	left ventricular assist device
LVEF	left ventricular ejection fraction
LVIDd	Left Ventricular Internal Diameter in Diastole
mAb	monoclonal antibody
MDex	melphalan and dexamethasone
MDSC	Myeloid derived suppressor cells
MM	Multiple myeloma
MOD-PFS	Major Organ Deterioration Progression-Free Survival
MRD	Minimal residual disease
MRU	Medical resource utilization
MTD	Maximum tolerated dose
MUGA	Multigated Acquisition
NCCN	National Comprehensive Cancer Network
NGF	Next Generation Flow
NGS	Next Generation Sequencing
NCI	National Cancer Institute
NYHA	New York Heart Association
OrRR	Organ response rate
ORR	Overall response rate
OS	Overall survival
PCP	Pneumocystis carinii pneumonia
PD	Progression of disease
PFS	Progression-free survival
PO	Oral
PQC	Product quality complaint
PR	Partial response
PRO	Patient-reported outcome
PS	Performance Status
RBCs	Red blood cells
SA	Sinoatrial
SC	Subcutaneous
SD	Stable disease
SF-36	Short Form-36 Health Survey
SIPPM	Site Investigational Product and Procedures Manual
SMT	Safety Management Team
SPEP	Serum protein electrophoresis
Tc99m-DPD	Technetium-99m dicarboxypropane diphosphonate
Tc99m-PYP	Technetium-99m pyrophosphate
TNT	Time to next treatment
TEAE	Treatment-emergent adverse events
TTE	Transthoracic Echocardiogram
ULN	Upper limit of normal
UPEP	Urine protein electrophoresis

Vd	Bortezomib and dexamethasone
VGPR	Very good partial response
WBC	White blood cell

1. INTRODUCTION

1.1. Amyloidosis

Amyloidosis is a term used for diseases that have in common the 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[1,2]. Systemic light chain amyloidosis (AL) is an acquired plasma cell disorder, in which clonal light chains produced by clonal CD38+ plasma cells, form amyloid fibrils.

There is no prevention for amyloidosis or an approved agent that can dissolve the amyloid fibrils deposited in tissues but elimination or reduction of the light chain production is the basis for the therapies that do exist. The goal of therapy is to achieve complete hematologic response (CR) 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[3-5]. In AL, unlike in myeloma, achieving a partial hematologic response or stable disease may not offer a clinical benefit as ongoing light chain production may result in further organ damage. Partial response (PR) should always be viewed in conjunction with organ response in the evaluation of treatment outcomes[4,6,7]. 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 multiple myeloma patients[5]. 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.

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 II studies have shown that lenalidomide in combination with dexamethasone is active in frontline and relapsed/refractory settings[8,9]. 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 II study in newly diagnosed patients, the combination of cyclophosphamide, lenalidomide and dexamethasone, resulted in an overall hematologic response rate of 60% (VGPR or better) (Kumar 2012). In this study, the hematologic toxicities were the predominant adverse events. Proof of concept and Phase II studies showing that regimens such as cyclophosphamide, thalidomide, dexamethasone (CTD), lenalidomide plus dexamethasone (RevDex), and bortezomib have clinical utility in AL amyloidosis have been reported[10-12] .

1.1.1. Current treatment approaches for the elimination of the plasma cell clone in AL amyloidosis

Bortezomib-based Treatment Options for Amyloidosis

The majority of data published on the safety and efficacy of bortezomib is derived from uncontrolled, retrospective analyses. However, Kastritis et al recently presented the results of the first prospective, randomized, phase III trial comparing melphalan and dexamethasone (MDex) and MDex with bortezomib (BMDex) in newly-diagnosed AL amyloidosis. The primary endpoint, hematologic response at 3 months, was reached showing a higher response rate with BMDex; 51% (28% CR/VGPR) hematologic response with MDex versus 78% (53% CR/VGPR) hematologic response with BMDex (P=0.001). Overall hematologic response at the end of treatment (median of 5 cycles) was 56% MDex and 81% 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 higher proportion of cardiac progression (32% vs 15%) in the MDex arm with borderline statistical significance (P=0.054). Renal response was 48% in both arms. After a median follow-up of 25 months, 26 patients (24%) died (MDex, 16 subjects; DMDex, 10 subjects) with no significant difference in survival. Achievement of hematologic and cardiac response at 3 months significantly improved survival. The conclusion of the study is that the introduction of novel therapy (bortezomib) results in superior efficacy compared to alkylating therapy + steroid alone**.** The regimen of Cytoxan, bortezomib, and dexamethasone (CyBorD), is commonly used for the treatment of newly diagnosed patients with AL Amyloidosis. For example, Mikhael et al conducted a retrospective study utilizing bortezomib (1.5 mg/m^2 weekly), cyclophosphamide (300 mg/m^2 orally weekly), and dexamethasone (40 mg weekly). Response was observed in 16 (94%) patients, with 71% of patients achieving complete hematologic response and 24% partial response. Time to response was 2 months. In a separate study of 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 VGPR with >90% decrease in difference between involved and uninvolved light chains (VGPR-dFLC) in 51.4%. 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. 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. However, although VCD/CyBorD is considered as a primary regimen for patients with AL, it is not clear whether the addition of cyclophosphamide to VD further and significantly improves efficacy, given the substantial activity of bortezomib itself.

In a retrospective comparison of the outcomes of 101 patients with AL amyloidosis who received either VD (n=59) or VCD/CyBorD (n=42) in two consecutive periods there was no significant difference in early mortality after adjustment for Mayo stage[14]. On intent to treat, hematologic response rate was 68% for patients treated with VD and 78% for patients treated with VCD (P=0.26); CR+VGPR rates were VD:47.5% and VCD:35%. Higher doses of dexamethasone or twice-weekly bortezomib were not associated with significantly higher CR+VGPR rates and organ responses occurred in similar rates between the two groups. Median survival was similar (33 vs 36 months, P=0.45) even after adjustment for Mayo stage and dose and schedule of bortezomib and dexamethasone. These data indicate that bortezomib even with low doses of dexamethasone is effective for the treatment of AL amyloidosis; higher doses of dexamethasone and addition of cyclophosphamide do not seem to have a profound effect on efficacy and survival. On the other hand, these data also indicate the limits of the current approaches of addition of alkylating agents to bortezomib and the need for innovative approaches for the treatment of the plasma cell clone in AL amyloidosis. It is notable that in all the above studies the outcomes of patients with high risk AL (i.e stage 3B per Mayo stage) remain extremely poor, the 6-month survival rates being below 50%.

1.2. Daratumumab

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

Daratumumab has multiple mechanisms of action, including antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). Importantly, daratumumab-induced ADCC and CDC do not appear to be affected by the presence of bone marrow stromal cells, indicating that daratumumab can effectively induce the killing of malignant cells in a tumor-preserving bone marrow microenvironment. In vivo studies have shown that daratumumab is highly active and interrupts xenograft tumor growth at low doses.

As of 15 November 2022, over 40 studies have been initiated in hematologic diseases/malignancies, solid tumors, and healthy volunteers in the daratumumab clinical development program. To date, an estimated 5,944 participants have received daratumumab in the clinical development program. Of these, 1,936 participants were exposed to daratumumab from monotherapy studies and 4,008 participants were exposed to daratumumab from combination therapy studies.

As monotherapy and as combination therapy, daratumumab IV has been approved at a dose of 16 mg/kg. As monotherapy and as combination therapy, daratumumab SC has been approved at a dose of 1,800 mg administered subcutaneously. Daratumumab SC has reduced the treatment burden for patients due to its shorter duration of administration and reduced rate of IRRs. Daratumumab administered as monotherapy or combination therapy has shown clinically

meaningful benefit in MM and newly diagnosed AL amyloidosis. Schedules of administration are specified based on each study.

Among 156 participants treated with 16 mg/kg daratumumab IV monotherapy in the 3 completed studies (MMY2002, GEN501, and MMY1002), 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.

The safety profile of daratumumab in combination with other agents is consistent with the known safety profiles of the backbone therapies (bortezomib, lenalidomide, pomalidomide, dexamethasone, melphalan, prednisone, thalidomide). With the exception of IRRs, the addition of daratumumab to standard multiple myeloma treatment regimens did not seem to add toxicity to the safety profiles previously reported with these backbone regimens.

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

Daratumumab in AL Amyloidosis

There is limited data published on daratumumab in the treatment of AL amyloidosis; however, the limited data that has been published has been positive. Data from Stanford University School of Medicine further support the efficacy and safety of daratumumab in AL amyloidosis[21]. In this retrospective analysis, 25 consecutive previously treated AL patients received daratumumab as IV infusion at 16mg/kg weekly for 8 weeks, then every 2 weeks for 8 doses, then every 4 weeks. Patients had received a median of 3 prior lines of therapy, with a previous hematologic CR in only 5 patients. The overall hematologic response rate to daratumumab was 76%, including CR in 36% and VGPR in 24%. Median time to response was one month. Therapy was well tolerated, even among patients with cardiac AL involvement (72% of total). Grade 1-2 infusion reactions occurred in 15 patients, but no grade 3 or 4 reactions were observed. The authors concluded that daratumumab is a highly effective agent that produced rapid and deep hematologic responses without unexpected toxicity in our cohort of heavily pretreated AL patients

Another study presented efficacy data from 4 patients with AL amyloidosis (AL) or multiple myeloma with AL (MM/AL) with hematologic and/or organ progression and who were treated with daratumumab Patients 01 and 02 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 henceforth. Patients 03 and 04 received the standard Daratumumab treatment of 16 mg/kg. Patients 01-03 received montelukast on the day prior, the day of and two days after daratumumab. Hematologic response was assessed by Consensus Criteria.

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

Subject ID	Diagnosis	No. Prior Regimens	Best Hematologic Response
01	MM/AL	6	CR
02	AL	4	PR
03	AL	4	unmeasurable
04	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 two patients with multiple myeloma whose disease was complicated by development of co-morbid AL amyloidosis[23]: the results were favorable as both patients achieved a hematologic response.

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[24]. Patients in stage 3B in particular are at a high-risk condition and treatment combinations may bring along non-manageable complications. The therapeutic options for AL amyloidosis should include eradication of plasma cells that produce the toxic protein deposits leading to organ failure. These plasma cells express CD38[25-27] and could be targeted by antibodies such as daratumumab that binds and eliminates CD38 expressing cells.

The median survival of stage 3B patients if both low Systolic Blood Pressure and NTproBNP > 8500 ng/L are present is quite poor, and in the Wechalekar et al report[45] it is about 3 months (with 30% 6-month survival rate), being 6 months (50% survival at 6 months) if any of the two criteria (low systolic blood pressure or NTproBNP > 8500 ng/L) is present. In the study by Dinner et al[46], the median survival of patients with stage 3 disease (that is stage 3A and 3B) was 1.75 months and the 1-year survival was 22%. In the report by Palladini et al[47], the median survival of patients with NTproBNP>8500 ng/L and NYHA≥3 either with BMDex or MDex was 3 months. In the study by Jaccard et al[48], the median survival in the group of patients with a pre-treatment serum NT-proBNP concentration over 9500 ng/L or BNP over 1100 ng/L was 4.4 months. In the paper by Palladini et al[15] on VCD treated patients, the median survival of stage 3B patients was 7 months, with stage 3B being the strongest poor-prognosis factor and many patients receiving low dose therapy due to risk of toxicity, and overall response rate of just 42% on intention to treat analysis. In another report by Palladini et al[49] 59% of Stage 3B patients died in the first 6 months, and 76% within a year from diagnosis. In the report by Kastritis et al[50] patients with stage 3B disease had an extremely poor outcome; in those who also had von Willebrand Factor Antigen > 230.0 U/dL the median survival was 2 months and for those with a lower level it was 6 months. Taken together, all the above data indicate that the prognosis of stage 3B patients is extremely poor.

Therapy with CyBorD is not able to reduce early mortality in stage 3B patients, except for those who have been able to survive for at least 3 months to receive enough treatment[15]. In general, ASCT is only indicated for the low-risk AL Amyloidosis population[4], as most patients would be too fragile for such a procedure, especially the Stage 3B subpopulation. Further, BMDex has not

been able to overcome the poor prognosis of patients with severe heart involvement (NT-proBNP>8500 ng/L and NYHA≥III)[41].

Therefore, it is of utmost importance to incorporate an agent which will be able to provide deep and rapid responses. Based on the available safety data from single-agent daratumumab studies (GEN501 & SIRIUS)[28], and from combination studies of daratumumab with lenalidomide[29] or bortezomib[30] or pomalidomide[31], the expected safety profile of daratumumab in this combination therapy study is considered manageable. In addition, the safety run-in phase of this study will provide information on the safety of daratumumab in the stage 3B AL patient population. Furthermore, there is substantial evidence that daratumumab may be able to show both rapid (median time: 1 month) and deep hematologic responses (PR or better in 76%) in AL-Amyloidosis[21] and with a good safety profile[42]. In a prospective study 63% of the patients showed a response after the first cycle, all of whom showed a decrease in dFLC of at least 30% after a single daratumumab administration[43]. More recently, the hematologic VGPR or better rate of Daratumumab at 3 months was reported to be 84.2%[44].

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

- There is a medical need for new treatments for stage 3B AL since no specific standard of care therapy in frontline or relapsed setting exist
- There is high morbidity and mortality in stage 3B AL subjects and the current treatment options are inadequate
- Preclinical data suggest that malignant plasma cells in AL express CD38 and therefore can be targeted by daratumumab
- There is substantial evidence that daratumumab may be efficacious and with a manageable safety profile in patients with AL

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

2.1. Objectives and Endpoints

Primary Objective

The primary objective is to evaluate the overall survival rate at 6 months following treatment with daratumumab in frontline AL patients with stage 3B disease.

Secondary Objectives

The secondary objectives are:

- To evaluate the overall (ORR), very good partial (VGPR) and complete (CR) hematologic response rates at 3 and 6 months
- To evaluate the Major Organ Deterioration Progression-Free Survival (MOD-PFS). This is a composite endpoint of clinically observable endpoints and will be defined from the start of study treatment (Cycle 1 Day 1) to any one of the following events (whichever occurs first)
  - Death
  - Clinical manifestation of cardiac failure:
    - Defined as development of dyspnea at rest (for at least 3 consecutive days and solely due to amyloidosis cardiac deterioration) that requires hospitalization for management, or need for cardiac transplant, or left ventricular assist device (LVAD), or intra-aortic balloon pump (IABP).
  - Clinical manifestation of renal failure:
    - Defined as the development of end stage renal disease (need for hemodialysis or renal transplant)
  - Development of hematologic PD as per consensus guidelines (two consecutive assessments are required, see section 9.2.1)
    - From CHR, abnormal free light chain ratio (light chain ratio must double).
    - 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
- To evaluate PFS based on all-cause mortality and progression of disease (PD, including hematologic PD and organ (heart and kidney) PD according to consensus guidelines)
- To evaluate the organ response rate (OrRR)
  - Heart
  - Kidney
  - Liver
- To evaluate treatment effects on patient-reported outcomes (PROs) such as the Short Form-36 Health Survey (SF-36), European Quality of Life-5 Dimensions Questionnaire

(EQ-5D-5L) and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30)

- To characterize time to and duration of response
- To assess the safety and tolerability of daratumumab in patients with stage 3B AL amyloidosis
- To describe the proportion of subjects who received additional treatment with bortezomib and low dose dexamethasone (at the investigator's discretion).

Exploratory Objectives

The exploratory objectives are:

- To evaluate CD38 expression and its correlation with response to daratumumab
- To explore minimal residual disease (MRD) status in amyloidosis patients as a surrogate for PFS and OS or as a biomarker for relapse
- To evaluate diastolic function following treatment with daratumumab based on analysis of transthoracic echocardiograms

Refer to Section 9 for evaluations related to endpoints.

2.2. Hypothesis

The primary hypothesis of this study is that the 6-month OS rate of patients with newly diagnosed stage 3B AL amyloidosis will exceed 50% after primary therapy with daratumumab.

3. STUDY DESIGN AND RATIONALE

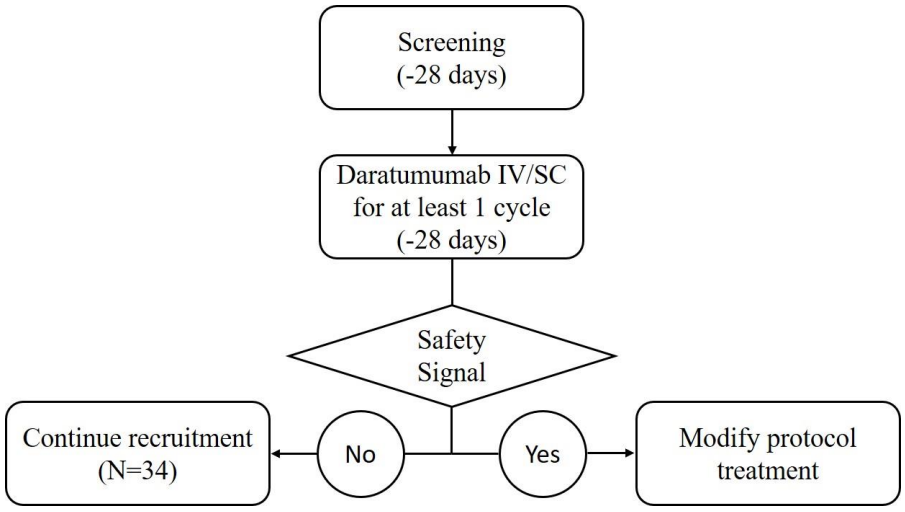
3.1. Overview of Study Design

This is an open-label, multicenter, Phase 2 study in subjects with newly diagnosed stage 3B light chain (AL) amyloidosis. Approximately 40 subjects will receive primary therapy with daratumumab. Subject participation will include a Screening Phase, a Treatment Phase, a Post-Treatment Observation Phase, and a Long-term Follow-up Phase.

A safety run-in will be conducted in 6 subjects treated with daratumumab for at least 1 cycle to establish safety of daratumumab in patients with stage 3B AL amyloidosis (Figure 1). Dosing of these 6 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 a Data Safety Monitoring Board (DSMB) after at least 1 cycle is completed for all 6 subjects. The evaluation of the safety run-in will not include patients who will not have completed the first cycle for reasons unrelated to study treatment. More specifically, this would refer to patients who die, withdraw from the study, or discontinue study treatment for reasons other than toxicity, i.e., disease progression, patient choice, patient lost to follow-up. If no safety signal is observed, the enrollment of the rest of the patients will begin. Further details will be provided in the DSMB charter.

Subjects in the safety run-in will continue all scheduled assessments as specified in the Time and Events Schedule (Table 1), and contribute to the overall safety evaluation.

Figure 1: Schematic Overview of the Safety Run-In

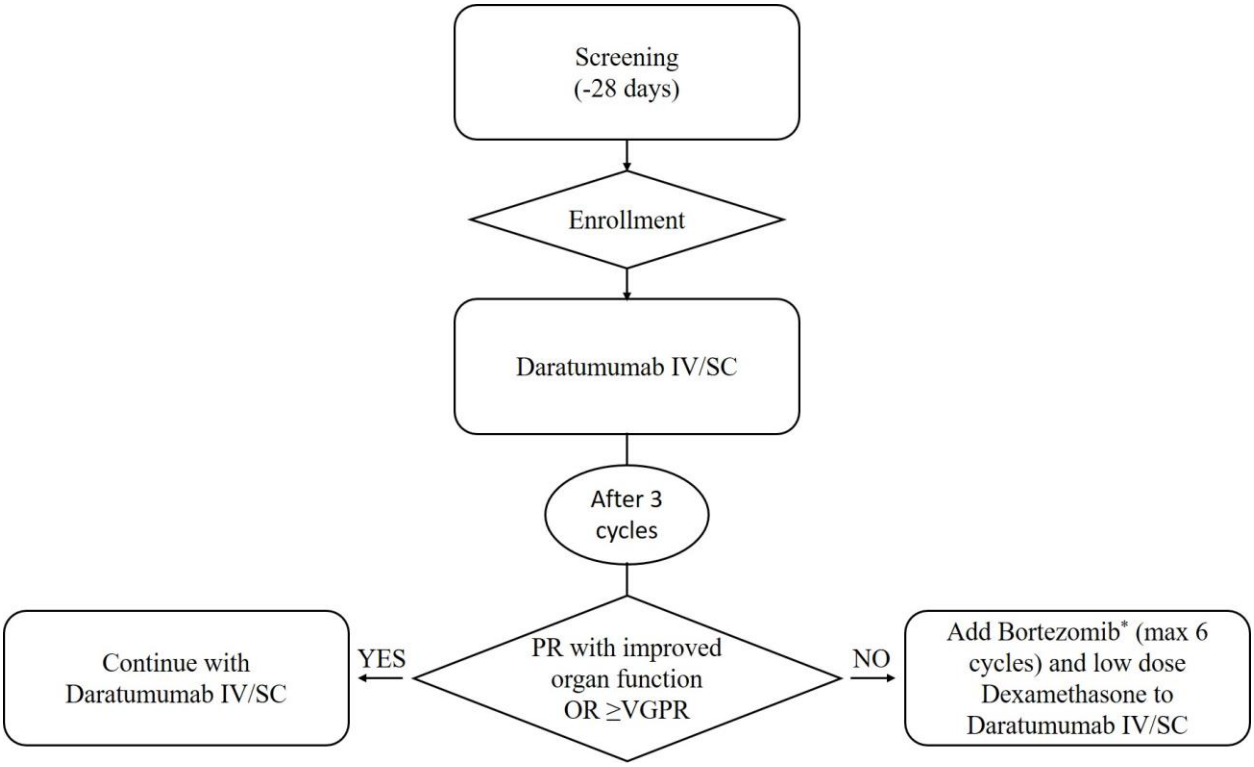


The original design of this study was to treat patients with intravenous daratumumab infusion (daratumumab IV). However, as of Protocol Amendment 1, all new subjects will be dosed subcutaneously with daratumumab co-formulated with recombinant human hyaluronidase rHuPH20 (daratumumab SC). Subjects who already began treatment with daratumumab IV (i.e., prior to Amendment 1) must switch to daratumumab SC, on the next administration date according to the protocol schedule. Subjects will receive daratumumab IV at a dose of 16 mg/kg and

daratumumab SC at a fixed dose of 1800 mg according to the dosing schedule referred in Section 6.2 and in Figure 2 and Figure 3. All treatment cycles are 4 weeks (28 days) in length. Subjects will receive daratumumab until disease progression (according to MOD-PFS), start of subsequent therapy, or a maximum of 2 years in total.

Patients who after 3 cycles of daratumumab monotherapy have not achieved at least a hematologic VGPR or a hematologic PR with improved major organ function (i.e cardiac or renal response per updated response criteria), may receive at the Investigator's discretion in addition to daratumumab weekly bortezomib (1.3 mg/m^2 weekly, for a maximum of 6 cycles) with low dose dexamethasone.

Figure 2: Schematic Overview of the Study



*Please refer to Section 6.4 regarding the full eligibility criteria for the addition of Bortezomib

3.2. Study Design Rationale

3.2.1. Rationale for Dose

Rationale for Daratumumab Intravenous Dose Selection

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 IV infusion until disease progression, start of subsequent therapy, or unacceptable toxicity. The dose selection for this study was based on an acceptable safety profile, maximal clinical activity, and pharmacokinetics consistent with saturation of the target.

Rationale for Study Treatment Regimen

Based on the mechanisms of action, daratumumab will target the neoplastic plasma cells responsible for producing pathologic FLC. Additionally, because of the similar pathophysiology of multiple myeloma and systemic AL amyloidosis, the clinical experience gained with daratumumab in multiple myeloma and in case series of patients with AL amyloidosis, the favorable toxicity profile of daratumumab and the activity of daratumumab given as single agent even in heavily pretreated MM patients, it can be assumed that daratumumab will be an effective therapy for patients with stage 3B AL amyloidosis.

The current study is designed to evaluate the efficacy of daratumumab monotherapy as an effective and safe / nontoxic therapy for patients with stage 3B AL amyloidosis. Patients with stage 3B AL amyloidosis have very poor outcomes and their management remains an unmet medical need. Current treatment options such as bortezomib based combinations have not changed significantly the outcomes of patients with stage 3B AL amyloidosis, while a toxicity signal associated with the introduction of current therapies in these frail patients has been observed.

With regard to the anticipated safety, daratumumab has been successfully administered alone or with various background regimens (including bortezomib, lenalidomide, pomalidomide, dexamethasone, melphalan, and prednisone) (MMY1001 ASH, MMY3003, MMY3004). Considering all studies for which data is available, the safety profile of daratumumab alone or with background myeloma therapy is consistent with the safety profile of the background therapy alone. It is therefore expected that daratumumab will be tolerated without significant unexpected toxicity by patients with stage 3B AL amyloidosis.

The safety of daratumumab treatment in combination with bortezomib and dexamethasone has been demonstrated in a Phase 3 Study (MMY3004 known also as CASTOR) comparing daratumumab, bortezomib, and dexamethasone (DVd) vs bortezomib and dexamethasone (Vd) in patients with multiple myeloma who had received at least 1 prior therapy (DVd=243 versus Vd=237)[30].

This study was a randomized, controlled, open-label study. All subjects received Vd (bortezomib 1.3 mg/m^2 on Day 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 additionally received daratumumab 16 mg/kg every week for the first 9 weeks (Cycles 1 to 3), then on Day 1 of every 3-week cycle until the end of Vd (Cycles 4 to 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, the 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 progression-free

survival rate was 61% versus 27%, respectively. 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.

In the DVd and Vd groups, the most common treatment- emerged adverse events (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. 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 AEs were low and balanced between treatment groups (DVd:7%, Vd:9% and 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 infusion related reactions (IRRs), the safety profile of this combination was similar to that of background therapy. Daratumumab in combination with bortezomib/dexamethasone was well tolerated and any safety outcomes could be effectively managed by standard clinical practice.

Study MMY1004 is an ongoing, open-label, dose-escalation, Phase 1b study to assess the safety and pharmacokinetics of SC administration of daratumumab. Part 1 is to evaluate the intermediate form of daratumumab SC which is a mix and-deliver SC presentation (Dara MD); Dara IV mixed with rHuPH20 at the study center before administration. Part 2 is to evaluate the final form of daratumumab SC (daratumumab coformulated with rHuPH20) (Dara CF or Dara SC). Preliminary efficacy data suggest that SC administration of Dara MD may enable comparable response rates with Dara IV. Furthermore, to date, the rate of IRRs with SC administration of Dara MD and Dara SC has been lower than the rate reported with Dara IV (see Section 2.3.1 for details). The SC administration of daratumumab would offer several tangible benefits for both patients and health care providers:

- Potential reduction in the incidence rate and severity of IRRs (compared with IV infusion), due to slower absorption of daratumumab into systemic circulation
- Shorter administration time (approximately 3 to 5 minutes compared with 4 to 7 hours for IV infusion)
- Reduced administration volume (SC administration of approximately 15 mL instead of 500 mL to 1000 mL IV infusion), which may be clinically meaningful for elderly patients with comorbid cardiac or renal insufficiency

COLUMBA is an ongoing phase 3, randomized, open-label, multicenter study that compares the efficacy, pharmacokinetics, and safety profile of daratumumab co-formulated with recombinant human hyaluronidase PH20, versus the intravenous administration of daratumumab. So far it has been shown that daratumumab SC is non-inferior to daratumumab IV, while at the same time it demonstrates significantly decreased IRR rate and administration time, and a comparable safety profile.

Rationale for Daratumumab Subcutaneous Dose Selection

Dara IV infusion requires a large volume (500 mL to 1000 mL) of infusate, resulting in a median infusion time of 7 hours for the first infusion. Subsequent infusions are approximately 3 to 4 hours. To shorten the infusion time and decrease the risk of IRRs, daratumumab is combined with a technology based on an rHuPH20 to facilitate subcutaneous (SC) administration. rHuPH20 is the active ingredient of the commercial product Hylenex® recombinant (hyaluronidase human injection), which was approved for use in the US in December 2005. Daratumumab has been administered in combination with rHuPH20 in a Phase 1 study (MMY1004).

The maximum trough concentration (C3D1 Ctrough) was defined as the daratumumab effective concentration based on exposure-ORR analyses from the historical IV monotherapy data. In Study MMY1004, the fixed dose for the SC infusion of 1800 mg was selected from Part 1 of the study based on cumulative review of pharmacokinetics and safety data. Similar or greater maximum trough concentrations (C3D1 Ctrough) were observed following administration of 1800 mg Dara MD compared to 16 mg/kg IV daratumumab when administered on the same dose schedule (weekly [QW] for 8 weeks, then every 2 weeks [Q2W] for an additional 16 weeks, then every 4 weeks [Q4W] thereafter). Preliminary data following administration of 1800 mg Dara CF in Part 2 of the study also supported selection of this dose level, indicating the dose is sufficient to produce a similar or greater maximum trough concentration compared with 16 mg/kg IV.

The mean daratumumab trough concentrations (C3D1) were reported as 744.20 µg/mL for daratumumab SC 1800 mg (MMY1004), versus 617.17 µg/mL (GEN501), and 573.49 µg/mL (SIRIUS) for daratumumab IV 16 mg/kg[51]. This shows that the trough concentration of the SC formulation is consistent with the IV administration observed in 2 studies. Infusion related reactions (IRRs) occurred in 24% of the patients receiving daratumumab SC 1800 mg in the MMY1004 study; the same rate for patients receiving daratumumab IV is approximately 50%. Additionally, no new safety signals appeared for daratumumab SC, and the toxicity grades were generally low, with most of the patients experiencing IRRs with grade ≤2. This is particularly important for patients with stage 3B AL-amyloidosis, who have poor prognosis and are at a high-risk and have a fragile state.

Overall, daratumumab exhibits a wide therapeutic window and there is no apparent relationship between drug exposure in the therapeutic dose range and AEs of interest, which also supports the feasibility of utilizing a fixed-dose approach in SC administration.

3.2.2. Rationale for Biomarker Collection

Biomarker studies will focus on the evaluation of CD38 expression on the malignant plasma cells. Assessment of MRD may be performed at each site's local laboratory; as MRD assessment of bone

marrow cells allows deeper evaluation of clinical response beyond standard measures. MRD has been shown to have prognostic significance in many hematological malignancies and may have utility in amyloidosis. MRD may be monitored in subjects who achieve hematologic CR and consent to a bone marrow aspiration at CHR. Methodologies such as the Clonoseq Next Generation Sequencing (NGS) assay that quantitatively evaluate neoplastic plasma cell DNA from bone marrow aspirates, or Next Generation Flow (NGF) based on the EuroFlow protocol may be used to evaluate MRD negativity.

3.2.3. Rationale for Patient-Reported Outcome Measures

Patient-reported outcome (PRO) measures including health-related quality of life (HRQOL) are included to complement data collected by other methods. This type of data may contribute to enhanced communication of results to patients, clinicians, regulators and payers.

4. SUBJECT POPULATION

Adult subjects aged 18 years or older with newly diagnosed amyloid light chain 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 registration 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 registered into the study. If the sponsor considers that the eligibility criteria have not been met, then the sponsor will contact the investigator to discuss the subject.

4.1. Inclusion Criteria

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

1. Men or women 18 years of age or older.

2. Diagnosis of amyloidosis, AL type, based on:

a. Histopathological diagnosis of amyloidosis based on detection by immunohistochemistry and polarizing light microscopy of green bi-refringent material in Congo Red stained tissue specimens (excluding 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 over 70 years of age who have cardiac involvement only, and subjects of African descent (black subjects), mass spectrometry, immunoelectron microscopy, or other immunohistochemistry-based typing of AL amyloid in a tissue biopsy or a negative bone scintigraphy with Tc99-PYP or –DPD is recommended to rule out other types of amyloidosis such as age related amyloidosis and/or hereditary amyloidosis (ATTR mutation)

AND

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

- serum monoclonal protein ≥0.5 g/dL by protein electrophoresis (routine serum protein electrophoresis and immunofixation performed at local lab)
- serum free light chain (FLC) ≥2.0 mg/dL (20 mg/L) with an abnormal kappa:lambda ratio or the difference between involved and uninvolved free light chains (dFLC) ≥2mg/dL (20 mg/L). Serum FLCs will be measured using the Freelite assay at a central laboratory.
- **Note:** Measurable disease by Urine Bence-Jones Proteinuria is not sufficient for study enrolment.

AND

c. Cardiac involvement by AL amyloidosis according to consensus guidelines (See ATTACHMENT 3)

3. Mayo Stage 3B disease, defined as both A. increased cardiac troponin (hsTnT >54 pg/ml) **AND** B. increased NT-proBNP ≥ 8500 pg/ml

4. For subjects with congestive heart failure, symptoms should be optimally managed and clinically stable with no cardiovascular-related hospitalizations within 2 weeks prior to Cycle 1 Day 1, as assessed by the Principal Investigator. [See also exclusion criteria 3]

5. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0, 1,2 or 3 (ATTACHMENT 1)

6 Subject must have pre-treatment 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)

c. Platelet count $\geq 75 \times 10^9$/L; platelet transfusions are NOT acceptable

d. Alanine aminotransferase level (ALT) ≤2.5 x ULN;

e. Aspartate aminotransferase (AST) ≤2.5 x ULN

f. Total bilirubin level ≤1.5 × ULN, except for subjects with history of Gilbert Syndrome, in which case direct bilirubin ≤ 2 × ULN

g. Estimated Glomerular Filtration Rate (eGFR) ≥20 mL/min; Please note that the eGFR is measured by using the CKD-EPI equation (see ATTACHMENT 6 for details)

7. Women of childbearing potential[a] 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 prior to dosing and continue for 3 months after discontinuation of daratumumab. 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 3 months after receiving the last dose of daratumumab, female subjects must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction.

9. 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, e.g., 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 3 months after discontinuation of daratumumab. All men must not donate sperm during the study and for 3 months after discontinuation of daratumumab.

[a] Females are not of reproductive potential if they have been in natural menopause for at least 24 consecutive months, or have had a hysterectomy and/or bilateral oophorectomy

10. Female subjects of childbearing potential must have a negative serum or urine pregnancy tests within 14 days prior to Cycle 1 Day 1. For requirements during the Treatment Phase, please see the Time and Events Schedule.

11. Each subject must sign an informed consent form (ICF) indicating that he or she understands the purpose of the 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 with the exception of 160 mg dexamethasone (or equivalent steroid) maximum exposure prior to Cycle 1 Day 1.

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

3. Evidence of significant cardiovascular conditions as specified below:

    a. New York Heart Association (NYHA) classification of heart failure, stages IIIB or IV (see ATTACHMENT 4)

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

    c. Hospitalization for unstable angina or myocardial infarction or percutaneous cardiac intervention with recent stent or coronary artery bypass grafting, all within the last 6 months prior to the first dose

    d. Subjects with a history of sustained ventricular tachycardia or aborted ventricular fibrillation or with a history of atrioventricular (AV) nodal or sinoatrial (SA) nodal dysfunction for which a pacemaker/ICD is indicated but will not be placed (subjects who do have a pacemaker/ICD are allowed in the study)

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

    f. Supine systolic blood pressure <90 mmHg, or symptomatic orthostatic hypotension, defined as a decrease in systolic blood pressure upon standing of

>20 mmHg despite medical management (e.g., midodrine, fludrocortisones) in the absence of volume depletion

4. Subjects planning to undergo a 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. Diagnosed or treated for malignancy other than AL, except:

    a. Malignancy treated with curative intent and with no known active disease present for ≥24 months before Cycle 1 Day 1

    b. Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease

    c. Adequately treated carcinoma in situ (e.g., cervical, breast) with no evidence of disease

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

7. Subject has known moderate or severe persistent asthma within the past 2 years (see ATTACHMENT 7) 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. Subject is known to be seropositive for human immunodeficiency virus (HIV). HIV positive subjects who are stable on highly active antiretroviral therapy (HAART) with no opportunistic infections within the last 6 months are eligible.

9. Subjects known to be:

    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. 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. Subject has any concurrent medical condition or disease (e.g., 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.

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

12. Subject has known allergies, hypersensitivity, or intolerance to monoclonal antibodies or human proteins, or their excipients (refer to Investigator Brochure), or known sensitivity to mammalian-derived products.

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

14. Subject is a woman who is pregnant or breast-feeding or planning to become pregnant while enrolled in this study or within 3 months following discontinuation of daratumumab.

15. Subject has received an investigational drug (including investigational vaccines) or used an invasive investigational medical device within 4 weeks prior to Cycle 1 Day 1.

16. Subject has had major surgery within 2 weeks prior to 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 drug administration. Note: subjects with planned surgical procedures to be conducted under local anesthesia may participate.

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 drug 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

This is a single arm, open label phase 2 study. Eligible subjects will receive therapy according to the schedule provided in section 6.2.1 . Each subject will be assigned a unique subject number.

Blinding

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

6. DOSAGE AND ADMINISTRATION

Treatment should be administered in the following order:

Premedication dexamethasone (refer to Section 6.3), followed by administration of daratumumab.

For subjects receiving additional treatment with bortezomib the following order should be followed:

Premedication dexamethasone (refer to Section 6.3), followed by administration of daratumumab, followed by administration of bortezomib.

6.1. Treatment Cycles

All cycles are 28-days in duration. Cycle 1 should begin within 72 hours of approval for enrollment. 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 CRF. Whenever study drug 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 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 administration of daratumumab will be supplied in the Site Investigational Product and Procedures Manual (SIPPM).

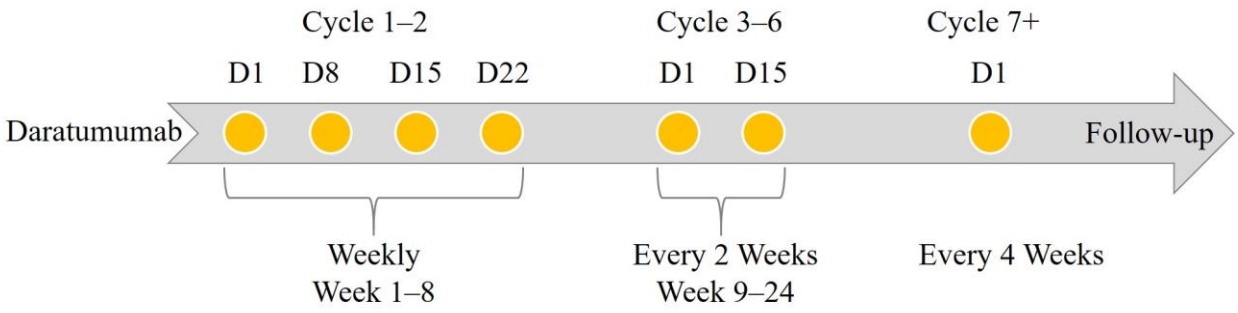
6.2.1. Treatment Schedule and Administration

The original design of this study was to treat patients with daratumumab intravenous (dara IV) infusion, however as of Protocol Amendment 1, all enrolled patients will switch from IV to subcutaneous (dara SC) administration, and all new patients will initiate treatment directly with SC, whenever daratumumab SC supplies become available at the Sites. It should be noted that throughout this document, text was added to highlight any differences between daratumumab IV and daratumumab SC dosing; and where there is no clarification, it is implied that the descriptions are the same for both IV and SC.

Daratumumab will be administered at a dose of 16 mg/kg as an IV infusion or 1800 mg subcutaneously weekly for the first 8 weeks (Cycles 1 and 2) of treatment and then every 2 weeks for 4 cycles (Cycles 3 to 6) and then every 4 weeks until progression of disease (according to MOD-PFS), unacceptable toxicity or subsequent therapy, for a maximum of 2 years in total.

For IV infusions, each subject's dose will be calculated based on the subject's weight rounded to the nearest kilogram. The dose does not need to be recalculated for weight changes that are < 10% from baseline. The weight will be used to determine the required volume of daratumumab from the vials needed for each subject. All infusions may be performed as outpatient visits. Subjects will receive pre-infusion and post-infusion medications as detailed in the protocol (Section 6.2.3). A schematic of the daratumumab IV dosing schedule is shown in Figure 3. Information and details regarding preparation and administration of daratumumab are provided in the SIPPM manual.

Figure 3: Daratumumab Dosing Schedule



The 6 subjects enrolled in the safety run-in phase of the study will be required to be kept in the hospital for observation for at least 24 hours after the end of the Cycle 1 Day 1 daratumumab administration. If deemed necessary based on safety observations, inpatient observation for at least 24 hours after the daratumumab administration may be implemented for subjects enrolled after the initial run in phase.

Study drug administration can be performed as outpatient visits. Every effort should be made to keep subjects on the planned dosing schedule. However, doses given within 3 days of the scheduled dose within an individual cycle are permitted. Thus, the 16 mg/kg dose of daratumumab IV and the 1800 mg of daratumumab SC dose will remain constant throughout the study.

The sponsor may modify the administration requirements or the pre-infusion medications prospectively based upon the information collected to date from this and other studies. Additional details for administration times and rates, as well as pre-infusion medications, will be provided in the SIPPM.

As noted in the Time and Events Schedule (Table 1), all subjects being administered daratumumab IV should have vital signs monitored before, during and at the end of all treatment infusions. Subjects who receive daratumumab SC should have their vital signs monitored only before drug administration. If a subject experiences any significant medical event, then the investigator should assess whether the subject should stay overnight for observation. If the subject has not experienced a significant medical event but is hospitalized overnight only for observation, then the hospitalization should not be reported as a serious adverse event.

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 primary method for managing daratumumab-related toxicities. On the first day of each new treatment cycle and before each dose of study drug, the subject will be evaluated by the treating physician for possible toxicities that may have occurred after the previous dose(s). Toxicities are to be assessed according to National Cancer Institute (NCI)-CTCAE, Version 4.03. Cycle delays will be based on the toxicity experienced during the previous cycle of therapy or newly encountered on Day 1 of a cycle.

6.2.2.2. Toxicity Management

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

- 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
- Grade 3 or higher non-hematologic toxicities with the following exceptions:

- Grade 3 nausea or Grade 3 vomiting that responds to antiemetic treatment within 7 days
- Grade 3 diarrhea that responds to antidiarrheal treatment within 7 days
- Grade 3 fatigue or asthenia that was present at baseline or that lasts for <7 days after the last administration of daratumumab

Daratumumab treatment should be resumed when the toxicity has resolved to ≤ Grade 2. If daratumumab administration does not commence within the pre-specified window (Table 4) of the scheduled administration date within an individual cycle, then the dose will be considered a missed dose. Administration may resume at the next planned dosing date. A missed dose will not be made up.

Table 4: Daratumumab-Related Toxicity Management

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. In addition, if the Day 1 of a cycle has been delayed, disease evaluations should not also be delayed but will continue to be performed according to the original schedule. Please refer to Section 9.2.1 of the protocol.

Any adverse event deemed to be related to daratumumab that requires a dose hold of more than 4 weeks (Cycle 1 to Cycle 6) or more than 6 weeks (Cycle 7 and beyond) will result in permanent discontinuation of daratumumab.

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 toxicity 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. NOTE: A cycle delay of 4 weeks is permissible to accomplish stem cell mobilization and harvesting.

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

For the purpose of this protocol 'infusion related reactions' are defined as systemic reactions related to the IV infusion or SC administration of the investigational agent.

6.2.3.1. Pre-infusion Medication

Pre-infusion medications include the following:

- Dexamethasone 20 mg IV or PO (an equivalent of long-acting corticosteroid may substitute [see ATTACHMENT 5 for conversion table])
- Paracetamol (acetaminophen) 650 to 1000 mg PO or IV
- An antihistamine (diphenhydramine 25 to 50 mg, or equivalent) either given IV or PO
- Montelukast (leukotriene inhibitor): Pre-dose 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 the IV/SC infusion as per investigator's discretion. If necessary, oral pre-infusion medications may be administered at the subject's home on the day of the daratumumab treatment, provided they are taken within 3 hours prior to the administration of daratumumab IV/SC infusion.

6.2.3.2. Post-infusion Medication

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

- Antihistamine (diphenhydramine or equivalent) on the first and second days after all daratumumab IV infusions
- Short-acting β2 adrenergic receptor agonist such as salbutamol aerosol
- Control medications for lung disease (e.g., 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)

In addition, these at-risk subjects may be hospitalized for monitoring for up to 2 nights after daratumumab IV/SC infusion. 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 a serious adverse event. Investigators may prescribe bronchodilators, antihistamines, and corticosteroids that are deemed necessary to provide adequate supportive care in the event a bronchospasm occurs after subjects are released from the hospital/clinic. If an at-

risk subject experiences no major infusion-related reactions, then these post-infusion medications may be omitted after 4 doses at the investigator's discretion.

6.2.3.3. Management of Infusion-Related Reactions

Infusion reactions may lead to the interruption of daratumumab administration. Pre-infusion medications should be administered prior to treatment to reduce the risk of IRRs (see Section 6.2.3.1).

Infusion-Related Reaction Management for Dara IV

Following dilution, daratumumab infusion should be administered IV at the appropriate initial infusion rate, as presented in the table below. Incremental escalation of the infusion rate should be considered only if the previous infusion of daratumumab was well tolerated.

Table 5: Infusion rates for daratumumab intravenous

	Dilution volume	Initial infusion rate (first hour)	Increments of infusion rate	Maximum infusion rate
First infusion	1,000 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Second infusion[a]	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Subsequent infusions[b]	500 mL	100 mL/hour	50 mL/hour every hour	200 mL/hour

[a] If the subject's first infusion of daratumumab is well tolerated (defined as an absence of >Grade 1 infusion-related reactions during the first 3 hours), the second infusion will be administered as indicated in the table above. If the previous infusion rate is not well tolerated, instructions for the first infusion volume and rate will be used for the second infusion.
[b] If the subject's first 2 infusions of daratumumab are well tolerated (defined as an absence of >Grade 1 infusion-related reactions during a final infusion rate of ≥100 mL/hour), subsequent infusions will be administered as indicated in the table above. If the previous infusion rate is not well tolerated, instructions for the second infusion rate will be followed.

Subjects should be observed carefully during daratumumab infusions. Trained study staff at the clinic should be prepared to intervene in case of an infusion reaction, and resources necessary for resuscitation must be available. Attention to staffing should be considered when multiple subjects will be dosed at the same time. For infusion-related reactions of any grade/severity, immediately interrupt the daratumumab infusion and manage symptoms. Management of infusion reactions may further require reduction in the rate of infusion, or treatment discontinuation of daratumumab.

- Grade 1-2 (mild to moderate): Once reaction symptoms resolve, resume the infusion at no more than half the rate at which the reaction occurred. If the subject does not experience any further reaction symptoms, infusion rate escalation may resume at increments and intervals as appropriate as outlined in Table 5
- Grade 3 (severe): Once reaction symptoms resolve, consider restarting the infusion at no more than half the rate at which the reaction occurred. If the subject does not experience additional symptoms, resume infusion rate escalation at increments and intervals as outlined in Table 5. Repeat the procedure above in the event of recurrence of Grade 3 symptoms. Permanently

discontinue daratumumab upon the third occurrence of a Grade 3 or greater infusion-related reaction.

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

Daratumumab SC

Dara SC will be administered by SC injection at a fixed dose of 1800 mg. Doses will be administered by manual push over 3-5 minutes in the abdominal SC tissue in left/right locations, alternating between individual doses. The volume of the SC solution will be 15 mL for the 1800 mg dose. Refer to the Daratumumab SC Site Investigational Product Procedures Manual (SIPPM) for additional guidance on the administration of Dara-SC. All subjects will be observed for at least 6 hours after the end of the SC injection during Cycle 1 Day 1 and, if deemed necessary by the investigator, after consecutive injections.

Local Injection-Site Reactions

In Study MMY1004 Part 1, SC administration of Dara MD 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. Injection-site reactions should be managed per institutional standards.

Infusion Related Reactions for Daratumumab SC

Subjects should be observed carefully during study drug administrations. Trained study staff at the clinic should be prepared to intervene in case of any IRRs, and resources necessary for resuscitation (eg, agents such as epinephrine and aerosolized bronchodilator, also medical equipment such as oxygen tanks, tracheostomy equipment, and a defibrillator) must be available at the bedside.
If an IRR develops, then daratumumab administration should be temporarily interrupted. Subjects who experience AEs during daratumumab administration must be treated for their symptoms. Subjects should be treated with acetaminophen, antihistamine, or corticosteroids, as needed. Intravenous saline may be indicated. For bronchospasm, urticaria, or dyspnea, subjects may require antihistamines, oxygen, corticosteroids, or bronchodilators. For hypotension, subjects may require vasopressors. In the event of a life-threatening IRR (which may include pulmonary or cardiac events) or anaphylactic reaction, daratumumab should be discontinued and no additional daratumumab should be administered to the subject.

Infusion-related Reactions of Grade 1 or Grade 2 for Dara SC

If the investigator assesses a Grade 1-2 IRR AE to be related to administration of study drug, then the daratumumab administration should be paused. When the subject's condition is stable, daratumumab administration may be restarted at the investigator's discretion.
If the subject experiences a Grade 2 or higher event of laryngeal edema, or a Grade 2 or higher event of bronchospasm that does not respond to systemic therapy and does not resolve within 6 hours from onset, then the subject must be withdrawn from daratumumab treatment.

Infusion-related Reactions of Grade 3 or Higher for Dara SC

For IRR AEs (other than laryngeal edema or bronchospasm) that are Grade 3, the daratumumab administration must be stopped and the subject must be observed carefully until resolution of the AE or until the intensity of the event decreases to Grade 1, at which point the daratumumab administration may be restarted at the investigator’s discretion. If the intensity of the AE returns to Grade 3 after restart of the daratumumab administration, then the subject must be withdrawn from daratumumab treatment.
For IRR adverse events that are Grade 4, the daratumumab administration must be stopped and the subject withdrawn from daratumumab treatment.

Recurrent Infusion-related Reactions for Dara SC

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

6.3. Dexamethasone

Dexamethasone will be administered as premedication at a maximum total dose of 20 mg weekly (ie, Days 1, 8, 15, 22 during the first two cycles) on days of daratumumab dosing. On weeks that daratumumab is not administered, dexamethasone will not be given. An appropriate substitute for dexamethasone is allowed (as per local standards; see ATTACHMENT 5 for conversion table).

Subjects that do not achieve either a hematologic VGPR or better, OR a hematologic PR with a major organ response by Cycle 4 (see Table 8 for more details), may receive, in addition to daratumumab, bortezomib (for a maximum of 6 cycles) and low dose dexamethasone. However, the maximum total dose of 20 mg weekly dexamethasone will not be exceeded (i.e. on weeks that daratumumab is to be administered no additional dexamethasone [apart from the pre-infusion requirement] will be given).

For management of dexamethasone toxicity see **Table 6**. 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 6: 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 H_2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measure, decrease dexamethasone dose by 50%.
	≥Grade 3 requiring hospitalization or surgery	Hold dexamethasone until symptoms adequately controlled. Restart at 50% of current dose along with concurrent therapy with H_2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measure, 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 above 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 above measure, 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 above measures, decrease dose to 50% of initial dose. Discontinue dexamethasone and do not resume if symptoms persist despite 50%.
Metabolic	≥Grade 3 hyperglycemia	Treatment with insulin or oral hypoglycemic agents as needed. If uncontrolled despite above measure, decrease dose by 25% decrements until levels are satisfactory.

6.4. Bortezomib

Subjects that do not achieve either a hematologic VGPR or better, OR a hematologic PR with a major organ response by Cycle 4 Day 1 (i.e after completion of cycle 3), may receive at the investigator's discretion, in addition to daratumumab, bortezomib and low dose dexamethasone.

These subjects will receive 1.3 mg/m^2 bortezomib* as an SC injection weekly (Days 1, 8, 15, 22) in 28-day cycles for a maximum of 6 cycles. The amount (in mg) of bortezomib to be administered will be determined by Body Surface Area (BSA), calculated according to a standard nomogram (ATTACHMENT 8). The total calculated dose of bortezomib may be rounded to the nearest decimal point (e.g., 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 SmPC). On daratumumab treatment days, subjects should receive bortezomib after daratumumab administration. The dose of bortezomib should be recalculated should the subject experience a weight change of more than 10% from baseline.

Eligibility criteria for the addition of Bortezomib

1 Subject has not achieved either a hematologic VGPR or better, OR a hematologic PR with a major organ response by Cycle 4 Day 1

2 Absence of known hypersensitivity to bortezomib, boron or mannitol

3 Absence of Grade 2 or higher sensory/peripheral neuropathy or Grade 1 painful peripheral neuropathy

4 NO prior history of pulmonary fibrosis

*Upon physician discretion subjects may receive initially bortezomib at a dose of 1 mg/m^2 and then increase to the full dose of 1.3 mg/m^2 if treatment is well tolerated.

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 7. 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 and dexamethasone may continue unless criteria exist to hold these medications as well.

6.4.2. Neurologic Toxicity

If a subject experiences peripheral neuropathy, then dose adjustments should be made according to the recommendations in Table 7.

Table 7: 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	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; CTCAE, 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.

7. TREATMENT COMPLIANCE

Study drug (daratumumab and bortezomib where applicable) will be administered by qualified site staff. The details of each administration will be recorded in the electronic case report form (eCRF). Additional details are provided in the Site Investigational Product Procedures Manual 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 post infusion

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 and/or plerixafor and/or cyclophosphamide is permitted while on study. A cycle delay of 4 weeks is permissible to accomplish stem cell mobilization and harvesting. Thereafter, the subject should continue treatment with study medications. Stem cell transplantation is not permitted during the first six cycles of study treatment.

8.1. Recommended Therapies

8.1.1. 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 9.6 and below.

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.

8.1.2. Prophylaxis for Pneumocystis carinii

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

8.1.3. Prophylaxis for Herpes Zoster Reactivation

Prophylaxis for herpes zoster reactivation is recommended during the Treatment Phase. Acceptable antiviral therapy includes acyclovir (e.g., 400 mg given orally 3 times a day, or 800 mg given orally 2 times a day or per institutional standards), famciclovir (e.g., 125 mg given orally, twice a day or per institutional standards), or valacyclovir (e.g., 500 mg given orally, twice a day or per institutional standards), initiated within 1 week after the start of study drug.

8.1.4. 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. 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, and/or inotropic agents. Use of these medications is permissible during the protocol and should be recorded in the eCRF as concomitant medications. Dose reductions of dexamethasone are also recommended according to Section 6.3 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:

- Antivirals, Antibacterial 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 Six Cycles of Therapy</u>

Concomitant administration of any other therapy for the intention of treating AL 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, i.e., adrenal insufficiency, rheumatoid arthritis, etc.

Concomitant administration of investigational agents is prohibited. Concurrent use of NEOD-001 (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, including systemic corticosteroids (>20 mg prednisone per day or equivalent) (other than those given for infusion-related reactions 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.

ONLY FOR subjects where bortezomib and low dose dexamethasone has been added to daratumumab monotherapy: Concomitant administration of strong CYP3A4 inducers is prohibited with the use of bortezomib. Administration of strong CYP3A4 inhibitors (e.g., 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 2.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedule 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 allowable to obtain the 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 visit 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 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 9.6).

Post-baseline disease evaluations may be conducted ±3 days from the scheduled visit date (based on Study Day 1, i.e., 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 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 estimated at approximately 252 mL during screening and the first 6 cycles, 25 mL at each subsequent cycle and 43 to 63 mL at the End-of-Treatment visit and the post-treatment visits. This includes laboratory assessments associated with safety and efficacy evaluations. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Central Laboratory Assessments

Only the following assessments will be sent to a central laboratory as detailed in the Table below:

Central Laboratory Assessment	Sample Type
sFLC (Freelite Assay)	Serum
Cardiac Biomarkers (HS Troponin T and NT-proBNP)	Serum
Mass Spectrometry Typing of AL – Amyloid (only for selected patients at screening so as to rule out age-related amyloid and/or hereditary amyloid [ATTR mutation])	Tissue Biopsy

Results will be made available to the site study staff. For more details regarding the handling and shipment of the samples to the central laboratories please refer to the Laboratory Manual for the study.

9.1.1.1. Bone Marrow Biopsy/Aspirate Considerations

Three unstained slides from the diagnostic core biopsy or 2 unstained slides and one H&E stained slide will be used by the local laboratory to assess CD38 expression on the plasma cells if feasible In addition to the core biopsy slides, fresh bone marrow aspirate (3 mL) may be collected for baseline MRD clone analysis only for local laboratories where MRD is detected via NGS(for local laboratories where NGF is used, no baseline sample for MRD is required). If a fresh bone marrow aspirate will not be performed at screening because a sample is available within 56 days prior to randomization, then non-decalcified diagnostic tissue (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 Hematologic CR.

A repeat bone marrow aspirate collection will be performed, if feasible, at the time that complete hematologic response is assessed. If a repeat sample is obtained at hematologic CR, 3 mLs of bone marrow aspirate will be used for MRD analysis at the local laboratory.

9.1.2. Screening Phase

The Screening Phase begins when the first screening procedure is conducted. During the Screening Phase, eligibility criteria will be reviewed and a complete clinical evaluation will be performed as specified in the Time and Event 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 must be performed within 14 days prior to first dose for women of child bearing potential. Blood type assessment and Indirect Coombs testing must be done before the Cycle 1 Day 1 infusion of daratumumab. Results from skeletal survey 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 5 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. If approved by the sponsor, subjects who are screen failures may be rescreened if their condition changes. Subjects who are determined eligible for rescreening must sign a new ICF.

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 (orangophillic/eosinophillic under bright light; apple green birefringence under polarized light (4-6µ thick sections)) followed by immunohistochemical confirmation.

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)
- a-hu β2 microglobulin (polyclonal)
- Fibrinogen (polyclonal)
- Lysozyme (polyclonal)

Electron microscopy appearance: unbranched 10nm thick fibrils

Mass Spectrometry Typing of Amyloid as AL ((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, immunoelectron microscopy, or other immunohistochemistry-based typing of amyloid as AL or a negative bone scintigraphy with Tc99m-PYP or –DPD in a tissue biopsy is recommended to rule out age-related amyloid and/or hereditary amyloid (ATTR mutation). Mass spectrometry typing will be performed at a central laboratory. Processes for collection and transmission to the central vendor can be found in the Lab Manual for the study.

9.1.2.2. Factor X Deficiency

Subjects with AL Amyloidosis may develop acquired Factor X deficiency[35]. Testing coagulation parameters and Factor X levels for all subjects is recommended, but not required. Any clinically excessive 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 approval of enrollment. Subjects will be closely monitored for adverse events, laboratory abnormalities, and clinical response. Clinical evaluations and laboratory assessments may be repeated more frequently, if clinically indicated.

A total duration of 2 years of daratumumab therapy from the start of the study treatment will be given per subject. Subjects will then have an End-of-Treatment (EoT) 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) as soon as possible and within 24 hours of disease progression assessment. Patients who meet disease progression criteria based only on organ biomarker progression will continue study therapy unless criteria for MOD-PFS endpoint is met. The medical monitor will confirm that treatment should be discontinued. If disease progression is confirmed by the sponsor, the subject will discontinue study treatment, complete the EoT visit, and enter the Long-Term Follow-up Phase.

9.1.3.1. Initiation of Subsequent Therapy and/or Autologous Stem Cell Transplantation During Treatment Phase (If Applicable)

Subsequent Therapy PRIOR to Completion of Six Cycles of Therapy

Prior to completion of 6 months (6 cycles) of treatment, subjects should not receive any non-protocol therapy for the treatment of AL amyloidosis unless the subject develops MOD-PFS as defined in the protocol (see section 2.1 for definition of MOD-PFS).

The sponsor recognizes that certain patients who have not had a response by the completion of cycle 3 have a poor prognosis and may benefit from a switch to second line therapy[3,5,32]. Therefore, per investigator discretion, any subject who has not achieved EITHER a hematologic VGPR or better, OR a hematologic PR with improved major organ function (i.e., cardiac or renal response per updated response criteria) (Table 11) by Cycle 4 Day 1, bortezomib and low – dose dexamethasone may be added to daratumumab study treatment (Table 8).

The sponsor must be notified prior to addition of bortezomib.

Table 8: Guidelines for Additional Therapy after 3 months of daratumumab monotherapy

Response after three cycles of initial therapy	**Action taken**
Hematologic PR with improved major organ function (i.e., cardiac or renal response per updated response criteria) OR Hematologic VGPR or better	Daratumumab monotherapy as per protocol
Hematologic PR with stable or worsening major organ function (provided that criteria for MOD-PFS are not met)	Addition of bortezomib (for a maximum of 6 cycles) and low dose dexamethasone to daratumumab (under protocol) may be considered at the Investigator's discretion
Hematologic Non-Response	Addition of bortezomib and low dose dexamethasone to daratumumab (under protocol) may be considered at the Investigator's discretion

Subsequent Therapy:

Subsequent therapy may be started if the subject has had an insufficient response to initial therapy (e.g., PR with stable or worsening organ function or stable disease (SD) after 6 months) or if there has been cardiac or renal deterioration. The guidelines in Table 9 should be considered.

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

Table 9: Guidelines for Subsequent Therapy after 6 months of daratumumab monotherapy

Response after six cycles of initial therapy	**Action taken**
Hematologic Response (PR or better) with improved major organ function (i.e., cardiac or renal response per updated response criteria)	Daratumumab monotherapy as per protocol
Hematologic Response (PR or better) with stable or worsening major organ function	Subsequent therapy (outside of this protocol) may be considered
Hematologic Non-Response with stable/improved organ function	Subsequent therapy (outside of this protocol) may be considered
Hematologic Non-Response with worsening organ function	Subsequent therapy (outside of this protocol) recommended

Autologous Stem Cell Collection Considerations

Stem cell collection is permitted during the study. Granulocyte colony stimulating factor and/or plerixafor may be used as mobilization agents. Cyclophosphamide may also be used for mobilization. After up to 6 cycles of study treatment and evaluation of the primary endpoint of complete hematologic response, subjects may electively discontinue from study treatment for stem cell transplantation. The reason for discontinuation of study treatment should be recorded in the CRF; 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. In addition, investigators will record details of the stem cell yield (number of days of collection, number of failed collections, and total CD34+ cells per kg), as well as 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 medications should be recorded for 30 days after the last dose of study medication.

9.1.3.2. 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 4 weeks (±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 adverse events that occur up to 30 days after the last dose of study treatment. Additional information on reporting of adverse events is presented in Section 12.

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

For subjects who discontinue study treatment, 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.

Subsequent anticancer treatment, response to subsequent treatment, and date of progression will be recorded and survival status will be obtained. Information on secondary malignancies will also be collected. If the information is obtained via telephone contact, then written documentation of the communication must be available for review in the source documents. If the subject has died, then the date and cause of death will be collected and documented on the eCRF.

9.2. Efficacy Evaluations

Disease response and progression will be based on assessments of hematologic response as defined in Section 9.2.1.

9.2.1. Hematologic Response Categories

Disease evaluations must be performed every 28 days on the scheduled assessment day (±5 days). If study treatment has been delayed for any reason, disease evaluations will continue be performed according to the original schedule, regardless of any changes to the dosing regimen.

All disease evaluation assessments, apart from sFLC assay, will be performed by a local laboratory according to the Time and Events Schedules (Table 1) until disease progression (based on MOD-PFS). For free light chain assessment, the investigator will use results provided by the central laboratory. This study will use the consensus recommendations for AL amyloidosis treatment response criteria[6, 39] presented in Table 10:

Table 10: International Amyloidosis Consensus Criteria

Hematologic response and progression criteria	
Response Category	*Criteria*
Complete	Normalization of free light chain ratio, negative serum and urine immunofixation
Very Good Partial	In subjects with baseline dFLC ≥ 50 mg/L, reduction in the dFLC to <40 mg/L
Partial	b. In subjects with baseline dFLC ≥ 50 mg/L, a reduction in dFLC by ≥ 50% (not fulfilling the VGPR criteria) c. A greater than 50% reduction in M protein concentration in subjects whose baseline dFLC is <50 mg/L and have a measurable M protein (≥5 g/L) d. ONLY in subjects with baseline dFLC ≥ 20 and < 50 mg/dL: dFLC < 10 mg/dL (but Immunofixation positive)
No response	Less than a PR
Progression	From CHR, abnormal free light chain ratio (light chain must be double) 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
Abbreviations: CHR, Complete hematologic response; dFLC difference between involved FLC and uninvolved FLC; FLC free light chain; PR, partial response; VGPR, very good partial response	

Hematologic response/disease progression must be consistently documented across clinical study sites using the criteria shown in Table 10: For all hematologic response categories two consecutive assessments are required at any time, based on discrete samples. It is important that instances of suspected disease progression be reported to the sponsor as soon as possible. Diagnosis and documentation of disease progression (MOD-PFS criteria) will be faxed within 24 hours to the sponsor (see Contact Information provided in the Investigator File). 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 drug. 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, the response will be determined on an ongoing basis by the investigator. For CR, the response criteria require subjects to have a negative serum and urine immunofixation electrophoresis (IFE) as well as normalization of FLC levels and ratio.

For subjects who discontinue study drug before disease progression (for example, due to an AE or start of subsequent therapy), disease evaluations should continue to be performed as described in the Time and Events Schedule (Table 1), until confirmed MOD-PFS endpoint, 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 drug is administered.

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 local laboratory. Only 1 serum and one 24-hour urine sample per time point are required 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 lab for analyses after the informed consent was obtained. Serum Free Light chains will be measured using the Freelite assay at a central laboratory.

- Serum M-protein quantitation by electrophoresis (SPEP) and serum immunofixation (IFE)
- Serum free light chain assay (Freelite assay, central laboratory)
- 24-hour urine M-protein quantitation by electrophoresis (UPEP) and Urine immunofixation (UIFE)

Blood and 24-hour urine samples will be collected as specified in Table 1. Serum and urine immunofixation test and serum free light chain assay will be performed at Screening and Day 1 of every cycle.

9.2.3. Determination of Organ Response

Organ disease that is considered to be quantifiable for response includes cardiac disease (central laboratory evaluation of NT-proBNP and high sensitivity troponin T), renal disease (proteinuria, creatinine clearance), hepatic disease (alkaline phosphatase). The organ response must be monitored by the International Amyloidosis Consensus Criteria shown in Table 11.

The cardiac biomarker NT-proBNP will be used to monitor cardiac response. A decrease of >30% in NT-proBNP levels (or >300 ng/L in subjects with baseline value of >650 ng/L) compared to baseline levels or NYHA class response (≥2 class decrease in subjects with NYHA class of 3A). The cardiac biomarkers (NT-proBNP and HS Troponin T) will be evaluated by central laboratory.

For kidney response, according to the recent Palladini et al 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.

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

Table 11: Organ Response and Progression Criteria

Organ	*Response*	*Progression*
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[a]) 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: NT-proBNP, N-terminal prohormone of brain natriuretic peptide; cTn, cardiac troponin; NYHA, New York Heart Association, Subjects with progressive worsening renal function cannot be scored for NT-proBNP progression [a] Based on Comenzo et al.[6] and Palladini et al.[40]consensus criteria [b] Based on Palladini et al.[33]		

9.2.4. Bone Marrow Assessment

At screening (baseline sample) bone marrow biopsy slides will be assessed by immunohistochemistry 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 only for local laboratories where MRD is detected via NGS (for local laboratories where NGF is used, no baseline sample for MRD is required). 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 hematological CR.

9.2.5. Endpoints

Primary Endpoint

The primary endpoint is OS rate at 6 months post initiation of treatment with daratumumab. OS is measured from the date of Cycle 1 Day 1 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.

Secondary Endpoints

The secondary efficacy endpoints include:

- MOD-PFS. This is a composite endpoint of clinically observable endpoints and will be defined from Cycle 1 Day 1 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) that requires hospitalization for management, or

need for cardiac transplant, or 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 (two consecutive assessments are required, see section 9.2.1):

   - From CHR, abnormal free light chain ratio (light chain ratio must double).
   - 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

- PFS is defined as the time from the date of Cycle 1 Day 1 to the date of first documentation of hematologic disease progression, or organ (cardiac, renal, or liver) progression/need for transplant, or need for additional therapy (excluding the addition of bortezomib under protocol) or death due to any cause, whichever occurs first according to central laboratory results and judged by international consensus guidelines. Subjects who are still alive and not yet progressed will be censored at the last disease assessment.
- Hematologic ORR is defined as the proportion of subjects who achieve a best hematologic response of PR or better.
- OrRR for kidney, heart, liver and is defined as the proportion of baseline organ involved subjects who achieve organ response in each corresponding organ.
- PRO/HRQOL: Subscales of the EORTC QLQ-C30, SF-36, EQ-5D-5L.
- Time to next treatment (TNT) defined as the time from the date of Cycle 1 Day 1 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 rate is defined as the proportion of subjects who achieve hematologic VGPR.
- Hematologic CR rate is defined as the proportion of subjects who achieve hematologic CR.
- Time to hematologic response is defined as the time between the date of Cycle 1 Day 1and the first efficacy evaluation that the subject has met all criteria for hematologic PR, VGPR or CHR. For subjects without a hematologic response data will be censored either at the date of progressive disease or, in the absence of progressive disease, at the last disease assessment.
- Duration of hematologic response is defined as the time between the date of initial documentation of hematologic PR, VGPR or CHR 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 organ response is defined as the time between the date of Cycle 1 Day 1and the first efficacy evaluation that the subject has each corresponding organ response. For subjects

without organ response, data will be censored either at the date of the corresponding organ progressive disease or, in the absence of organ progressive disease, at the last disease assessment.

- 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 without organ progression, data will be censored at the last disease assessment.
- Proportion of subjects who received bortezomib and low-dose dexamethasone after Cycle 3.

Exploratory Endpoint

Exploratory endpoints are:

- Evaluation of CD38 expression
- Evaluation of minimal residual disease status in subjects who achieve complete hematologic response in bone marrow.
- Assessment of diastolic heart function based on analysis of transthoracic echocardiograms

9.3. 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. 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 PFS and OS. Minimal residual disease may be monitored in subjects who achieve hematologic CR. Methodologies such as the Clonoseq NGS assay that quantitatively evaluate neoplastic plasma cell DNA from bone marrow aspirates, or NGF based on the EuroFlow protocol may be used to evaluate MRD negativity.

9.4. Medical Resource Utilization

Medical resource utilization (MRU) 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 and/or LVAD), and/or 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.

9.5. 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 paper 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[34]. The EORTC QLQ C30 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, four additional items will be used from the EORTC Item Bank to assess symptoms (upper and lower body swelling, neuropathy, dizziness) reported by patients with amyloidosis (Lin et al. 2015; EORTC website). The recall period is 1 week (the past week). The EORTC QLQ-C30 has been widely used among cancer patients. Scores are transformed to a 0 to 100 scale. Reliability, validity, and clinically meaningful change of the EORTC QLQ C30 has been demonstrated in multiple myeloma patients[36,37].

The European Quality of Life Five Dimensions Questionnaire (EQ-5D-5L) is a generic measure of health status. For purposes of this study, the EQ-5D-5L will be used to generate utility scores for use in cost effective analyses. The EQ-5D-5L is a 5 item questionnaire that assesses 5 domains including mobility, self-care, usual activities, pain/discomfort and anxiety/depression plus a visual analog scale rating “health today” with anchors ranging from 0 (worst imaginable health state) to 100 (best imaginable health state)[38]. The scores for the 5 separate questions are categorical and are cannot be analyzed as cardinal numbers. However, the scores for the 5 dimensions are used to compute a single utility score ranging from zero (0.0) to 1 (1.0) representing the general health status of the individual. Administration time for each questionnaire is up to approximately 10 minutes.

The SF-36 Health Survey is a generic measure of health status. The SF-36 consists of 36 questions that yield an eight-scale profile of functional health and well-being, as well as two physical and mental health summary measures and a preference-based health utility index. Administration time for the questionnaire is approximately 10 minutes. Samples of PRO instruments are provided in ATTACHMENT 9 through ATTACHMENT 12.

9.6. Safety Evaluations

Safety will be measured by adverse events, 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) from the time a signed and date informed consent is obtained until 30 days following the last dose of study drug. Adverse events will be followed by the investigator as specified in Section 12, Adverse Event Reporting.

Clinical Laboratory Tests

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

The following tests will be performed by the local laboratory,

Hematology Panel

-hemoglobin	-platelet count
-white blood cell (WBC) count with absolute neutrophils and lymphocytes	

Serum Chemistry Panel

-sodium	-total bilirubin
-potassium	-direct bilirubin if history of Gilbert's syndrome
-creatinine (to derive Creatinine Clearance)	-alkaline phosphatase
-aspartate aminotransferase (AST)	
-alanine aminotransferase (ALT)	- total protein in the Urine
-TSH and T4 (at screening only and subsequently if clinically indicated)	-Optional: Coagulation studies (PTT, PT), Factor X levels

Serum or urine Pregnancy Testing: Women of childbearing potential only.

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

Hepatitis B Virus (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 1 is implemented will be required to have HBV serology performed locally upon signing the updated ICF.

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

HBV DNA Tests

Subjects who are positive for Anti-HBc or Anti-HBs will undergo testing for hepatitis B DNA by PCR. Subjects with serologic findings suggestive of HBV vaccination (Anti-HBs positivity as the only serologic marker) and a known history of prior HBV vaccination do not need to be tested for HBV DNA by PCR. During and following study treatment, subjects who have history of HBV infection 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.

Electrocardiogram (ECG)

ECGs 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 (e.g., 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:

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 as per CTCAE, for example) should be reported in the CRF. Alternative cardiac assessments including MUGA, cardiac MRI and cardiac catherization are acceptable methods of evaluating LVEF if TTE is not used. In case of a decrease in LVEF that meets the criteria of cardiac progression, the PFS event must be also registered in the eCRF.

To assess diastolic function, several attributes of the echocardiogram (with units) will be captured in the CRF. 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:

Vital Signs

Temperature and blood pressure 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 Event 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 physical examination should be reported as an AE. ECOG performance status will be used to evaluate the impact of disease status on 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. Subject RBC phenotyping (standard or extended) is an alternative option to the IAT test, if locally required. Either method must be completed prior to the first daratumumab IV infusion.

Daratumumab interferes with the IAT, which is a routine pre-transfusion test performed to identify a subject's antibodies to minor antigens so that suitable donor blood can be given for transfusion. Daratumumab does not interfere with ABO/RhD typing. CD38 is expressed at very low levels on erythrocytes. Daratumumab binds to the CD38 on erythrocytes, which results in a positive IAT (Indirect Coombs Test). This positive result masks the detection of antibodies to minor antigens and may prevent or delay blood banks from issuing donor blood for transfusion. This effect occurs during daratumumab treatment and for up to 6 months after treatment ends. Subjects will receive a patient identification wallet card for the study that includes the blood profile (ABO, Rh, and IAT or phenotyping) determined before the first administration of daratumumab along with information on the IAT interference for healthcare providers/blood banks. Subjects are to carry this card throughout the treatment period and for at least 6 months after treatment ends. Blood banks can eliminate the daratumumab interference with IAT by treating reagent red blood cells (RBCs) with dithiothreitol (DTT)[39].

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 DTT-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.

9.7. 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 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 Central Laboratory Manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the Central Laboratory Manual.

All collected tissues or any other biological samples will not be retained and they will be destroyed at the end of the study.

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.

10.2. Discontinuation of Study Treatment/Withdrawal from the Study

Discontinuation of Study Treatment

A subject will not be automatically withdrawn from the study if they have to discontinue treatment before the end of the treatment regimen. 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 (e.g., adverse event) it is in the best interest of the subject to discontinue study treatment.
2. The subject becomes pregnant.
3. The subject withdraws consent for administration of study drug.
4. The subject initiates treatment with a prohibited medication.
5. The subject receives concurrent (non-protocol) treatment for AL amyloidosis.
6. The subject experiences unacceptable toxicity, including daratumumab infusion-related reactions as described in Section 6.2.3.
7. The subject's dose is held for more than 4 weeks in Cycles 1-6 (or more than 6 weeks from Cycle 7 onwards) due to toxicity, or if 3 or more consecutive planned doses are missed for reasons other than toxicity unless agreed upon by the investigator and sponsor to continue (NOTE: A cycle delay of 4 weeks is permissible to accomplish stem cell mobilization and harvesting).
8. The subject experiences disease progression (according to MOD-PFS)
9. The subject receives a 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 endpoint, sites will complete a disease progression form and fax the 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.

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.

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 enrolled subjects who received at least one dose of daratumumab. 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 meet all inclusion and exclusion criteria, receive study drug, and had at least one post-baseline disease assessment. Continuous variables will be summarized using descriptive statistics such as mean, standard deviation, and range. Categorical variables will be summarized using frequency tables. For time-to-event variables, the Kaplan-Meier method will be used for descriptive summaries.

11.2. Sample Size Determination

According to published data the 6-month overall survival rate of patients with stage 3B amyloidosis is about 30%. Assuming a 6-month survival rate of at least 50% in patients treated with daratumumab IV/SC a sample size of 40 subjects provides 85% power to detect a difference using a 1-sided alpha of 0.05.

11.3. Efficacy Analyses

For the primary endpoint analysis, the Kaplan-Meier estimate of the 6-month OS rate will be presented, along with the respective 95% CI.

Moreover, time-to-event analysis will be conducted and the Kaplan-Meier estimates of the median (e.g., OS, PFS, MOD-PFS, TTP etc.) along with the respective 95% CIs will be presented.

11.4. Biomarker Analyses

Any biomarker measurements will be listed, tabulated, and where appropriate, plotted.

Results of biomarker 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.

11.5. Patient-Reported Outcomes

EORTC QLQ-C30, EQ-5D-5L, and SF36 scores will be summarized at each time point. The relationship between response and change in domain scores will be explored. Especially for the EORTC QLQ-C30, the results will also be presented in two groups (SC and IV daratumumab administration), if the sample size in each group is at least 10 patients, since the respective questionnaire includes two questions related to the treatment ("Has your physical condition or medical treatment interfered with your social activities?" and "Has your physical condition or medical treatment caused you financial difficulties?").

11.6. Safety Analyses

Adverse Events

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

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

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the Statistical Analysis Plan) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point. Changes from baseline results will be presented in pre- versus post-treatment cross-tabulations (with classes for below, within, and above normal ranges). Worst toxicity grade during treatment will be presented, according to 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)

ECG data will be summarized. Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the abnormalities will be made.

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. Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the abnormalities will be made.

Vital Signs Including Weight

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 changes from baseline will be summarized at each scheduled time point.

11.7. Interim Analysis

No interim analysis for efficacy is planned for this study.

However, in order to achieve a comprehensive evaluation of safety, an interim safety analysis will be performed by external experts. A DSMB consisting of 2 clinicians and 1 statistician, will be established to review safety results after the first 20 subjects (50%) have been treated with at least 1 dose of daratumumab. The DSMB will review the cumulative safety data from these subjects (including the group of subjects that have received daratumumab, bortezomib and dexamethasone after Cycle 3). If a safety signal is detected and the DSMB deems, in the recommendation sent to the Sponsor, that the safety profile of the study treatment is unfavorable, the recruitment of the rest of the subjects will be interrupted and the study may be stopped due to safety concerns.

In the event of such a study termination all current subjects that are receiving study treatment may receive subsequent alternative treatment outside the study as per the investigator's judgement and routine practice. More details on the Interim Safety Review will be provided in the Statistical Analysis Plan for this study as well as in the DSMB Charter.

12. ADVERSE EVENT REPORTING

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

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

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

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

Note: The sponsor collects adverse events starting with the signing of the ICF (refer to Section 12.4.1, All Adverse Events, for time of last adverse event recording).

Serious Adverse Event

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

1. Results in death
2. 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.)
3. Requires inpatient hospitalization or prolongation of existing hospitalization
4. Results in persistent or significant disability/incapacity
5. Is a congenital anomaly/birth defect
6. Is a suspected transmission of any infectious agent via a medicinal product
7. Is Medically Important*

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

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

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For daratumumab and bortezomib (where applicable), the expectedness of an adverse event will be determined by whether or not it is listed in the IB and the SPC, respectively.

Adverse Event Associated with the Use of the Drug

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

12.1.2. Attribution Definitions

Not Related

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

Unlikely to Be Related

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

Possibly Related

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

Probably Related

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

Definitely Related

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

12.1.3. Severity Criteria

The severity assessment for an adverse event or serious adverse event should be completed using the NCI-CTCAE Version 4.03. Any adverse event or serious adverse event 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): Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

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

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

Grade 4: Life-threatening of disabling adverse event

Grade 5: Death related to the adverse event

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

12.2. Adverse Events of Special Interest

Adverse Events of Special Interest (AESI) identified for Daratumumab include:

- Infusion reactions: ≥ Grade 3
- Infections: ≥ Grade 4
- Cytopenias: ≥ Grade 4
- Tumor lysis syndrome
- Other malignancies
- Intravascular hemolysis: all grades

All AESI must be recorded in the Serious Adverse Event Report Form and sent by email to drugsafety@emnresearch.it within 24 hours of knowledge of the event, following the same timelines and procedures with SAE reporting provided in Section 12.4.2.

12.3. Special Reporting Situations

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

1. Overdose of a study drug (risk of overdose with daratumumab SC is negligible as it is administered by a health care professional in a single vial).
2. Suspected abuse/misuse of a sponsor study drug.
3. Inadvertent or accidental or occupational exposure to a study drug.
4. Medication error involving a study drug (with or without subject/patient exposure to the sponsor study drug, e.g., name confusion).

Special reporting situations should be recorded in the CRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page of the CRF, and a Serious Adverse Event Report Form, should be sent by email to drugsafety@emnresearch.it within 24 hours of knowledge of the event, following the same timelines and procedures with SAE reporting provided in Section 12.4.2.

12.4. Procedures

12.4.1. All Adverse Events

All adverse events (including AESI) 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 medication (bortezomib, dexamethasone and/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 within 30 days after the last study drug administration. For subjects who have received additional treatment with therapeutic intent for AL during the adverse event reporting period, only adverse events that are considered to be possibly, probably, or definitely 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 drug, and those that are considered related to the study investigational medicinal products 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.

Disease progression should not be recorded as an adverse event or serious adverse event term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the serious adverse event definition (refer to Section 12.1.1, Adverse Event Definitions and Classifications). Death should not be recorded as an adverse event or serious adverse event, but as the outcome of an adverse event. The adverse event that resulted in the death should be reported as a serious adverse event. All events that meet the definition of a serious adverse event will be reported as serious adverse events, regardless of whether they are protocol-specific assessments.

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

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

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

1. Subject's name
2. Study number
3. Investigator's name and 24-hour contact telephone number
4. Sponsor local representative's name and 24-hour contact telephone number
5. Statement, in the local language(s), that the subject is participating in a clinical study

12.4.2. Serious Adverse Events

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

Information regarding serious adverse events will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by the principal investigator or the sub-investigator from the study site, and transmitted to the sponsor within 24 hours. The initial and

follow-up reports of a serious adverse event should be downloaded from the eCRF once signed (a notification email is sent). In case of technical difficulties, SAE notification can be carried via email to drugsafety@emnresearch.it or by fax using the following number: Fax: +39 01 101 331 82 (or updated contact information supplied by the Sponsor if the email address and/or fax number change during the conduct of the study).

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

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

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

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

12.4.3. Pregnancy

All initial reports of pregnancy must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge by sending the Pregnancy Reporting Form via email to drugsafety@emnresearch.it. In case of technical difficulties, pregnancy notification can be carried by fax using the following number: Fax: +39 01 101 331 82 (or updated contact information supplied by the Sponsor if the email address and/or fax number change during the conduct of the study). Abnormal pregnancy outcomes (e.g., spontaneous abortion, stillbirth, and congenital

anomaly) are considered serious adverse events and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must promptly discontinue further study treatment. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

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

12.5. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed 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, i.e., 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.

13.1. Procedures

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

If the defect is combined with a serious adverse event, the study-site personnel must report the PQC to the sponsor according to the serious adverse event reporting timelines (refer to Section 12.4.2, 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

13.3. Product Quality

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

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drug(s)

Daratumumab for IV infusion supplied for this study is a colorless to yellow liquid and sterile concentrate of 20 mg/mL as a liquid vial. It will be provided under the responsibility of the sponsor. Refer to the IB for a list of excipients.

Daratumumab SC will be provided as a fixed dose, combination drug product containing rHuPH20 drug substance (2000 U/mL) and daratumumab drug substance (120 mg/mL) in a single vial.

ONLY for subjects receiving additional treatment as per protocol:

Bortezomib will be provided in 3.5 mg single-use vials as a lyophilized powder. Bortezomib must be prepared in an aseptic manner according to local standards. Please refer to the SIPPM for further instructions on preparation, handling and storage.

14.2. Packaging

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

Daratumumab SC is supplied in glass vials containing daratumumab at a concentration of 120 mg/mL.

14.3. Labeling

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

14.4. Preparation, Handling, and Storage

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

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

14.5. Drug Accountability

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

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

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

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

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

1. Investigator's Brochure or SmPC
2. Study site investigational product and procedures manual
3. Laboratory manual
4. PRO questionnaires
5. eDC Manual
6. Sample ICF

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

This is a phase 2 study testing daratumumab IV in patients with stage 3B AL amyloidosis. Currently there are no approved therapies for patients with AL amyloidosis and specifically for patients with stage 3B AL, the treatment modalities that are used are associated with poor outcomes and a median survival below 6 months. Disease related complications and treatment related toxicities are the main reasons for early death in this advanced stage of AL amyloidosis. The current study will provide a treatment that has shown efficacy and a very favorable safety profile with the aim to rapidly induce hematologic response, with low toxicity, in order to improve the outcomes of these patients. The study is designed to specifically address the unmet need of a rapidly acting and safe therapy for frail AL patients, based on the best currently available knowledge on the disease and available treatments. All patients will receive therapy with the active drug. Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled.

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.

GCP 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 and Competent Authority

This study will be undertaken only after the IEC/IRB and Competent Authority (CA) 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 the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and CA 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 and CA for their review and approval, where appropriate:

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

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 and CA for review and approval before implementation of the change(s).

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

16.2.3. Informed Consent

Each subject 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 CA 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 data privacy laws and regulations, as well as any 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 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 study related procedures if needed.

The subject 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 the subject's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject.

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, including the provisions of the General Data Protection Regulation (GDPR) (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016. 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 Sponsor will ensure that all personal data will be pseudonymized in order to protect the subjects' rights.

The informed consent obtained from the subject 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, as well as the right to transfer, delete, limit or object the processing of their personal data. 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. The subjects have also the right to lodge a complaint to the relevant data privacy supervisory authority.

The Sponsor will ensure that the study ICF contains adequate information according to all applicable data privacy regulations.

Exploratory DNA biomarker 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.

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

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

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

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

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

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

17.2.2. Required Pre-study Documentation

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

1. Protocol and amendment(s), if any, signed and dated by the principal investigator
2. A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, and any recruiting materials. 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.
3. 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.
4. Regulatory authority approval or notification, if applicable
5. Signed and dated statement of investigator (e.g., Form FDA 1572), if applicable
6. Documentation of investigator qualifications (e.g., curriculum vitae)
7. Completed investigator financial disclosure form from the principal investigator, where required
8. Signed and dated Clinical Trial Agreement, which includes the financial agreement
9. Any other documentation required by local regulations

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

1. Completed investigator financial disclosure forms from all sub-investigators
2. Documentation of sub-investigator qualifications (e.g., curriculum vitae)
3. 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

4. Local laboratory documentation demonstrating competence and test reliability (e.g., 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 or year of birth, if required. In cases where the subject is not enrolled into the study, the date seen and date or year of birth will be used.

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

17.4. Source Documentation

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

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

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

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

17.5. Case Report Form Completion

Electronic data capture (eDC) will be used for this study. Electronic case report forms (eCRF) 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 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 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 monitor 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 CRF completion will be provided and reviewed with study-site personnel before the start of the study.

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

17.7. Record Retention

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

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

Furthermore, essential documents (written and electronic) should be retained for a period of not less than twenty-five (25) years from the completion of the study, unless the Sponsor provides written permission to dispose of them earlier or requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.
The subjects' medical files will be archived in accordance with the national laws.

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

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

17.8. Monitoring

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

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

17.9. Study Completion/Termination

17.9.1. Study Completion/End of Study

The end of study will take place at the last visit of the last subject, and it is defined to be 2 years after the last subject is enrolled (total study duration = 64 months and 5 days). The final data from

the study sites will be sent to the Sponsor 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 solid and valid 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:

1. 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
2. Inadequate recruitment of subjects by the investigator
3. 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 the sponsor's operations supplied by the sponsor to the investigator and not previously published, and any data, including exploratory research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection to addressing the study objectives, 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 exploratory analyses performed after the clinical study report has been issued will be reported in a separate report and will not require a revision of the clinical study report. Study subject identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

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

Registration of Clinical Studies and Disclosure of Results

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

REFERENCES

1. Merlini G, Bellotti V. Molecular mechanisms of amyloidosis. N Engl J Med 2003;349:583-96.
2. Merlini G, Stone MJ. Dangerous small B-cell clones. Blood 2006;108:2520-30.
3. Wechalekar AD, Gillmore JD, Hawkins PN. Systemic amyloidosis. Lancet 2016;387:2641-54.
4. Palladini G, Merlini G. What is new in diagnosis and management of light chain amyloidosis? Blood 2016;128:159-68.
5. Kastritis E, Dimopoulos MA. Recent advances in the management of AL Amyloidosis. Br J Haematol. 2016;172:170-86.
6. Comenzo RL, Reece D, Palladini G, Seldin D, Sanchorawala V, Landau H, Falk R, Wells K, Solomon A, Wechalekar A, Zonder J, Dispenzieri A, Gertz M, Streicher H, Skinner M, Kyle RA, Merlini G. Consensus guidelines for the conduct and reporting of clinical trials in systemic light-chain amyloidosis. Leukemia 2012;26:2317-25.
7. Palladini G, Dispenzieri A, Gertz MA, Kumar S, Wechalekar A, Hawkins PN, Schonland S, Hegenbart U, Comenzo R, Kastritis E, Dimopoulos MA, Jaccard A, Klersy C, Merlini G. New criteria for response to treatment in immunoglobulin light chain amyloidosis based on free light chain measurement and cardiac biomarkers: impact on survival outcomes. J Clin Oncol 2012;30:4541-9.
8. Sanchorawala V, Wright DG, Rosenzweig M, Finn KT, Fennessey S, Zeldis JB, Skinner M, Seldin DC. Lenalidomide and dexamethasone in the treatment of AL amyloidosis: results of a phase 2 trial. Blood 2007;109(2):492-6.
9. Dispenzieri A, Lacy MQ, Zeldenrust SR, Hayman SR, Kumar SK, Geyer SM, Lust JA, Allred JB, Witzig TE, Rajkumar SV, Greipp PR, Russell SJ, Kabat B, Gertz MA. The activity of lenalidomide with or without dexamethasone in patients with primary systemic amyloidosis. Blood 2007;109(2):465-70.
10. Kumar SK, Hayman SR, Buadi FK, Roy V, Lacy MQ, Gertz MA, Allred J, Laumann KM, Bergsagel LP, Dingli D, Mikhael JR, Reeder CB, Stewart AK, Zeldenrust SR, Greipp PR, Lust JA, Fonseca R, Russell SJ, Rajkumar SV, Dispenzieri A. Lenalidomide, cyclophosphamide, and dexamethasone (CRd) for light-chain amyloidosis: long-term results from a phase 2 trial. Blood 2012;119(21):4860-7.
11. Kastritis E, Terpos E, Roussou M, Gavriatopoulou M, Pamboukas C, Boletis I, Marinaki S, Apostolou T, Nikitas N, Gkortzolidis G, Michalis E, Delimpasi S, Dimopoulos MA. A phase 1/2 study of lenalidomide with low-dose oral cyclophosphamide and low-dose dexamethasone (RdC) in AL amyloidosis. Blood 2012;119(23):5384-90.
12. Palladini G, Russo P, Milani P, Foli A, Lavatelli F, Nuvolone M, Perlini S, Merlini G. A phase II trial of cyclophosphamide, lenalidomide and dexamethasone in previously treated patients with AL amyloidosis. Haematologica 2013;98(3):433-6.
13. Kastritis E, Leleu X, Arnulf B, Zamagni E, Cibeira MT, Kwok F, Mollee P, Hajek R, Moreau P, Jaccard A, Schönland S, Filshie R, Nicolas-Virelizier E, Augustson B, Mateos M-V, Wechalekar A, Hachulla E, Milani P, Dimopoulos MA, Fermand J-P, Foli A, Gavriatopoulou M, Palumbo A, Sonneveld P, Johnsen HE, Merlini G, Palladini G. A Randomized Phase III Trial of Melphalan and Dexamethasone (MDex) Versus Bortezomib, Melphalan and Dexamethasone (BMDex) for Untreated Patients with AL Amyloidosis. Blood 2016;128:646-.
14. Kastritis E, Gavriatopoulou M, Roussou M, Fotiou D, Ziogas DC, Migkou M, Eleutherakis-Papaiakovou E, Panagiotidis I, Kanellias N, Psimenou E, Papadopoulou E, Pamboucas C, Manios E, Gakiopoulou H, Ntalianis A, Tasidou A, Giannouli S, Terpos E, Dimopoulos MA. Addition of cyclophosphamide and higher doses of dexamethasone do not improve outcomes of patients with AL amyloidosis treated with bortezomib. Blood Cancer J 2017;7(6):e570.
15. Palladini G, Sachchithanantham S, Milani P, Gillmore J, Foli A, Lachmann H, Basset M, Hawkins P, Merlini G, Wechalekar AD. A European collaborative study of cyclophosphamide, bortezomib, and dexamethasone in upfront treatment of systemic AL amyloidosis. Blood 2015; 30;126(5):612-5.

16. Venner CP, Lane T, Foard D, Rannigan L, Gibbs SD, Pinney JH, Whelan CJ, Lachmann HJ, Gillmore JD, Hawkins PN, Wechalekar AD. Cyclophosphamide, bortezomib, and dexamethasone therapy in AL amyloidosis is associated with high clonal response rates and prolonged progression-free survival. Blood 2012;119(19):4387-90.
17. Mikhael JR, Schuster SR, Jimenez-Zepeda VH, Bello N, Spong J, Reeder CB, Stewart AK, Bergsagel PL, Fonseca R. Cyclophosphamide-bortezomib-dexamethasone (CyBorD) produces rapid and complete hematologic response in patients with AL amyloidosis. Blood 2012;119(19):4391-4.
18. van der Veer MS, de Weers M, van Kessel B, Bakker JM, Wittebol S, Parren PW, Lokhorst HM, Mutis T. The therapeutic human CD38 antibody daratumumab improves the anti-myeloma effect of newly emerging multi-drug therapies. Blood Cancer J 2011;1(10):e41.
19. de Weers M, Tai YT, van der Veer MS, Bakker JM, Vink T, Jacobs DC, Oomen LA, Peipp M, Valerius T, Slootstra JW, Mutis T, Bleeker WK, Anderson KC, Lokhorst HM, van de Winkel JG, Parren PW. Daratumumab, a novel therapeutic human CD38 monoclonal antibody, induces killing of multiple myeloma and other hematological tumors. J Immunol 2011;186(3):1840-8.
20. van der Veer MS, de Weers M, van Kessel B, Bakker JM, Wittebol S, Parren PW, Lokhorst HM, Mutis T. Towards effective immunotherapy of myeloma: enhanced elimination of myeloma cells by combination of lenalidomide with the human CD38 monoclonal antibody daratumumab. Haematologica 2011;96(2):284-90.
21. Kaufman GP, Schrier SL, Lafayette RA, Arai S, Witteles RM, Liedtke M. Daratumumab yields rapid and deep hematologic responses in patients with heavily pretreated AL amyloidosis. Blood 2017; 17;130(7):900-2.
22. Weiss B, Waxman A, Cohen A, Dember L, Zonder J. Clinical experience with daratumumab in AL amyloidosis and MM with AL amyloidosis. In: The XVth International Symposium on Amyloidosis. UPPSALA 2016:PB 98.
23. Sher T, Fenton B, Akhtar A, Gertz MA. First report of safety and efficacy of daratumumab in 2 cases of advanced immunoglobulin light chain amyloidosis. Blood. 2016;128(15):1987-1989.
24. Merlini G, Comenzo RL, Seldin DC, Wechalekar A, Gertz MA. Immunoglobulin light chain amyloidosis. Expert Rev Hematol 2014;7:143-56.
25. Matsuda M, Gono T, Shimojima Y, Sakashita K, Koike K, Ikeda S. Evaluation of intensive chemotherapy in AL amyloidosis: usefulness of flow cytometric analysis of plasma cells in bone marrow. Amyloid 2003;10(4):250-6.
26. Matsuda M, Gono T, Shimojima Y, Hoshii Y, Ikeda S. Phenotypic analysis of plasma cells in bone marrow using flow cytometry in AL amyloidosis. Amyloid 2003;10(2):110-6.
27. Shimojima Y, Matsuda M, Gono T, Ishii W, Fushimi T, Hoshii Y, Yamada T, Ikeda S. Correlation between serum levels of free light chain and phenotype of plasma cells in bone marrow in primary AL amyloidosis. Amyloid 2005;12(1):33-40.
28. Usmani SZ, Weiss BM, Plesner T, Bahlis NJ, Belch A, Lonial S, Lokhorst HM, Voorhees PM, Richardson PG, Chari A, Sasser AK, Axel A, Feng H, Uhlar CM, Wang J, Khan I, Ahmadi T, Nahi H. Clinical efficacy of daratumumab monotherapy in patients with heavily pretreated relapsed or refractory multiple myeloma. Blood 2016;128:37-44.
29. Dimopoulos MA, Oriol A, Nahi H, San-Miguel J, Bahlis NJ, Usmani SZ, Rabin N, Orlowski RZ, Komarnicki M, Suzuki K, Plesner T, Yoon SS, Ben Yehuda D, Richardson PG, Goldschmidt H, Reece D, Lisby S, Khokhar NZ, O'Rourke L, Chiu C, Qin X, Guckert M, Ahmadi T, Moreau P. Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma. N Engl J Med 2016;375:1319-31.
30. Palumbo A, Chanan-Khan A, Weisel K, Nooka AK, Masszi T, Beksac M, Spicka I, Hungria V, Munder M, Mateos MV, Mark TM, Qi M, Schecter J, Amin H, Qin X, Deraedt W, Ahmadi T, Spencer A, Sonneveld P. Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma. N Engl J Med 2016;375(8):754-66.
31. Chari A, Suvannasankha A, Fay JW, Arnulf B, Kaufman JL, Ifthikharuddin JJ, Weiss BM, Krishnan A, Lentzsch S, Comenzo R, Wang J, Nottage K, Chiu C, Khokhar NZ, Ahmadi T, Lonial

S. Daratumumab plus pomalidomide and dexamethasone in relapsed and/or refractory multiple myeloma. Blood 2017;130(8):974-981.

32. Merlini G, Comenzo RL, Seldin DC, Wechalekar A, Gertz MA. Immunoglobulin light chain amyloidosis. Expert Review of Hematology 2014;7(2):143-56.
33. Palladini G, Hegenbart U, Milani P, et al. A staging system for renal outcome and early markers of renalresponse to chemotherapy in AL amyloidosis. Blood 2014;124(15):2325-2332.
34. Lin HM, Seldin D, Hui AM, Berg D, Dietrich CN, Flood E3. The patient's perspective on the symptom and everyday life impact of AL amyloidosis. Amyloid. 2015;22(4):244-51. doi: 10.3109/13506129.2015.1102131.
35. Choufani EB, Sanchorawala V, Ernst T, Quillen K, Skinner M, Wright DG, Seldin DC. Acquired factor X deficiency in patients with amyloid light-chain amyloidosis: incidence, bleeding manifestations, and response to high-dose chemotherapy. Blood. 2001;97(6):1885-7.
36. Wisløff F, Eika S, Hippe E, Hjorth M, Holmberg E, Kaasa S, Palva I, Westin J. Measurement of health-related quality of life in multiple myeloma. Nordic Myeloma Study Group. Br J Haematol. 1996;92(3):604-13.
37. Wisløff F, Hjorth M. Health-related quality of life assessed before and during chemotherapy predicts for survival in multiple myeloma. Nordic Myeloma Study Group. Br J Haematol. 1997;97(1):29-37.
38. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, Bonsel G, Badia X. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20(10):1727-36. doi: 10.1007/s11136-011-9903-x. Epub 2011 Apr 9.
39. Chapuy CI, Nicholson RT, Aguad MD, Chapuy B, Laubach JP, Richardson PG, Doshi P, Kaufman RM. Resolving the daratumumab interference with blood compatibility testing. Transfusion. 2015;55(6 Pt 2):1545-54. doi: 10.1111/trf.13069. Epub 2015 Mar 12
40. Palladini G, Dispenzieri A, Gertz M A, Kumar S, Wechalekar A, Hawkins P. N., Merlini G. (2012). New Criteria for Response to Treatment in Immunoglobulin Light Chain Amyloidosis Based on Free Light Chain Measurement and Cardiac Biomarkers: Impact on Survival Outcomes. J Clin Oncol. 2012;30(36):4541-9
41. Palladini G, Milani P, Foli A, Vidus Rosin M, Basset M, Lavatelli F, Nuvolone M, Obici L, Perlini S, Merlini G. Melphalan and dexamethasone with or without bortezomib in newly diagnosed AL amyloidosis: a matched case-control study on 174 patients. Leukemia 2014;28(12):2311-6.
42. Khouri J, Bicky T, Reu FJ, Samaras CJ, Liu HD, Karam MA, Reed J, Faiman BM, Valent J. Daratumumab is safe and highly effective in AL amyloidosis. Blood 2017;130:1819.
43. Roussel M, Stoppa AM, Perrot A, Karlin L, Arnulf B, Macro M, Huart A, Frenzel L, Morel P, Boyle E, Dorvaux V, Merlini G, Palladini G, Lavergne D, Bridoux F, Jaccard A. A prospective phase II of daratumumab in previously-treated systemic light-chain (AL) amyloidosis. Blood 2017;130:508.
44. Sanchorawala V, Sarosiek S, Sloan JM, Brauneis D, Migre ME, Mistark M, Santos S, Cruz R, Fennessey S, Shelton AC. Safety, tolerability, and response rates of daratumumab in patients with relapsed light chain (AL) amyloidosis: results of a phase II study. Blood 2018;132:2005.
45. Wechalekar AD, Schonland SO, Kastritis E, Gillmore JD, Dimopoulos MA, Lane T, Foli A, Foard D, Milani P, Rannigan L, Hegenbart U, Hawkins PN, Merlini G, Palladini G. A European collaborative study of treatment outcomes in 346 patients with cardiac stage III AL amyloidosis. Blood 2013; 121:3420-3427.
46. Dinner S, Witteles W, Afghahi A, Witteles R, Arai S, Lafayette R, Schrier SL, Liedtke M. Lenalidomide, melphalan and dexamethasone in a population of patients with immunoglobulin light chain amyloidosis with high rates of advanced cardiac involvement. Haematologica. 2013 Oct; 98(10): 1593–1599.
47. Palladini G, Milani P, Foli A, Rosin MV, Basset M, Lavatelli F, Nuvolone M, Obici L, Perlini S & Merlini G. Melphalan and dexamethasone with or without bortezomib in newly diagnosed AL amyloidosis: a matched case-control study on 174 patients. Leukemia 2014; 28:2311–2316.

48. Jaccard A, Comenzo RL, Hari P, Hawkins PN, Roussel M, Morel P, Macro M, Pellegrin JL, Lazaro E, Mohty D, Mercie P, Decaux O, Gillmore J, Lavergne D, Bridoux F, Wechalekar AD, Venner CP. Efficacy of bortezomib, cyclophosphamide and dexamethasone in treatment-naïve patients with high-risk cardiac AL amyloidosis (Mayo Clinic stage III). Haematologica. 2014 Sep; 99(9): 1479–1485.
49. Palladini G, Milani P, Riva E, Basset M, Foli A, Merlini G. Accurate Risk Stratification Identifies Patients with AL Amyloidosis Benefiting Most from Upfront Bortezomib Combinations: A Study of Treatment Outcomes in 984 Patients. Blood (2015) 126 (23): 190.
50. Kastritis E, Papassotiriou I, Terpos E, Roussou M, Gavriatopoulou M, Komitopoulou A, Skevaki C, Eleutherakis-Papaiakovou E, Pamboucas C, Psimenou E, Manios E, Giannouli S, Politou M, Gakiopoulou H, Papadopoulou E, Stamatelopoulos K, Tasidou A, Dimopoulos MA. Clinical and prognostic significance of serum levels of von Willebrand factor and ADAMTS-13 antigens in AL amyloidosis. Blood 2016; 128(3): 405–9.
51. Usmani SZ, Nahi H, Mateos MV, van de Donk NWCJ, Chari A, Kaufman JL, Moreau P, Oriol A, Plesner T, Benboubker L, Hellemans P, Masterson T, Clemens PL, Luo M, Liu K, San-Miguel J. Subcutaneous delivery of daratumumab in relapsed or refractory multiple myeloma. Blood (2019) 134 (8): 668–677.

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

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649-55

ATTACHMENT 2: 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, efavirinez, etrrvirine, modafinil, nifcillin	Ameprenavir, aprepitant, armodafinil, clobazamechinacea, 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, aprepriant, atazanavir; ciprofloxacin, crizotinib, daraunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, imatinib, verapamil	Alprazolam, amiodarone, amlodipine, atorvastatin, bicalutamide, cilostazol, cimetidine, cyclosporine, fluozetine, fluvoxamine, ginkgo, goldenseal, isoniazid, lapatinib, nilotinib, oral contraceptives, pazopanib, ranitidine, ranolazine, tpranavir/ritonavir, ticagrelor, zileuton

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

ATTACHMENT 3: Definition of Organ Involvement based on Amyloidosis Consensus Criteria

Kidney	24 hr urine protein >0.5 g/day, predominantly albumin
Heart	Echo: mean wall thickness >12 mm, no other cardiac cause or an elevated NT-ProBNP (>332 ng/L) in the absence of renal failure or atrial fibrillation
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

ATTACHMENT 4: 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	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 and/or radiologic images.

ATTACHMENT 5: CONVERSION TABLE FOR GLUCOCORTICOID DOSE

Generic Name	Oral or Intravenous Dose (mg)
Betamethasone	0.60
Dexamethasone	0.75
Hydrocortisone	20
Methylprednisolone	4
Prednisolone	5
Prednisone	5

ATTACHMENT 6: 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 (CKD-EPI)

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

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

ATTACHMENT 7: GUIDELINE FOR ASTHMA ELIGIBILITY CRITERIA

Components of Severity		Classification of Asthma Severity ≥12 years of age			
		Intermittent	Persistent: Mild	Persistent: Moderate	Persistent: 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		Step 1	Step 2	Step 3 and consider short course of oral systemic corticosteroids	Step 4 or 5
(See figure 4–5 for treatment steps.)		In 2–6 weeks, evaluate level of asthma control that is achieved and adjust therapy accordingly.			

ATTACHMENT 8: BODY SURFACE AREA NOMOGRAM

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

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

or

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

ATTACHMENT 9: EORTC QLQ



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

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ATTACHMENT 10: 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
LC29, Item #45	Have you been dizzy?	1	2	3	4

ATTACHMENT 11: EQ-5D-5L



(English version for the UK)

SAMPLE

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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

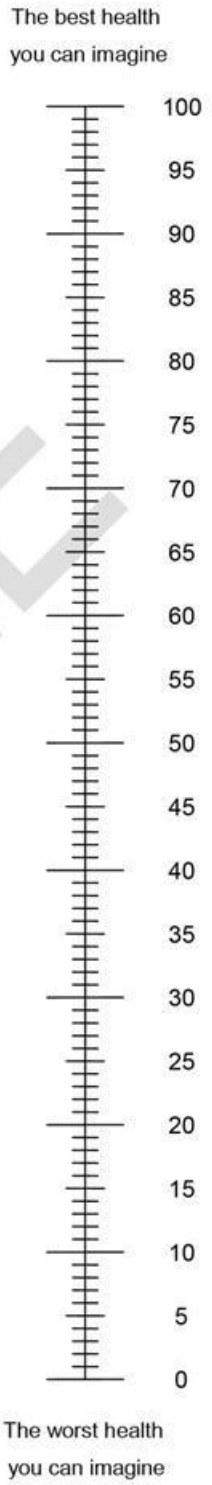
- I am not anxious or depressed ☐
- I am slightly anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am severely anxious or depressed ☐
- I am extremely anxious or depressed ☐

SAMPLE

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- 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 = ☐



SAMPLE

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ATTACHMENT 12: SF-36

SF-36 QUESTIONNAIRE

Name:_____ **Ref. Dr:**_____ **Date:** _

ID#: _____ **Age:** _____ **Gender: M / F**

Please answer the 36 questions of the **Health Survey** completely, honestly, and without interruptions.

GENERAL HEALTH:
In general, would you say your health is:
Excellent Very Good Good Fair

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
Somewhat worse now than one year ago
Much worse than one year ago

LIMITATIONS OF ACTIVITIES:
The following items are about activities you might do during a typical day. Does your health now limit yc activities? If so, how much?

Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.
Yes, Limited a lot Yes, Limited a Little No, Not Limited at all

Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf
Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all

Lifting or carrying groceries
Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all

Climbing several flights of stairs
Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all

Climbing one flight of stairs
Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all

Bending, kneeling, or stooping
Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all

Walking more than a mile
Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all

Walking several blocks
Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all

Walking one block
Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all

Bathing or dressing yourself
Yes, Limited a Lot | Yes, Limited a Little | No, Not Limited at all

PHYSICAL HEALTH PROBLEMS:
During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

Cut down the amount of time you spent on work or other activities
Yes | No

Accomplished less than you would like
Yes | No

Were limited in the kind of work or other activities
Yes | No

Had difficulty performing the work or other activities (for example, it took extra effort)
Yes | No

EMOTIONAL HEALTH PROBLEMS:
During the past 4 weeks, 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)?

Cut down the amount of time you spent on work or other activities
Yes | No

Accomplished less than you would like
Yes | No

Didn't do work or other activities as carefully as usual
Yes | No

SOCIAL ACTIVITIES:
Emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all | Slightly | Moderately | Severe | Very Severe

PAIN:
How much bodily pain have you had during the past 4 weeks?

None | Very Mild | Mild | Moderate | Severe | Very Severe

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

ENERGY AND EMOTIONS:
These questions are about how you feel and how things have been with you during the last 4 weeks. For each question, please give the answer that comes closest to the way you have been feeling.

Did you feel full of pep?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you been a very nervous person?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you felt so down in the dumps that nothing could cheer you up?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you felt calm and peaceful?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Did you have a lot of energy?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you felt downhearted and blue?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Did you feel worn out?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you been a happy person?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Did you feel tired?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

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

- All of the time
- Most of the time
- Some of the time
- A little bit of the time
- None of the Time

GENERAL HEALTH:
How true or false is each of the following statements for you?

I seem to get sick a little easier than other people
○ Definitely true ○ Mostly true ○ Don't know ○ Mostly false ○ Definitely false

I am as healthy as anybody I know
○ Definitely true ○ Mostly true ○ Don't know ○ Mostly false ○ Definitely false

I expect my health to get worse
○ Definitely true ○ Mostly true ○ Don't know ○ Mostly false ○ Definitely false

My health is excellent
○ Definitely true ○ Mostly true ○ Don't know ○ Mostly false ○ Definitely false

ATTACHMENT 13: JSH GUIDELINES FOR THE MANAGEMENT OF HEPATITIS B VIRUS INFECTION

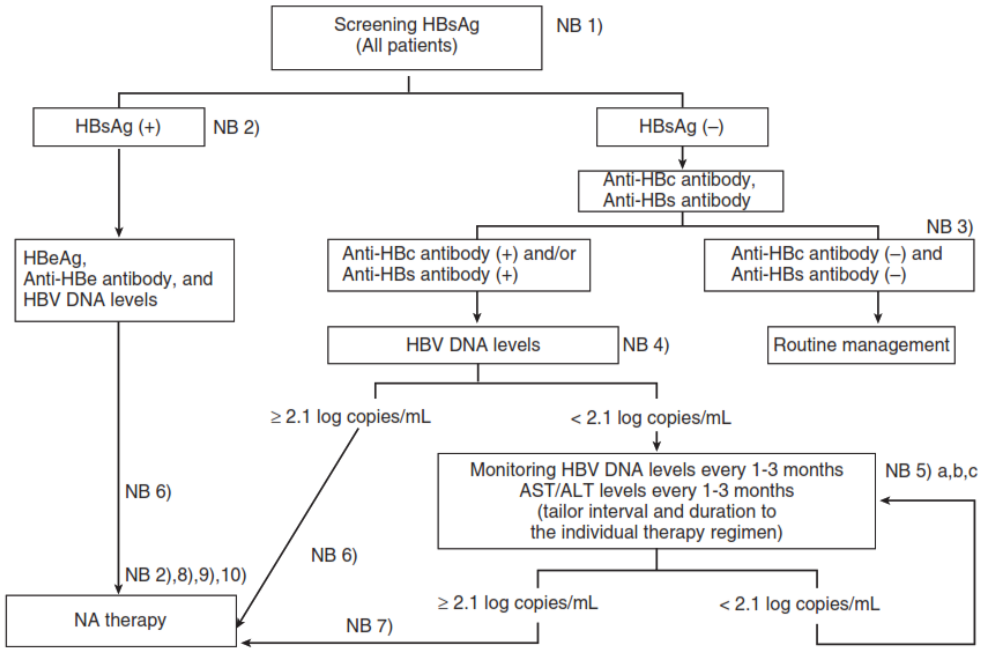


Figure: Guidelines for the prevention of hepatitis B virus reactivation in patients receiving immunosuppressive therapy or chemotherapy.

Addendum: Caution is required when administering powerful chemotherapeutic agents for hematological malignancies, as during or following completion of treatment some HBsAg positive or negative patients will develop hepatitis B due to reactivation of HBV, and some of these will go on to suffer fulminant hepatitis. Consideration should also be given to the possibility of HBV reactivation in association with standard chemotherapy for hematological malignancies or solid cancers, and immunosuppressive therapy for autoimmune diseases, such as rheumatic and collagen diseases. The incidences of HBV reactivation, hepatitis and fulminant hepatitis associated with standard chemotherapy and immunosuppressive therapy are not known, and there is a lack of evidence on which to base guidelines. Furthermore, prevention of fulminant hepatitis is not guaranteed with NA therapy.

NB 1) HBV carriers and patients with resolved hepatitis B should be screened prior to immunosuppressive therapy or chemotherapy. First HBsAg testing should be performed to determine whether they are an HBV carrier. HBsAg negative patients should be tested for anti-HBc antibody and anti-HBs antibody, to confirm past infection. Highly sensitive testing methods should be used for measurements of HBsAg, anti-HBc antibody and anti-HBs antibody.

NB 2) A hepatologist should be consulted concerning HBsAg positive patients. A hepatologist should preferably be consulted for all patients administered NAs.

NB 3) In some patients undergoing retreatment who did not undergo testing for anti-HBc or HBs antibody at the time of their initial chemotherapy, and in patients who have already commenced immunosuppressive therapy, antibody titers may be low, in which case measurement of HBV DNA levels is preferable.

NB 4) Patients with resolved HBV infection should be screened using real-time PCR measurement of HBV DNA levels.

NB 5)

a. Caution is required when treating patients with resolved HBV infection with rituximab + corticosteroid or fludarabine chemotherapy, or when they undergo hematopoietic stem cell transplantation, as these patients are at high risk of HBV reactivation. HBV DNA levels should be monitored on a monthly basis during treatment, and for at least 12 months afterward. Long-term monitoring is required for hematopoietic stem cell transplant recipients.

b. Although the incidence is low, there is a risk of HBV reactivation with standard chemotherapy regimens. HBV DNA levels should be measured every 1–3 months, with the interval and duration tailored to the individual therapy regimen. It is best to err on the side of caution with patients undergoing treatment for hematological malignancies.

c. There is also a risk of HBV reactivation associated with immunosuppressive therapy using corticosteroids, immunosuppressant agents, or molecular targeted therapy with immunosuppressant or immunomodulator activity. HBV DNA levels should be monitored on a monthly basis in patients on immunosuppressive therapy for at least 6 months after commencement or alteration (including cessation) of treatment. After 6 months, the interval and duration should be tailored to the individual therapy regimen.

NB 6) Administration should be commenced as soon as possible, before commencement of immunosuppressive therapy or chemotherapy.

NB 7) Administration should be commenced as soon as the HBV DNA levels exceed 2.1 log copies/mL, during or after immunosuppressive therapy or chemotherapy. If this occurs during treatment, it is preferable to consult with a hepatologist, and not immediately cease the immunosuppressant or antineoplastic agent with immunosuppressive activity.

NB 8) Entecavir is the recommended NA.

NB 9) Cessation of NA therapy can be considered if the following criteria are met.

In patients who were HBsAg positive at the time of screening, when the criteria for cessation of NA therapy in cases with chronic hepatitis B are met.

In patients who were anti-HBc antibody and/or anti-HBs antibody positive at the time of screening:

1 NA therapy has been continued for at least 12 months after completion of immunosuppressive therapy or chemotherapy.

2 ALT (GPT) levels have been normalized during this period (excluding causes of elevated ALT levels other than HBV).

3 negative conversion of HBV DNA has occurred during this period.

NB 10) Patients should be carefully monitored, including measurement of HBV DNA levels, for at least 12 months following completion of NA therapy. Monitoring methods depend on package inserts of each NA. NA therapy should be immediately resumed if HBV-DNA levels exceed 2.1 log copies/mL during monitoring period.

ATTACHMENT 14: SIGNATURES

I. SPONSOR'S SIGNATURE

Study title: Phase 2 study of daratumumab monotherapy in previously untreated patients with stage 3B light chain (AL) amyloidosis

Protocol No: EMN22/54767414AMY2005

Version: 6.0

Date: 31 March 2023

Sponsor Representative:

Signature: ……..……... ……

Prof. Pieter Sonneveld Date (DD Mmm YYYY)
Erasmus MC
Wytemaweg 80
Rotterdam, The Netherlands

II. CO-ORDINATING INVESTIGATOR'S SIGNATURE

Study title: Phase 2 study of daratumumab monotherapy in previously untreated patients with stage 3B light chain (AL) amyloidosis

Protocol No: EMN22/54767414AMY2005

Version: 6.0

Date: 31 March 2023

I have read all pages of this clinical study protocol and I agree that it contains all the information required to conduct this study.

Signature:

……..……... ……
Date (DD Mmm YYYY)

Co-ordinating Investigator:
Prof. Efstathios Kastritis
Department of Clinical Therapeutics, National and Kapodistrian University of Athens School of Medicine, Athens - Greece
80 Vas. Sofias Ave & Lourou Str., PC 11528, Athens, Greece

III. SCIENTIFIC CO-ORDINATING INVESTIGATOR'S SIGNATURE

Study title: Phase 2 study of daratumumab monotherapy in previously untreated patients with stage 3B light chain (AL) amyloidosis

Protocol No: EMN22/54767414AMY2005

Version: 6.0

Date: 31 March 2023

I have read all pages of this clinical study protocol and I agree that it contains all the information required to conduct this study.

Signature:

……..…….. ……
Date (DD Mmm YYYY)

Prof. Meletios Athanasios Dimopoulos
Department of Clinical Therapeutics, University of Athens School of Medicine, General Hospital of Athens "ALEXANDRA"
80 Vas. Sofias Ave & Lourou Str., PC 11528, Athens, Greece

IV. NATIONAL CO-ORDINATING INVESTIGATOR'S SIGNATURE

Study title: Phase 2 study of daratumumab monotherapy in previously untreated patients with stage 3B light chain (AL) amyloidosis.

Protocol No: EMN22/54767414AMY2005

Version: 6.0

Date: 31 March 2023

I have read all pages of this clinical study protocol and I agree that it contains all the information required to conduct this study.
Signature: ……..…….. …… <*name, title, address*> Date (DD Mmm YYYY)

V. PRINCIPAL INVESTIGATOR'S SIGNATURE

Study title: Phase 2 study of daratumumab monotherapy in previously untreated patients with stage 3B light chain (AL) amyloidosis.

Protocol No: EMN22/54767414AMY2005

Version: 6.0

Date: 31 March 2023

I have read all pages of this clinical study protocol and agree to conduct the study as outlined in the protocol and to comply with all the terms and conditions set out therein. I confirm that I will conduct the study in accordance with ICH GCP guidelines and applicable local regulations. I will also ensure that Sub-investigator(s) and other relevant members of my staff have access to copies of this protocol and the ICH GCP guidelines to enable them to work in accordance with the provisions of these documents.

Principal Investigator:

Signature: .....

<Insert name and qualifications of the Investigator> Date (DD Mmm YYYY)

Printed Name: .....

Address: .....

.....