Document Type:	Study Protocol
Official Title:	A Phase 3, Randomized, Multicenter, Double-Blind, Placebo-Controlled, 2-Arm, Efficacy and Safety Study of NEOD001 Plus Standard of Care vs. Placebo Plus Standard of Care in Subjects with Light Chain (AL) Amyloidosis
NCT Number:	NCT02312206
Document Date:	06 November 2017

This protocol for Study NEOD001-CL002 was amended three times.

Date of Original Protocol:	23 October 2014
Date of Amendment 1:	24 February 2015
Date of Amendment 2:	28 April 2016
Date of Amendment 3:	06 November 2017

The following key changes were made between amendments:

Overview of Major/Substantial Changes in Amendment 1:

- Addressed Sponsor name change
- Clarified standard of care to include bortezomib
- Revised and clarified eligibility criteria and study assessments
- Added renal stage as a stratification factor
- Clarified the role of the Clinical Events Committee in adjudicating primary endpoint events

Overview of Major/Substantial Changes in Amendment 2:

- Revised and clarified eligibility criteria and study assessments
- Revised and reordered secondary and exploratory objectives and endpoints
- Revised windows for post-dose monitoring, sampling times, and visit dates
- Aligned to Clinical Events Committee manual of operations and Data Monitoring Committee charter
- Updated appendices to consolidate and provide additional organ response and progression criteria; rename the "Peripheral Neuropathy Assessment Form" to the "Neuropathy Impairment Scale – Lower Limbs (NIS-LL)" and update the content; delete Borg Scale, add a sample VASPI tool, and add an appendix with a list of coagulation indices

Overview of Major/Substantial Changes in Amendment 3:

- Aligned with updated case report form and statistical analysis plan
- Removed requirement for monthly collection of additional coagulation indices
- Removed sample collection for quantitative/renal biomarkers
- Allowed postbaseline 6MWT to be administered on the same calendar day that study drug is administered
- Increased the number of subjects
- Clarified timing of serious adverse event collection

CLINICAL RESEARCH PROTOCOL

Study Title:	A Phase 3, Randomized, Multicenter, Double-Blind, Placebo-Controlled, 2-Arm, Efficacy and Safety Study of NEOD001 Plus Standard of Care vs. Placebo Plus Standard of Care in Subjects with Light Chain (AL) Amyloidosis
Protocol Number:	NEOD001-CL002
Investigational Product:	NEOD001
US IND Number:	122,912
EudraCT Number:	2014-003865-11
Indication:	Light Chain (AL) Amyloidosis
Sponsor:	Prothena Therapeutics Limited Adelphi Plaza, Upper George's Street Dun Laoghaire, Co. Dublin A96 T927, Ireland
Sponsor Representative:	Prothena Biosciences Inc 331 Oyster Point Boulevard South San Francisco, CA 94080 USA
Sponsor's Chief Medical Officer:	[redacted]
Medical Monitor:	Contact information available in the Study File Notebook
Development Phase:	Phase 3
Date of Original Protocol:	23 October 2014
Date of Amendment 1:	24 February 2015
Date of Amendment 2:	28 April 2016
Date of Amendment 3:	06 November 2017

PROTOCOL APPROVAL PAGE

Protocol Title: A Phase 3, Randomized, Multicenter, Double-Blind, Placebo-Controlled, 2-Arm, Efficacy and Safety Study of NEOD001 Plus Standard of Care vs. Placebo Plus Standard of Care in Subjects with Light Chain (AL) Amyloidosis

Protocol Number: NEOD001-CL002

Date of Original Protocol: 23 October 2014

Date of Amendment 1: 24 February 2015

Date of Amendment 2: 28 April 2016

Date of Amendment 3: 06 November 2017

Declaration of Sponsor

This clinical study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the study drug, as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki and the guidelines on Good Clinical Practices applicable to this clinical study.

This protocol has been approved by Prothena. The following person is authorized on behalf of Prothena to approve this protocol and the signature below documents this approval.

[redacted] [redacted]

Chief Medical Officer Date

INVESTIGATOR SIGNATURE PAGE

Protocol Title: A Phase 3, Randomized, Multicenter, Double-Blind, Placebo-Controlled, 2-Arm, Efficacy and Safety Study of NEOD001 Plus Standard of Care vs. Placebo Plus Standard of Care in Subjects with Light Chain (AL) Amyloidosis

Protocol Number: NEOD001-CL002

Date of Original Protocol: 23 October 2014

Date of Amendment 1: 24 February 2015

Date of Amendment 2: 28 April 2016

Date of Amendment 3: 06 November 2017

I have read the foregoing protocol and agree to conduct this study in accordance with the current protocol.

Investigator Signature	Date

Investigator Name (Print)

Please **sign, date, and return** this form to Prothena or its designee. Contact details will be provided to the Investigator. Please retain a copy for your study files.

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PROTOCOL SYNOPSIS

Title	A Phase 3, Randomized, Multicenter, Double-Blind, Placebo-Controlled, 2-Arm, Efficacy and Safety Study of NEOD001 Plus Standard of Care vs. Placebo Plus Standard of Care in Subjects with Light Chain (AL) Amyloidosis
Study Phase	Phase 3
Indication	NEOD001 is indicated for the treatment of patients with AL amyloidosis.
Primary Objective	To evaluate the efficacy of NEOD001 plus standard of care vs. placebo plus standard of care when administered intravenously in subjects with AL amyloidosis by assessing time to all-cause mortality or cardiac hospitalization.
Key Secondary Objectives	To evaluate NEOD001 plus standard of care compared to placebo plus standard of care on the following: • Change from baseline in health-related quality of life using the Short Form-36 questionnaire (SF-36v2) • Change from baseline in cardiac functional response using the 6-Minute Walk Test (6MWT) • Cardiac best response rate as assessed by N-terminal pro-brain natriuretic peptide (NT-proBNP; Appendix 1)
Additional Secondary Objectives	To evaluate NEOD001 plus standard of care compared to placebo plus standard of care in the organ-specific populations below. In addition, the safety and tolerability of NEOD001 plus standard of care will be evaluated. • Renal best response rate using established criteria (Appendix 1) in subjects with renal involvement at baseline • Change from baseline in peripheral neurological function using the Neuropathy Impairment Score – Lower Limbs (NIS-LL; Appendix 10) in subjects with peripheral neuropathy involvement at baseline • Hepatic best response rate according to consensus criteria (Appendix 1) in subjects with hepatic involvement at baseline
Exploratory Objectives	To evaluate NEOD001 plus standard of care compared to placebo plus standard of care on other cardiac, renal, peripheral neuropathy, hepatic, and disease-related clinical outcome measures.

Study Design	This is a multicenter, international, randomized, double-blind, placebo-controlled, two-arm efficacy and safety study in subjects with AL amyloidosis. Newly diagnosed subjects with AL amyloidosis will be randomized in a 1:1 ratio to NEOD001 or placebo. Subjects will be stratified at randomization based on three factors: • Mayo Clinic Stage (Appendix 2): Stages I and II vs. Stages III and IV • Renal Stage (Appendix 2): Stage I vs. Stages II and III • 6MWT distance: < 300 meters vs. ≥ 300 meters Subjects will remain on study until study completion, which will occur when approximately 156 primary endpoint events (all-cause mortality or cardiac hospitalizations as adjudicated by the Clinical Events Committee [CEC]) have been reached. If the subject discontinues study drug prior to the end of the study but is willing to continue to participate in study visits, the subject should have an Early Treatment Discontinuation (ETD) Visit within 28-35 days after the last study drug administration (per Table 1 and Section 7.1.6) and then have assessments every third month per Appendix 3. ***The most important visit is the Month 9-Day 1 Visit, so if a subject is unwilling to continue visits every third month, every effort should be made for the subject to return and complete the Month 9-Day 1 Visit on schedule.*** All visits after the ETD Visit should occur on schedule, that is, at the time when the visit would have occurred had the subject remained on study drug. New SAEs occurring beyond the EOT/ETD Visit or >28 days after the last administration of study drug, whichever is later, will be reported to the Sponsor or its designee only if, in the judgment of the Investigator, the SAE is associated with any protocol intervention (i.e., related to study procedure or previous study drug exposure). Follow-up phone calls should be made to randomized subjects (or their caregivers) who received a dose of study drug and are no longer receiving study drug every 3 months, beginning approximately 3 months from the subject's last visit. The subject's health status, as well as details of any hospitalizations will be collected accordingly in the study database to ensure adequate capture of primary endpoint events.

	At the time of study completion (i.e., once approximately 156 events have been reached), all subjects still on study (i.e., subjects still receiving study drug [NEOD001 or placebo] treatment, subjects who discontinue study drug early but agree to return for assessments after the ETD Visit, and subjects participating in the vital status phone call follow up) may be considered for entry into a separate open-label extension study of NEOD001.
Outline of Procedures	Subject screening will occur during the 28 days prior to the first administration of study drug on Month 1-Day 1. The Screening period may be extended upon approval by the Medical Monitor. Screening assessments are listed in Table 1. Individual test results that do not meet eligibility requirements may be repeated, with the exception of 6MWT; full rescreening is allowed once per subject. Two Screening 6MWTs are required before the first administration of study drug. The first Screening 6MWT is required to be performed between Days -28 and -5, at least 4 days ***prior*** to the second Screening 6MWT, which should be performed within 2 days ***prior*** to Month 1-Day 1. The postbaseline 6MWTs may be performed on the same day as study drug administration, if the 6MWT is completed before initiation of the study drug infusion. If all eligibility requirements are met, the subject will be randomized, Month 1-Day 1 assessments will be completed, and treatment will be initiated. Each visit will be denoted by its "month" and "day" such that the first study drug (NEOD001 or placebo) infusion day is denoted as Month 1-Day 1; subsequent months will use sequential numbers (e.g., the second dose is administered on Month 2-Day 1). "Cycle" is reserved to denote administration of chemotherapy. Assessment and visit windows are described in the Schedule of Events (Table 1). Each month, subjects will receive their study drug infusion on Day 1 at the study site. For Months 1 through 3, subjects will be assessed weekly, although not all visits are required to be at the study site. For Month 3 and all subsequent months until the end of the study, subjects will only be required to return to the study site every 28 days for Day 1 dosing of study drug. First-line chemotherapy must be a bortezomib-containing regimen, with bortezomib administered subcutaneously

	(SC), weekly. The first administration of chemotherapy, including bortezomib, will be administered after Month 1-Day 1 study drug administration (following the post-study drug infusion observation period) such that Month 1-Day 1 of the study will be equivalent to Cycle 1-Day 1 of chemotherapy. In addition to the visits outlined above, during the first cycle of chemotherapy, the subject must return to the study site for each weekly administration of bortezomib and for assessments prior to the administrations. During the second and third cycles of chemotherapy, bortezomib must be administered at the study site during the Month 2-Day 1, Month 2-Day 15, and Month 3-Day 1 visits (i.e., Cycle 2-Day 1, Cycle 2-Day 15, and Cycle 3-Day 1, respectively). If, for any reason in the opinion of the Investigator, the subject should continue to be seen weekly at the study site (e.g., toxicity that appears to exceed the anticipated side effects of the chemotherapy), then the other Cycle 2 and Cycle 3 weekly bortezomib administrations may be performed at the study site, as well. At the Investigator's discretion, if the subject is not experiencing any unanticipated or significant toxicity, the subject may be administered the Cycle 2-Days 8 and 22 and the Cycle 3-Days 8, 15 and 22 bortezomib by their local physician, rather than by the Investigator. Within 1 day prior to or on the day of each administration of bortezomib by the local physician, a Prothena-sponsored healthcare professional must administer the FACT-GOG NTX and obtain pre-dose vital signs and central laboratory samples. However, if bortezomib is administered on a Monday (or there is an intervening holiday), then it is acceptable for the Homecare visit to take place on the previous Friday. The number of cycles of first-line chemotherapy that is administered is at the discretion of the Investigator, and subsequent chemotherapy regimens may be prescribed as per standard of care at the Investigator's discretion. Details regarding commonly accepted treatment practice are provided in Section 6.5.3. In the event that bortezomib doses are missed, the chemotherapy cycles may become misaligned with the monthly study drug dosing. In this case, the weekly visits during Months 1 through 3 should continue as described above in order to closely monitor subjects' health during the initial months of concomitant chemotherapy. Throughout the study, monthly doses of study drug should

	not be delayed or skipped due to adjustments that are made to chemotherapy dosing. Safety and efficacy assessments will be performed at each visit as outlined in the Schedule of Events (Table 1). Autologous stem cell transplant (ASCT) is not allowed while on study.
Number of Sites and Subjects	This is a multicenter, international study in approximately 75 centers. Up to 260 subjects will be enrolled in the study, with approximately 130 subjects per arm.
Estimated Study Duration	This is an event-driven trial that will continue until approximately 156 primary endpoint events have occurred. All subjects who discontinue will be followed until the last event is adjudicated. The estimated overall study duration is approximately 42 months, including the enrollment and treatment periods.
Summary of Subject Eligibility Criteria	**Inclusion Criteria** (subjects must meet ***all*** of the following criteria): 1. Aged ≥ 18 years 2. Newly diagnosed and AL amyloidosis treatment naïve 3. Bone marrow demonstrating clonal plasma cells 4. Confirmed diagnosis of AL amyloidosis by the following: • Histochemical diagnosis of amyloidosis determined by polarizing light microscopy of green birefringent material in Congo red-stained tissue specimens **OR** characteristic electron microscopy appearance **AND** • Confirmatory immunohistochemistry **OR** mass spectroscopy of AL amyloidosis 5. Confirmed diagnosis of AL amyloidosis by mass spectrometry or immunoelectron microscopy of amyloid material in tissue biopsy if the subject meets any of the following: • Is black or African American • Is over 75 years of age with concurrent monoclonal gammopathy • Has a history of familial amyloidosis and has concurrent monoclonal gammopathy **OR**

	• If the subject meets any of the above 3 conditions and has echocardiographic evidence of amyloidosis, biopsy-proven amyloidosis with a monoclonal gammopathy and no tissue is available for mass spectrometry or immunoelectron microscopy, the subject must have gene sequencing consistent with transthyretin (TTR) wild type (e.g., no TTR mutation present) **AND** must score 0 in technetium-99m-3,3-diphosphono-1,2 propanodicarboxylic acid (^{99m}Tc-DPD; Rapezzi 2011), hydroxymethylenediphosphonate (^{99m}Tc-HMDP; Galat 2015), or pyrophosphate (^{99m}Tc-PYP; Bokhari 2013) scintigraphy 6. Cardiac involvement as defined by ***all*** of the following: • Past documented or presently noted clinical signs and symptoms supportive of a diagnosis of heart failure in the setting of a confirmed diagnosis of AL amyloidosis in the absence of an alternative explanation for heart failure • Either an endomyocardial biopsy demonstrating AL amyloidosis or an echocardiogram demonstrating a mean left ventricular wall thickness at diastole > 12 mm in the absence of other causes (e.g., severe hypertension, aortic stenosis), which would adequately explain the degree of wall thickening • NT-proBNP ≥ 650 pg/mL and ≤ 8500 pg/mL 7. Planned first-line chemotherapy contains bortezomib administered weekly and subcutaneously (SC) 8. Adequate bone marrow reserve, hepatic function, and renal function, as demonstrated by: • Absolute neutrophil count (ANC) ≥ 1.0×10^9/L • Platelet count ≥ 75×10^9/L • Hemoglobin ≥ 9 g/dL • Total bilirubin ≤ 2 times the upper limit of normal (× ULN) • Aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase (SGOT) ≤ 3 × ULN • Alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase (SGPT) ≤ 3 × ULN

	• Alkaline phosphatase (ALP) ≤ 5 × ULN (***except*** for subjects with hepatomegaly and isozymes specific to liver, rather than bone) • Estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73 m^2 as estimated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation 9. Seated systolic blood pressure 90-180 mmHg 10. Distance walked during each Screening 6MWT is ≥ 30 meters and ≤ 550 meters 11. Women of childbearing potential (WOCBP) must have two negative pregnancy tests during Screening, the second within 24 hours prior to the first administration of study drug, and must agree to use highly effective physician-approved contraception (Appendix 4) from Screening to 90 days following the last study drug administration 12. Male subjects must be surgically sterile or must agree to use highly effective physician-approved contraception (Appendix 4) from Screening to 90 days following the last study drug administration 13. Ability to understand and willingness to sign an informed consent form prior to initiation of any study procedures **Exclusion Criteria** (subjects must meet ***none*** of the following criteria): 1. Non-AL amyloidosis 2. NT-proBNP < 650 pg/mL or > 8,500 pg/mL 3. Meets the International Myeloma Working Group (IMWG) definition of Multiple Myeloma (Appendix 5) *Note that subjects who meet the IMWG definition of symptomatic multiple myeloma with signs and/or symptoms attributable only to associated amyloidosis are potentially eligible upon approval of the Sponsor. 4. Subject is eligible for ***and*** plans to undergo ASCT or organ transplant 5. Symptomatic orthostatic hypotension that in the medical judgment of the Investigator would interfere with subject's ability to safely receive treatment or complete study assessments

	6. Myocardial infarction, uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic (ECG) evidence of acute ischemia, within 6 months prior to the Month 1-Day 1 Visit 7. Severe valvular stenosis (e.g. aortic or mitral stenosis with a valve area <1.0 cm^2) or severe congenital heart disease 8. ECG evidence of acute ischemia or active conduction system abnormalities ***with the exception*** of any of the following: • First degree AV-block • Second degree AV-block Type 1 (Mobitz Type 1 / Wenckebach type) • Right or left bundle branch block • Atrial fibrillation with a controlled ventricular rate (uncontrolled [i.e., >110 bpm] ventricular rate is not allowed [determined by an average of three beats in Lead II or three representative beats if Lead II is not representative of the overall EKG]) 9. Peripheral neuropathy assessed as National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Grade 2 with pain, Grade 3, or Grade 4 10. Subject is receiving oral or IV antibiotics, antifungals or antivirals within 1 week of Month 1-Day 1 with the exception of prophylactic oral agents 11. Prior treatment with hematopoietic growth factors, transfusions of blood or blood products within 1 week of Month 1-Day 1 12. Prior radiotherapy within 4 weeks of Month 1-Day 1 13. Major surgery within 4 weeks of Month 1-Day 1 or planned major surgery during the study 14. Active malignancy ***with the exception*** of any of the following: • Adequately treated basal cell carcinoma, squamous cell carcinoma, or in situ cervical cancer • Adequately treated Stage I cancer from which the subject is currently in remission and has been in remission for 2 years

	• Low-risk prostate cancer with Gleason score < 7 and prostate-specific antigen < 10 mg/mL • Any other cancer from which the subject has been disease-free for ≥ 2 years 15. History of severe allergy to any of the components of NEOD001 such as histidine/L histidine hydrochloride monohydrate, trehalose dehydrate, or polysorbate 20 or history of Grade ≥ 3 infusion-related AEs or hypersensitivity to another monoclonal antibody, or known hypersensitivity to diphenhydramine (or an equivalent H1 antihistamine) or acetaminophen (or its equivalent, paracetamol) 16. Known or history of uncontrolled, active HIV, hepatitis B or hepatitis C infection 17. Prior treatment with plasma cell-directed chemotherapy, NEOD001, 11-1F4, anti-serum amyloid P antibody, doxycycline for amyloid, or other investigational treatment directed at amyloid 18. Treatment with another investigational agent within 30 days of Month 1-Day 1 19. Women who are pregnant or lactating 20. Any condition which could interfere with, or the treatment for which might interfere with, the conduct of the study or which would, in the opinion of the Investigator, unacceptably increase the subject's risk by participating in the study 21. Subject is under legal custodianship 22. History of epilepsy or seizure disorder ***with the exception of*** childhood febrile seizures 23. Waldenström's macroglobulinemia and/or immunoglobulin M (IgM) monoclonal gammopathy
Drug, Drug Dosage and Formulation	**Study Drug:** Study drug consists of NEOD001 (24 mg/kg) or placebo. The active study drug, NEOD001, is supplied as a sterile, lyophilized dosage form in a 20/25 mL vial containing 500 mg NEOD001. Each vial will be reconstituted with 9.6 mL sterile water for injection (WFI) to a concentration of 50 mg/mL resulting in a buffered, isotonic, preservative-free solution. Study drug will be administered once every 28 days as an initial 120 (±10)-minute IV infusion. If the subject tolerates

	the initial infusion, subsequent infusions may be administered over 60 (±10) minutes. The length of the infusion may be extended over a longer period of time if and when it is clinically indicated per Section 6.5.1. Every effort must be made to ensure doses are given 28 days from the previous dose. If logistic considerations intervene, a minimum of 21 days between doses is required. **Premedication:** All subjects will be premedicated for each dose of study drug with 25 mg diphenhydramine (or an equivalent dose of a H1 antihistamine) and 650 mg acetaminophen (or an equivalent paracetamol dose) within 30-90 minutes prior to study drug administration. **Standard of Care Chemotherapy:** All subjects will receive concomitant standard of care chemotherapy, which must include bortezomib administered subcutaneously on a weekly basis for the initial, first-line chemotherapy regimen. Subsequent chemotherapy regimens may be prescribed as per standard of care at the Investigator's discretion (see Section 6.5.3). Antiviral prophylaxis is required.
Control Group	Normal saline will be used as the placebo control.
Route of Administration (Study Drug)	Intravenous infusion
Primary Efficacy Endpoint	Time to all-cause mortality or cardiac hospitalization as adjudicated by the CEC
Key Secondary Efficacy Endpoints	• Change from baseline to Month 9 in the Physical Component Summary (PCS) score of the SF-36v2 • Change from baseline to Month 9 in the 6MWT distance (meters) • NT-proBNP (cardiac) best response from baseline through Month 9
Additional Secondary Efficacy Endpoints	• For renal evaluable subjects, renal best response from baseline through Month 9 • For peripheral neuropathy evaluable subjects, change from baseline to Month 9 in NIS-LL total score • For hepatic evaluable subjects, hepatic best response from baseline to Month 9

Exploratory Efficacy Endpoints	See Section 3.4.1.4 for a list of exploratory efficacy endpoints.
Safety Endpoints	• Safety as assessed by vital signs, 12-lead ECGs, routine laboratory assessments, frequency and severity of AEs, and immunogenicity
Statistical Considerations	*Analysis Populations* The Intent-to-Treat (ITT) Population will include all randomized subjects with AL amyloidosis who receive any amount of study drug (NEOD001 or placebo). The ITT Population will be the primary population used for efficacy analyses. The Safety Population will include all subjects with AL amyloidosis who receive any amount of study drug (NEOD001 or placebo). The Safety Population will be the primary population used for safety analyses. Efficacy Subset Populations: The Renal Evaluable Population will include subjects who had renal involvement (i.e., proteinuria >0.5 g/24 hours [measured by 24-hour urine total protein excretion]) at baseline and at least 1 postbaseline assessment of proteinuria. The Peripheral Neuropathy Evaluable Population will include subjects who had peripheral nerve involvement at baseline (only if the subject had ascending sensorimotor neuropathy at screening due to AL amyloidosis etiologies answered as yes) and had a baseline NIS-LL total score of 2 or greater and at least 1 postbaseline peripheral neuropathy assessment. The Hepatic Evaluable Population will include subjects who had hepatic involvement defined as one of the following: 1) >1.5 × ULN alkaline phosphatase at baseline and at least 1 postbaseline assessment of alkaline phosphatase or 2) baseline total liver size (i.e., craniocaudal dimension) >15 cm and at least 1 postbaseline assessment total liver size. **Efficacy Analyses** ***Primary Analysis*** - The primary endpoint is time to all-cause mortality or cardiac hospitalization as adjudicated by the CEC. For all-cause mortality, all deaths occurring after the first infusion of study drug (i.e., Study Day 1) through the study's last subject last visit (LSLV) will be included. Cardiac hospitalization occurring ≥91 days after a subject's first infusion of study drug through LSLV will be included. Each subject will be counted only once in the primary analysis,

	based on their first adjudicated occurrence of an endpoint event. The distribution of the primary endpoint in the two treatment groups will be summarized using the Kaplan-Meier method. The two treatment groups will be compared using a two-sided stratified (by the randomization stratification factors) log-rank test at the alpha=0.05 level of significance. Each component of the primary endpoint will be analyzed as well. ***Key Secondary Efficacy Analyses*** – If the primary analysis is statistically significant ($p<0.05$) in favor of NEOD001, the following key secondary endpoints will be analyzed using a fixed-sequence testing procedure in the order specified below to control the overall level of significance: • Change from baseline to Month 9 in the PCS score of the SF-36v2 • Change from baseline to Month 9 in the 6MWT distance (meters) • NT-proBNP (cardiac) best response from baseline through Month 9 For each of these endpoints, the treatment groups will be compared using a two-sided test at the alpha=0.05 level of significance. However, once a nonsignificant result ($p>0.05$) occurs, the results of all subsequent analyses will be considered nominal, descriptive, and exploratory rather than confirmatory. The SF-36v2 PCS score change from baseline at Month 9 will be analyzed using a restricted maximum likelihood (REML) based mixed-effect model for repeated measures (MMRM) model including fixed effects for randomization strata, treatment group, categorical time point, and the treatment group × time point interaction, and with the baseline value included as a covariate. The unstructured covariance model will be used. The 6MWT distance (meters) change from baseline at Month 9 will be analyzed using a rank analysis of covariance (ANCOVA) model including fixed effects for randomization strata and treatment group, with the ranked baseline value included as a covariate. The Hodges-Lehman estimate of the median treatment difference with associated 95% CI will be presented. The NT-proBNP (cardiac) best response rates in the 2 treatment groups will be compared using the Cochran-Mantel-Haenszel (CMH) test stratified by the randomization stratification factors.

	Additional Secondary Efficacy Analyses **-** For the Renal Evaluable Population, renal best response will be analyzed in the same manner described for NT-proBNP (cardiac) best response. For the Peripheral Neuropathy Evaluable Population, the change from baseline in NIS-LL total score will be analyzed in the same manner described for the SF-36v2 PCS score. For the Hepatic Evaluable Population, hepatic best response will be analyzed in the same manner described for NT-proBNP (cardiac) best response. ***Exploratory Efficacy Analyses*** - Endpoints that are defined as time-to-event variables will be analyzed in the same manner as the primary endpoint. Quantitative exploratory endpoints will be analyzed in the same manner as described for the SF-36v2 PCS score. Exploratory endpoints that are defined as proportions will be analyzed in the same manner described for NT-proBNP (cardiac) best response. All exploratory analyses will be carried out using two-sided tests at the alpha=0.05 level of significance. **Safety Analyses** Safety data, including AEs, and clinical laboratory observations will be summarized by treatment group using the Safety Population. ***Adverse Events*** - AEs will be coded using the Medical Dictionary of Regulatory Activities. Summary tables of treatment-emergent AEs (TEAEs) will be provided. The incidence of TEAEs will be tabulated by system organ class and preferred term for each treatment group, and by severity and relationship to treatment. Tables of TEAEs leading to study drug discontinuation and serious adverse events (SAEs) will be provided. ***Clinical Laboratory Evaluations*** - Descriptive statistics summarizing central laboratory data will be presented for all study visits. Changes from baseline to each study visit will also be summarized by treatment group. In addition, mean change from baseline will be summarized for the maximum and minimum post-treatment values and for the values at the EOT/ETD Visit. The number and percent of subjects with a lab value with CTCAE Grade ≥3 and the number and percent of subjects with a CTCAE shift of ≥2 grades will be presented. ***Additional Safety Analyses*** - Additional safety assessments include vital signs and ECGs. Descriptive statistics of the vital sign and ECG parameters will be presented by treatment group

	and study visit, as well as the change from baseline at each visit. **Pharmacokinetic Analyses** Serum NEOD001 concentrations and elapsed time from the preceding NEOD001 dose will be listed. Serum NEOD001 concentrations from this study will be pooled with data from similar samples from other NEOD001 studies in a population PK analysis. There will be no PK analyses for this protocol. **Immunogenicity** Serum anti-NEOD001 antibody titers will be listed and, if sufficient data exist, summarized by treatment group. Serum anti-NEOD001 antibody titers may be correlated with serum NEOD001 concentrations and select safety endpoints, if sufficient data exist. **Determination of Sample Size** For the endpoint of time to all-cause mortality or cardiac hospitalization, the assumed 18-month event rate in the control arm is 60%, based on Kumar 2012. The 18-month event rate in the active arm is assumed to be 42%, a relative reduction of 30%. These assumptions correspond to a hazard ratio of 0.594. For a two-arm study with 1:1 randomization, and based on the use of a two-sided test at the alpha=0.05 level of significance, a total of 156 events (both arms combined) are required for 90% power. The study is designed to have 90% power in accordance with common practice for the design of confirmatory trials. Assuming an accrual period of 24 months, and a treatment/follow-up period of 18 months (i.e., a total study duration of 42 months), a total sample size of approximately 236 subjects will be required to attain 156 events.
Data Monitoring Committee	An independent DMC will review data on a regular basis at selected intervals to ensure that NEOD001 is safe and well-tolerated. The guidelines for the DMC operations will be reported in a separate DMC Charter.
Clinical Events Committee	An independent CEC blinded to treatment groups, will provide independent central adjudication of deaths and hospitalizations. The members of this committee will not participate in the enrollment or treatment of subjects in this trial, nor will they participate in the DMC. The guidelines for

	the adjudication process will be reported in a separate Manual of Procedures.
Sponsor	Prothena Therapeutics Limited

Table 1: Schedule of Events

Assessments	Screening[1]		Month 1		Month 2		Month 3		Months 6, 9, 12, etc. (Every 3rd Month)	All Other Months	
	Day-28 to Day -1	Day -2 or Day -1	Day 1	Days 8, 15, 22 (±2)	Day 1 (±2)	Days 8[2], 15, 22[2] (±2)	Day 1 (±2)	Days 8[2], 15[2], 22[2] (±2)	Day 1 (±5)	Day 1 (±5)	EOT/ ETD[3]
Written Informed Consent	X										
Eligibility Review	X										
Medical History[4]	X										
Confirmation of AL Amyloidosis[5]	X										
SF-36v2 Health Survey[6]		X			X		X		X		X
KCCQ[6]		X			X		X		X		X
FACT-GOG NTX[6,7]	X	X	X	X	X	X	X	X	Per Section 7.4 & Table 2		X
Echocardiogram	X[8]								Every 6th mo[8]		X[8]
Liver Imaging (CT)	X[9]								Every 6th mo[10]	X[10]	X[10]
12-lead Triplicate ECG[11]	X		X		X		X		X	X	X
Complete PE[12]	X										X
Symptom-Directed PE[13]			X		X		X		X	X	
ECOG PS & NYHA Class	X		X		X		X		X	X	X
NIS-LL[14]	X		X		X		X		Per Section 7.4 & Table 2		X
VASPI[15]	X		X		X		X		Per Section 7.4 & Table 2		X
Local Laboratory											
Hematology & Chemistry[16]				X	X	X[17]	X	X[17]	X	X	
Serum Pregnancy (WOCBP)			X[18]		X		X		X	X	X[19]
Central Laboratory[20]											
Hematology & Chemistry	X	X		X	X	X	X	X	X	X	X
Amylase	X	X			X		X		X	X	X
Coagulation[21]		X			X		X		X	X	X
Complements C_3, C_4		X					X		X		X
Troponin T	X	X			X		X		X	X	X
NT-proBNP[22]	X	X			X		X		X	X	X

Assessments	Screening[1]		Month 1		Month 2		Month 3		Months 6, 9, 12, etc. (Every 3rd Month)	All Other Months	EOT/ ETD[3]
	Day-28 to Day -1	Day -2 or Day -1	Day 1	Days 8, 15, 22 (±2)	Day 1 (±2)	Days 8[2], 15, 22[2] (±2)	Day 1 (±2)	Days 8[2], 15[2], 22[2] (±2)	Day 1 (±5)	Day 1 (±5)	
Tryptase		X									
Serum Free Light Chains (sFLCs)	X	X			X		X		X	X	X
Serum Pregnancy (WOCBP)	X										X
Serum IFE/PEP[23]	X						X		X[24]	X[24]	X
Urinalysis	X	X			X		X		X	X	X
24-hour Urine Collection for:											
Urine Protein Excretion[25]	X	X					X		Odd months	Odd months	X
Urine IFE/PEP[23,25]	X						X		Odd months[26]	Odd months[26]	X
6-Minute Walk Test (6MWT)[22,27]	X[28]	X[28]					X		X		X
Bioanalytical Laboratory											
PK Samples[29]			X	Day 15	X		X	Day 8	X	X	X
Anti-NEOD001 Antibody Sample (pre-dose)			X		X		X		X	X	X
Archive Sample (pre-dose)[30]			X		X		X		X	X	X
Randomization			X								
Premedication Administration[31]			X		X		X		X	X	
Vital Signs[32]	X		X	X	X	X	X	X	X	X	X
Study Drug Infusion[33]			X		X		X		X	X	
Chemotherapy & Antiviral Prophylaxis[34]			X[35]	X[35]	X[35]	X[35,36]	X[35]	X[36]	X[35]	X[35]	
Adverse Event Assessment	X	X	X	X	X	X[17]	X	X[17]	X	X	X[37]
Concomitant Medications	X	X	X	X	X	X[17]	X	X[17]	X	X	X
Vital Status Phone Call											X[38]

ALP = alkaline phosphatase; BP = blood pressure; CT = computed tomography; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EOI = end of infusion; EOT = End of Treatment; ETD = Early Treatment Discontinuation; FACT-GOG NTX = Functional Assessment of Cancer Therapy – Gynecologic Oncology Group Neurotoxicity Subscale; HR = heart rate; IFE = immunofixation electrophoresis; KCCQ = Kansas City Cardiomyopathy Questionnaire; NGAL = neutrophil gelatinase-associated lipocalin; NIS-LL = Neuropathy Impairment Score – Lower Limbs; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; PE = physical exam; PEP = protein electrophoresis; PK = pharmacokinetic; RBP = retinol-binding protein; RR = respiratory rate; SC = subcutaneous; 6MWT = 6-minute walk test; SF-36v2 = Short Form-36 Version 2; ULN = upper limit of normal; VASPI = Visual Analog Scale – Pain Intensity; WOCBP = women of childbearing potential.

1. The 28-day Screening period may be extended upon approval by the Medical Monitor. Individual test results that do not meet eligibility requirements may be repeated, with the exception of 6MWT; full rescreening is allowed once per subject.
2. Cycle 2-Days 8 and 22 and Cycle 3-Days 8, 15 and 22 bortezomib-containing chemotherapy should be administered by the Investigator at the study site if subject had significant toxicity; otherwise, it may be administered by local physician at Investigator's discretion. See more detail in Footnote 35.
3. EOT/ETD Visit to occur 28-35 days after the last study drug administration.
4. Obtain comprehensive cardiac, hematologic, and oncologic medical history; additionally for all other conditions obtain relevant medical history for the past 5 years (including all major hospitalizations and surgeries), as well as the subject's current medical status.
5. Results from mass spectrometry tissue typing, immunoelectron microscopy, gene sequencing, and/or ^{99m}Tc scintigraphy must be obtained prior to randomization to assess eligibility for subjects identified in Inclusion Criterion #5.
6. At visits where one or more questionnaires are to be administered, the following order occurs prior to the performance of any other study assessments on the day they are administered: SF-36v2 (Appendix 7), KCCQ (Appendix 8), and FACT-GOG NTX (Appendix 9).
7. Administer the FACT-GOG NTX (Appendix 9) per Table 2.
8. If an echocardiogram has been conducted within 90 days prior to Screening Day -28, it does not need to be repeated during Screening and the previous result can be used for eligibility. After Screening, perform echocardiograms every 6 months within 10 days prior to Day 1; repeat at EOT/ETD if not performed within 60 days prior to visit. To be eligible for the additional cardiac imaging analysis, the subject must have had a 4-chamber view, 2-dimensional echocardiogram with Doppler.
9. Perform CT imaging of the abdomen for liver measurement for subjects with an ALP > 1.5 × ULN at Screening per Section 7.6 (*Exception*: not required in Germany). If CT imaging has been conducted within 60 days prior to Screening Day -28 and it meets acquisition guidelines, it does not need to be repeated during Screening and the previous result can be used for eligibility.
10. For subjects with liver involvement at Screening, perform *scheduled* repeat CT imaging of the abdomen for liver measurement every sixth month and *unscheduled* repeat CT imaging as needed per Section 7.6 (*Exception*: not required in Germany). Repeat at EOT/ETD as needed per Section 7.6.
11. ECG to be performed in triplicate as follows: **Month 1-Day 1:** within 30 minutes before dosing and 1 hour (±15 min) post-EOI; **All Other Visits:** within 30 minutes before dosing or any time on non-infusion days. Medications given for prophylaxis chemotherapy-induced side effects should not be administered prior to completion of the postinfusion ECG.
12. Complete PE includes height (Screening only), weight, and examination of the following: general appearance; head, ears, eyes, nose, and throat; neck; skin; cardiovascular system; respiratory system; gastrointestinal system; and nervous system. Assess macroglossia, submandibular nodes/fullness, adenopathy, ecchymoses, liver/spleen size (palpable +/-), ascites (+/-), and edema (which should be quantified on a scale of 0-4).
13. Symptom-directed PE should be as clinically indicated and also include weight, and assessment of macroglossia, submandibular nodes/fullness, adenopathy, ecchymoses, liver/spleen size (palpable +/-), ascites (+/-), and edema (which should be quantified on a scale of 0-4).
14. Administer NIS-LL (Appendix 10) per Table 2.
15. Administer VASPI (Appendix 11) per Table 2.
16. Local laboratory results for hematology and chemistry will be used for subject management and should be reviewed for safety assessment prior to administration of chemotherapy, but will not be collected in the electronic case report forms or the clinical database.
17. Perform only if subject returns to study site for this visit.
18. Use local lab for serum pregnancy test within 24 hours prior to Month 1-Day 1 study drug administration.
19. Obtain local laboratory serum pregnancy test 90 (±5) days after the last study drug administration.
20. Collect central laboratory samples before 6MWT, if being performed on the same day.
21. Collect PT/INR and PTT at each time point. At the second Screening visit, EOT/ETD visit, and as clinically indicated, citrated plasma samples may be collected for freezing and for potential analysis of coagulation indices at a later date; these analyses may include, but may not be limited to, the indices listed in Appendix 12.

22. NT-proBNP should be drawn before conducting 6MWT if being performed on the same calendar day.
23. The serum and urine PEP must be conducted before the NEOD001 infusion, if being performed on the same calendar day.
24. Perform serum IFE/PEP monthly. If a subject's first on-study hematologic complete response was assessed at the previous visit, perform serum IFE/PEP (and 24-hour urine IFE/PEP) at least 28 days after the initial assessment of response to confirm response.
25. The 24-hour urine protein excretion and 24-hour urine IFE/PEP tests will be performed using the same 24-hour urine collection sample when required at the same visit.
26. If a subject's first on-study hematologic complete response was assessed at the previous visit, perform 24-hour urine IFE/PEP (and serum IFE/PEP) at least 28 days after the initial assessment of response to confirm response. Repeat every odd-numbered month (to correspond with 24-hour urine protein excretion collection) to assess for continuing response or progression. If the initial response confirmation needs to occur on an even-numbered month, perform an additional 24-hour urine collection.
27. Subjects should plan to be able to return to the same clinical site for each 6MWT from first Screening through Month 9. The postbaseline 6MWT may be administered on the same calendar day that study drug is administered (i.e., Months 3, 6, 9, etc.) as long as the NT-proBNP sample is drawn before conducting the 6MWT and the 6MWT is completed before initiation of the study drug infusion. Collect BP and HR pre- and post-6MWT administration.
28. The first Screening 6MWT must be performed between Days -28 and -5, at least 4 days prior to the second Screening 6MWT, which should be performed within 2 days prior to the Month 1-Day 1 visit (i.e., on Day -2 or Day -1).
29. Collect PK samples **pre-dose** on study drug or chemotherapy dosing days, anytime during **EOT/ETD** Visit, and at these additional time points: **Month 1-Day 1**: EOI (+5 min), 0.5 hour (±5 min) post-EOI, and 1 hour (±10 min) post-EOI; **Month 2-Day 1**: EOI (+5 min), and 1 hour (±10 min) post-EOI; **Month 6-Day 1 and Month 12-Day 1**: EOI (+5 min), 0.5 hour (±5 min) post-EOI, and 1 hour (±10 min) post-EOI. Additional samples may be collected as clinically indicated, such as when significant toxicity occurs.
30. Archive serum samples will only be collected from those subjects who have consented to the collection and archiving of their samples for future correlative testing.
31. All subjects are to receive 25 mg diphenhydramine (or an equivalent dose of a H1 antihistamine) and 650 mg acetaminophen (or an equivalent paracetamol dose) within 30-90 minutes prior to the start of infusion.
32. Vital signs include BP, HR, RR, and temperature; assess in same position for all time points after the subject has been at rest for ≥5 minutes. Pre-dose assessments should be performed ***after*** administration of premedication. **Screening and non-infusion days:** any time; **Month 1-Day 1**: Within 30 minutes before dosing, halfway through infusion (i.e., approximately 60 minutes after the start of the infusion), immediately at EOI (+10 min), 0.5 hour (±10 min) post-EOI, and 1 hour (±10 min) post-EOI. **All Other Months-Day 1:** Within 30 minutes before dosing, EOI (+10 min), and 1 hour (±10 min) post-EOI.
33. Administer per Section 6.5.1. Subjects should be closely monitored for 90 (±10) minutes following completion of the study drug infusion. The Investigator may increase this standard monitoring time if deemed appropriate or per local standards. In the event of any clinical concerns or suspicious signs or symptoms after the infusion, the subject will remain under observation for as long as the Investigator deems it appropriate.
34. First-line chemotherapy must be a bortezomib-containing regimen, with bortezomib administered weekly, SC, according to the approved prescribing information and local institutional practices. Antiviral prophylaxis is required. When chemotherapy is administered on same day as study drug, the chemotherapy must be administered **AFTER** the post-study drug infusion observation period. Number of first-line chemotherapy cycles and subsequent chemotherapy regimens will be administered per standard of care at the Investigator's discretion.
35. Bortezomib must be administered at the study site for Cycle 1-Days 1, 8, 15, and 22; Cycle 2-Days 1 and 15; and on Day 1 of subsequent cycles, after review of local labs, study drug administration, and the post-study drug infusion observation period.
36. Cycle 2-Days 8 and 22, and Cycle 3-Days 8, 15, and 22 chemotherapy may be administered by local physician with a Homecare visit by a Prothena-sponsored healthcare professional to the subject within 1 day prior to or pre-dose on the day of each bortezomib administration to administer FACT-GOG NTX, and to obtain vital signs, blood samples for central laboratory testing, and bioanalytical samples (if applicable). If bortezomib is administered on a Monday, the Homecare visit may occur on the previous Friday. If significant toxicity occurs during Cycle 1, subject should return to the study site for Cycle 2 and Cycle 3 visits until Investigator deems it appropriate for local administration.
37. New SAEs occurring beyond the EOT/ETD Visit or >28 days after the last administration of study drug, whichever is later, will be reported to the Sponsor or its designee only if, in the judgement of the Investigator, the SAE is associated with any protocol intervention (i.e., related to study procedure or previous study drug exposure).
38. For all subjects who are randomized and received a dose of study drug: Conduct vital status phone call per Section 7.1.8 approximately 3 months after the subject's last visit and approximately every 3 months thereafter.

GLOSSARY OF TERMS

Abbreviation/Acronym	Definition
AA	Amyloid A
ADA(s)	Anti-drug antibody(ies)
ADL	Activities of Daily Living
AE(s)	Adverse event(s)
AEF	Amyloid-enhancing factor
AL	Amyloid light chain
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ASCT	Autologous stem cell transplant
AST	Aspartate aminotransferase
BP	Blood pressure
BSA	Bovine serum albumin
BUN	Blood urea nitrogen
CBC	Complete blood count
CEC	Clinical Events Committee (previously referred to as the Clinical Adjudication Committee [CAC])
CFR	Code of Federal Regulations
CR	Complete response
CT	Computerized tomography
D	Aspartic acid
dFLC	Difference between involved and uninvolved free light chain
DMC	Data Monitoring Committee
E	Glutamic acid
EC	Ethics Committee
ECG	Electrocardiogram
ECL	Electrochemiluminescent

Abbreviation/Acronym	Definition
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EOI	End of Infusion
EOT	End of Treatment
ETD	Early Treatment Discontinuation
EU	European Union
FACT-GOG NTX	Functional Assessment of Cancer Therapy – Gynecologic Oncology Group Neurotoxicity Subscale
FDA	Food and Drug Administration
GCP	Good Clinical Practice
Hct	Hematocrit
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
HR	Heart rate
ICF	Informed consent form
ICH	International Conference on Harmonisation
IFE	Immunofixation electrophoresis
IgG1	Immunoglobulin G1
IL-6	Interleukin-6
IMWG	International Myeloma Working Group
INR	International normalized ratio
IRB	Institutional Review Board
ITT	Intent to Treat
IV	Intravenous
IXRS	Interactive Voice and Web Response System

Abbreviation/Acronym	Definition
KCCQ	Kansas City Cardiomyopathy Questionnaire
LDH	Lactate dehydrogenase
LSLV	Last subject last visit
MMRM	Mixed-effect model for repeated measures
N	Number of observations
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGAL	Neutrophil gelatinase-associated lipocalin
NOAEL	No-observable-adverse-effect-level
NR	No response
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
PCD	Plasma cell dyscrasia
PCS	Physical Component Summary
PE	Physical examination
PEP	Protein electrophoresis
PK	Pharmacokinetic(s)
PN	Peripheral neuropathy
PR	Partial response
PS	Performance status
PT	Prothrombin time
PTT	Partial thromboplastin time
RBP	Retinol-binding protein
REML	Restricted maximum likelihood
RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous(ly)

Abbreviation/Acronym	Definition
sFLC	Serum-free light chain
SF-36v2	Short Form-36 questionnaire Version 2
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
6MWT	6-Minute Walk Test
TEAE(s)	Treatment emergent adverse event(s)
TRIAD	Transgenic Rapidly Inducible Amyloid Disease
ULN	Upper limit of normal
US	United States
USP	United States Pharmacopeial Convention
VGPR	Very good partial response
WFI	Water for Injection
WOCBP	Women of childbearing potential

1 INTRODUCTION

1.1 Light Chain (AL) Amyloidosis

Systemic amyloidoses are a complex group of diseases caused by tissue deposition of misfolded proteins that result in progressive organ damage. The most common type, light chain (AL) amyloidosis or primary systemic amyloidosis, involves a hematologic disorder caused by clonal plasma cells that produce misfolded immunoglobulin light chains. Overproduction of misfolded light chains by plasma cells results in both soluble, aggregated forms of light chains and insoluble, fibrillar deposits of abnormal AL protein (amyloid), in the tissues and organs of individuals with AL amyloidosis. Clinical features of AL amyloidosis include a constellation of symptoms and organ dysfunction including cardiac, renal, and hepatic dysfunction, gastrointestinal involvement, neuropathy, and macroglossia. The mechanisms by which amyloidogenic immunoglobulin light chains result in organ dysfunction are not well characterized, however, it is hypothesized that both amyloid deposits and prefibrillar aggregates may contribute to cytotoxic effects on organs observed in patients with AL amyloidosis.

AL amyloidosis is a rare disorder. Although the exact incidence of AL amyloidosis in the United States (US) is unknown, a weighted average from 5 sources (Kyle 1992) (Kyle 2002) (Kyle 2006) (Simms 1994) (Junicon Study) estimates the incidence to be 7.6 new cases per million population per year, which is approximately 2,300 new cases per year. By comparison, the estimated minimum incidence of systemic amyloidosis in England in 2008 was calculated to be 0.4/100,000 based on new referrals to the National Amyloidosis Centre with a peaked incidence at age 60-79 years. However, other data suggest that the incidence of systemic amyloidosis in England exceeds 0.8/100,000 (8 cases per million) of the population (Pinney 2013), which is similar to estimates from other countries. With an estimated total population of 63.7 million, the overall incidence of systemic amyloidosis in England may be approximately 500 per year.

Approximately, three-fourths of AL amyloidosis patients present with one or two major organ systems involved (e.g., cardiac, renal, gastrointestinal tract, hepatic, autonomic nervous system, peripheral nervous system, soft tissues) while a quarter of patients present with more than two systems involved (Palladini 2005) (Gertz 2010). AL amyloidosis is most commonly associated with cardiac and/or renal dysfunction, with overt restrictive cardiomyopathy observed in approximately 50% of all cases, and subclinical cardiac involvement detected in almost every case at autopsy or on endomyocardial biopsy (Falk 2010).

AL amyloidosis has two important disease components. The first component is the plasma cell dyscrasia (PCD), which results in the overproduction of immunoglobulin light chain, and the second component is the impact of the soluble and insoluble amyloid on organ structure and function, leading to the clinical manifestations of the disease. While there are currently no approved treatments for AL amyloidosis, the current standard of care for these patients is aimed at reducing or eliminating the bone marrow disorder, the PCD. The most aggressive treatment options include autologous stem cell transplant (ASCT) and high-dose chemotherapy for those patients who can tolerate it. Other treatment regimens include combinations of drugs often used to treat hematological malignancies including melphalan, prednisone, dexamethasone and proteasome inhibitors (e.g., bortezomib), in an attempt to reduce light chain production. There

are no currently approved treatments for AL amyloidosis, and none that directly target potentially toxic forms of the amyloidogenic proteins.

1.2 Rationale for Clinical Study

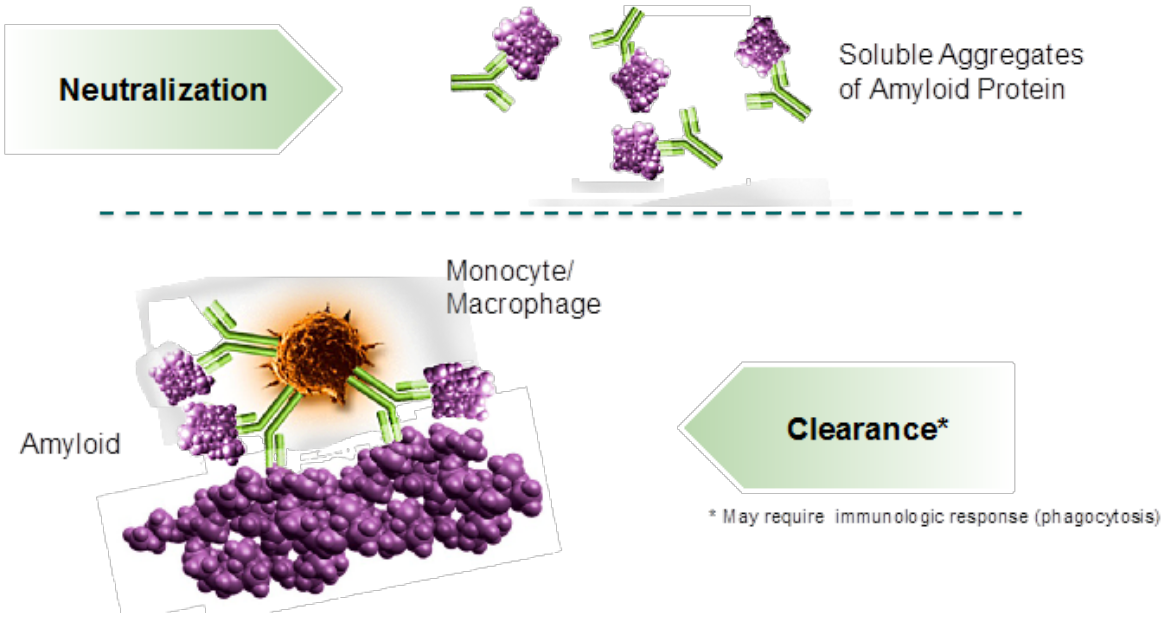
Unlike other hematologic disorders such as multiple myeloma, the morbidity and mortality of AL amyloidosis is almost entirely related to organ dysfunction and not hematologic parameters. One of the major determinants of prognostic outcome in AL amyloidosis patients is the extent of cardiac involvement; 75% of the deaths are due to cardiac amyloidosis (Merlini 2011). The process of amyloid formation results in cellular injury, tissue damage, and organ dysfunction through mechanisms that are not completely understood. Because the current available treatment options are limited to treatment for the PCD component of the disease, the rate of organ function improvement or stabilization ("organ response") after achieving hematologic response from chemotherapy regimens is highly variable, ranging from 25% to 78% based on published information (Michael 2010) (Cibeira 2011) (Cohen 2007). Furthermore, the incidence of treatment-related mortality following high dose melphalan and ASCT was 13% within the first 100 days in patients with AL amyloidosis (Skinner 2004) and with the greatest mortality in patients with cardiac involvement. Though the ASCT approach is effective and results in rapid hematologic response, the average treatment related mortality in four single-center studies ranged from 21% to 39% (Falk 2010). Therefore, there is an urgent need to develop a treatment that can directly target the misfolded proteins to increase their clearance and to alleviate direct organ toxicity. Treatments that reduce or eliminate PCD in conjunction with treatments that target toxic soluble aggregates and insoluble amyloid may be of great clinical benefit in the treatment of AL amyloidosis.

1.3 Background on NEOD001

Prothena Therapeutics Limited (Prothena) is developing NEOD001, a humanized immunoglobulin G1 (IgG1), kappa version of 2A4, the parent murine monoclonal antibody, which is directed against a cryptic epitope on amyloid fibrils. NE0D001 specifically targets misfolded light chain aggregates and amyloid deposits. Nonclinical studies to date suggest little cross-reactivity of the antibody with normal immunoglobulins of the immune system. NEOD001, administered by intravenous (IV) infusion, is proposed for use to target the misfolded light chain protein in subjects with AL amyloidosis. (Refer to the Investigator's Brochure for detailed NEOD001 nonclinical and clinical information.)

The proposed mechanism of action for NEOD001 is thought to be two-pronged (Figure 1). First, is the direct interaction of NEOD001 with soluble aggregates resulting in the neutralization of the soluble, toxic aggregated moieties. The second is clearing the insoluble toxic amyloid deposited in organs/tissues. Here, it is believed that NEOD001 attaches to the amyloid deposits and the intact Fc portion of NEOD001 signals monocytes/macrophages to the area; and via phagocytosis, clearance of the insoluble, toxic deposits occurs (e.g., opsonization of the deposited amyloid). It is believed that both mechanisms may contribute to potential clinical benefit.

Figure 1: Proposed Mechanism of Action for NEOD001



Since NEOD001 and 2A4 recognize a conserved epitope in both the AL and amyloid A (AA) proteins, nonclinical efficacy was evaluated in mouse models of both systemic serum AA amyloidosis (H2/hIL-6 Transgenic Rapidly Inducible Amyloid Disease [TRIAD] mouse model) and AL (amyloidoma xenograft model) using the parent murine monoclonal antibody, 2A4. In the AL xenograft model, treatment with ~5 mg/kg of 2A4 subcutaneously (SC), 3 times a week resulted in a statistically significant reduction in the size of the amyloidomas that were formed (by weight and volume). Efficacy studies in the TRIAD mouse model at the same dose demonstrated improvements in survival and, in some experiments, reductions in amyloid load. A single experiment using high doses of 2A4 (40 mg/kg) at either 1 week after disease induction vs. 3 weeks after disease induction (when organ amyloid burden is well established) generated conflicting results; with increased organ amyloid burden in the early treatment arm, but decreased organ amyloid burden in the late treatment arm. At this time, no explanation for these differences has been found.

The pharmacokinetic (PK) parameters of NEOD001 as determined in the cynomolgus monkey were typical of humanized monoclonal antibodies within this species, with a terminal elimination half-life of 12-20 days and a clearance of 0.150 to 0.179 mL/h/kg. However, the target of NEOD001 is absent in the monkey. Pharmacokinetics in the TRIAD mouse where large amounts of amyloid target are available demonstrated rapid binding of the antibody to its target in amyloid burdened organs with resultant loss of antibody from the circulating blood pool, initially. Available evidence indicates that this is a saturable phenomenon. The PK of second or later administrations may, therefore, not exhibit the same profile, particularly for the early distribution phase, until this saturation is achieved.

Imaging, autoradiography, and biodistribution studies demonstrated specific binding of NEOD001 and 2A4 to their amyloid target in the TRIAD and AL xenograft models. No evidence has been found that would indicate relevant off-target binding of NEOD001 (e.g., to endogenous parent proteins of the amyloid), consistent with the results of the human tissue cross-reactivity study with NEOD001 discussed below.

1.3.1 Nonclinical Safety

Nonclinical safety was evaluated in the cynomolgus monkey, the TRIAD mouse model, and an *in vitro* study examining binding to human tissue.

Cynomolgus monkey: Important amino acid contributions to the epitope in AL amyloidosis are glutamic acid (E) and aspartic acid (D) at positions 81 and 82, respectively, on IgG light chain and these are conserved in this species; i.e., the incidence of E and D at these positions is > 90% in both cynomolgus monkey and human. Though the aspartic acid is buried in the normally folded light chain, if physiologic conditions arise that result in the revealing of this epitope, or if there is binding to similar epitopes on other proteins, then the consequence would be evaluable in this species.

In a 28-day, weekly IV dose study of NEOD001 in cynomolgus monkeys with a 28-day dose-free period for control and high dose animals, treatment was well-tolerated at all dose levels (10, 50, and 100 mg/kg/week). There were no NEOD001-related changes in any of the study parameters evaluated and thus the no-observable-adverse-effect-level (NOAEL) for NEOD001

in this species was 100 mg/kg. Serum levels of NEOD001 were maintained throughout the treatment period. The data suggest a low risk of off-target toxicity.

H2/hIL-6 TRIAD mice: The TRIAD mouse model of AA amyloidosis has limitations relative to safety assessment for AL amyloidosis; e.g., 1) this transgenic model overexpresses human interleukin-6 (IL-6), creating a proinflammatory baseline state that is important for disease progression but can confound safety evaluation, 2) the disease state is also promoted by injection with an amyloid extract, called amyloid enhancing factor (AEF), intended to seed tissue with amyloid, and 3) it involves an amyloid protein (AA) that is different than the one targeted in this population (AL), despite the fact that 2A4 recognizes both proteins. However, this model contributes to the safety assessment of NEOD001 as it is the only nonclinical model available that offers the ability to assess the potential hazards of antibody binding to amyloid embedded in various vital organs, primarily liver, spleen, and kidney. The murine homologue of NEOD001, 2A4, maintains full effector function and was used in these studies.

Two TRIAD mouse studies were used in the nonclinical safety assessment: a 22-day toxicity study by the IV route of administration and a 28-day toxicity study by IV and SC routes of administration. In addition, a 22-day special immunogenicity/toxicity study in H2/hIL-6 mice (no AEF) was conducted to compare 2A4 against the immunogenic potential of an unrelated protein, bovine serum albumin (BSA). These are detailed in the Investigator's Brochure and the key points are summarized below.

As intended for this disease model, the TRIAD mouse has background pathology. Appropriate controls demonstrated the effect of the IL-6 transgene (plasmacytosis in spleen, thrombus formation in mesenteric vessels) and the effect of the IL-6 transgene with AEF added (amyloid deposition in kidney, liver, spleen, and other tissues; inflammatory infiltrates in the heart; and renal pathology, including tubular degenerative changes and papillary necrosis). Importantly, no additional pathology was observed that was attributable to 2A4 treatment at the doses studied, 4 and 40 mg/kg/week.

In both toxicity studies, mortality was observed acutely following the third weekly dose (Study Day 15) when 2A4 was administered by bolus IV administration. No pathology was present to indicate mechanism of the cause of death. The timing of the adverse reaction being within minutes to hours of the third weekly dose, and the presence of anti-drug antibodies (ADAs), suggest that the effect is an ADA-mediated phenomenon in this model. In animals that survived, there were no adverse effects described surrounding deposited amyloid, or in other tissues. ADA reactions in animal species are not predictive of human responses and therefore these effects are not considered to contribute to human risk assessment (Bugelski 2004) (Pimm 1992). Additionally, while it is possible that ADAs might develop, it is not known whether or not this would be associated with any clinical significance.

A special immunogenicity/toxicity study was conducted to explore whether the mortality observed following IV dosing of 2A4 in the TRIAD mouse can be observed with an unrelated, but immunogenic, protein. Nontransgenic/wild-type mice and H2/hIL-6 transgenic mice (no AEF administered) were treated once weekly by IV administration with 2A4 at 4 mg/kg. The nontransgenic mice showed no systemic effects; however, the IL-6 overproducing mice developed profound signs (decreased motor activity, hunched posture, ataxia, cold to touch)

immediately after dosing on Days 15 and 22, replicating what was observed in the TRIAD mouse safety studies above. Mortality and moribundity occurred post-dosing on Day 22. Another group of H2/hIL-6 transgenic mice was treated once weekly by IV administration with BSA at 50 mg/kg. A similar clinical course occurred although signs began one week earlier; i.e. after dosing on Day 8 (the second dose). Again, mortality was observed in some animals after dosing on Day 22. This study demonstrates the importance of elevated IL-6 in the morbidity and mortality observed in this model and further demonstrates that the mortality is not unique to 2A4 but can be seen with other proteins that are immunogenic in this mouse model.

Human tissue cross-reactivity: In a human tissue cross-reactivity study of NEOD001 designed to examine potential off-target effects, a limited number of tissues demonstrated any binding. Cytoplasmic staining was observed in the heart, kidney, pancreas, pituitary, and testis. Cytoplasmic staining is generally not considered to be relevant to IV dosing as these sites are not accessible to the administered antibody. Rare to occasional, mild-intensity membrane staining was observed on ductular and tubular epithelial cells of the pancreas and testis, respectively. No pathologic changes were observed in these organs in the repeat-dose studies suggesting limited safety liabilities from potential binding in these tissues. Overall, these data confirm the prediction of a low potential for binding of NEOD001 to normal tissue.

In summary, the available nonclinical data support clinical development of NEOD001 for the treatment of AL amyloidosis. No target organ toxicity has been described. Based on available models, there are limitations on the ability to assess the interaction of NEOD001 with deposited or soluble AL amyloid. The investigations in an AA amyloidosis model (the TRIAD mouse) provide some reassurance that binding of 2A4, an antibody with full effector function, does not appear to adversely react with deposited amyloid in tissue. Nevertheless, monitoring for changes in disease pathology, as would typically be performed in clinical development, is warranted.

1.3.2 Clinical Experience

The safety and tolerability of NEOD001 are being investigated in an ongoing, open-label, dose escalation Phase 1/2 study (Study NEOD001-001) of the IV administration of single-agent NEOD001 in subjects with AL amyloidosis in the US. Further details can be found in the latest edition of the NEOD001 Investigator's Brochure.

As of an interim analysis with a data cutoff date of 30 September 2015, 27 subjects were enrolled and treated in the Escalation Phase of the study and 42 subjects were enrolled and treated in the Expansion Phase.

As of the data cutoff, the most frequently reported TEAEs overall in Study NEOD001-001 (occurring in ≥ 10% of subjects [N=69], regardless of relationship to NEOD001) were fatigue, upper respiratory tract infection, diarrhea, nausea, edema, anemia, cough, increased blood creatinine, headache, peripheral edema, and rash. No dose limiting toxicities (DLTs) or related SAEs have been reported. No systemic hypersensitivity reactions have been reported and there have been no clinically significant changes solely attributable to NEOD001 in clinical laboratory determinations, vital signs, electrocardiogram (ECG) changes, or physical exams.

Based on the data available to date, NEOD001 is safe and well-tolerated in subjects with AL amyloidosis and no clinically significant safety signals have been identified.

1.4 Rationale for Dose Selection

The majority of subjects with AL amyloidosis present late in the course of their disease with significant organ involvement, especially subjects with cardiac involvement. The amyloid burden in each individual subject cannot be determined at baseline and may vary significantly. With cardiac involvement, the amyloid burden remains significant and there is an urgency to treat cardiac subjects as quickly as possible in an attempt to reduce or reverse the significant cardiac morbidity and mortality associated with cardiac AL amyloidosis. Therefore, administering the safest, highest tolerated dose is recommended. The highest dose tested in the Phase 1/2 study was 24.0 mg/kg, which was deemed to be safe and well-tolerated.

2 OBJECTIVES

2.1 Primary Objective

To evaluate the efficacy of NEOD001 plus standard of care vs. placebo plus standard of care when administered intravenously in subjects with AL amyloidosis by assessing time to all-cause mortality or cardiac hospitalization.

2.2 Key Secondary Objectives

To evaluate NEOD001 plus standard of care compared to placebo plus standard of care on the following:

- Change from baseline in health-related quality of life using the Short Form-36 questionnaire (SF-36v2)
- Change from baseline in cardiac functional response using the 6-Minute Walk Test (6MWT)
- Cardiac best response rate as assessed by N-terminal pro-brain natriuretic peptide (NT-proBNP) (Appendix 1)

2.3 Additional Secondary Objectives

To evaluate NEOD001 plus standard of care compared to placebo plus standard of care in the organ-specific populations below. In addition, the safety and tolerability of NEOD001 plus standard of care will be evaluated.

- Renal best response rate using established criteria (Appendix 1) in subjects with renal involvement at baseline
- Change from baseline in peripheral neurological function using the Neuropathy Impairment Score – Lower Limbs (NIS-LL; Appendix 10) in subjects with peripheral neuropathy involvement at baseline
- Hepatic best response rate according to consensus criteria (Appendix 1) in subjects with hepatic involvement at baseline

2.4 Exploratory Objectives

To evaluate NEOD001 plus standard of care compared to placebo plus standard of care on other cardiac, renal, peripheral neuropathy, hepatic, and disease-related clinical outcome measures.

3 STUDY PLAN

3.1 Study Design

This is a multicenter, international, randomized, double-blind, placebo-controlled, two-arm efficacy and safety study in subjects with AL amyloidosis.

Newly diagnosed subjects with AL amyloidosis will be randomized in a 1:1 ratio to NEOD001 or placebo. Subjects will be stratified at randomization based on three factors:

- Mayo Clinic Stage (Appendix 2): Stages I and II vs. Stages III and IV
- Renal Stage (Appendix 2): Stage I vs. Stages II and III
- 6MWT distance: < 300 meters vs. ≥ 300 meters

Subjects will remain on study until study completion, which will occur when approximately 156 primary endpoint events (all-cause mortality or cardiac hospitalizations as adjudicated by the CEC) have been reached.

Each visit will be denoted by its "month" and "day" such that the first study drug (NEOD001 or placebo) infusion day is denoted as Month 1-Day 1; subsequent months will use sequential numbers (e.g., the second dose is administered on Month 2-Day 1). "Cycle" is reserved to denote administration of chemotherapy. Assessment and visit windows are described in the Schedule of Events (Table 1).

If the subject discontinues study drug prior to the end of the study, but is willing to continue to participate in study visits, the subject should have an Early Treatment Discontinuation (ETD) Visit within 28-35 days after the last study drug administration (per Table 1 and Section 7.1.6) and then have assessments every third month per Appendix 3. ***The most important visit is the Month 9-Day 1 Visit, so if a subject is unwilling to continue visits every third month, every effort should be made for the subject to return and complete the Month 9-Day 1 Visit on schedule.*** All visits after the ETD Visit should occur on schedule, that is, at the time when the visit would have occurred had the subject remained on study drug.

New SAEs occurring beyond the EOT/ETD Visit or >28 days after the last administration of study drug, whichever is later, will be reported to the Sponsor or its designee only if, in the judgment of the Investigator, the SAE is associated with any protocol intervention (i.e., related to study procedure or previous study drug exposure).

Follow-up phone calls should be made to randomized subjects (or their caregivers) who received a dose of study drug and are no longer receiving study drug every 3 months, beginning approximately 3 months from the subject's last visit (Section 7.1.8). The subject's health status, as well as details of any hospitalizations will be collected accordingly in the study database to ensure adequate capture of primary endpoint events.

At the time of study completion (i.e., once approximately 156 events have been reached), all subjects still on study (i.e., subjects still receiving study drug [NEOD001 or placebo] treatment,

subjects who discontinue study drug early but agree to return for assessments after the ETD Visit, and subjects participating in the vital status phone call follow up) may be considered for entry into a separate open-label extension study of NEOD001.

3.2 Rationale for Study Design

As a pivotal study to support potential licensure, a randomized, double-blind, placebo-controlled, parallel-group design was selected as an adequate and well-controlled study to demonstrate the safety and efficacy of NEOD001 vs. placebo against a background of standard of care in subjects with AL amyloidosis.

3.3 Number of Sites and Subjects

This is a multicenter, international study in approximately 75 centers. Up to 260 subjects will be enrolled in the study, with approximately 130 subjects per arm.

3.4 Endpoints

3.4.1 Efficacy Endpoints

3.4.1.1 Primary Efficacy Endpoints

- Time to all-cause mortality or cardiac hospitalization as adjudicated by the CEC

3.4.1.2 Key Secondary Efficacy Endpoints

- Change from baseline to Month 9 in the Physical Component Summary (PCS) score of the SF-36v2
- Change from baseline to Month 9 in the 6MWT distance (meters)
- NT-proBNP (cardiac) best response from baseline through Month 9

3.4.1.3 Additional Secondary Efficacy Endpoints

- For renal-evaluable subjects, renal best response from baseline through Month 9
- For peripheral neuropathy evaluable subjects, change from baseline to Month 9 in the NIS-LL total score
- For hepatic evaluable subjects, hepatic best response from baseline to Month 9

3.4.1.4 Exploratory Efficacy Endpoints

3.4.1.4.1 Cardiac Endpoints

3.4.1.4.1.1 Cardiac Biomarkers (NT-proBNP and Troponin T)

- Cardiac response (Appendix 1), as assessed by NT-proBNP response criteria, at each visit
- Cardiac best response (Section 3.4.1.2), as assessed by NT-proBNP response criteria, through Month 3 visit, Month 6 visit, and Month 12 visit, and over course of study

- Change and percent change from baseline in NT-proBNP and troponin T at each visit

3.4.1.4.1.2 Select Echocardiogram Cardiac Parameters

- Change and percent change from baseline to each visit in selected cardiac parameters, as determined by a 4-chamber view from a 2-dimensional echocardiogram with Doppler, as follows:
  - LVEF = Left ventricular ejection fraction
  - IVSd = Intraventricular septal at end diastole
  - LPWd = Left posterior wall at end diastole

3.4.1.4.2 Functional Endpoint

3.4.1.4.2.1 6MWT Distance

- Change and percent change from baseline in the 6MWT distance (meters) to each visit (except Month 9 [key secondary endpoint])

3.4.1.4.3 Quality of Life Endpoints

3.4.1.4.3.1 SF-36v2

- Change and percent change from baseline in SF-36v2 PCS score (except Month 9 [key secondary endpoint]), Mental Component Summary score, and the 8 subscales to each visit

3.4.1.4.3.2 KCCQ

- Change and percent change from baseline in KCCQ subscores and overall summary score to each visit

3.4.1.4.4 Renal Endpoints

The following endpoints will be evaluated in the Renal Evaluable Population.

3.4.1.4.4.1 Renal Response

- Renal response (Appendix 1) at each visit
- Renal best response through Month 3 visit, Month 6 visit, and Month 12 visit, and over course of study

3.4.1.4.4.2 Creatinine, Proteinuria, and Estimated Glomerular Filtration Rate (eGFR)

- Change and percent change from baseline to each visit in creatinine, proteinuria, and eGFR
- Time to eGFR ≤15 mL/min/1.73m^2 (Chronic Kidney Stage 5)
- Shifts from baseline in Chronic Kidney Stage

- Time to doubling of creatinine

3.4.1.4.5 Peripheral Neuropathy Endpoints

The following endpoints will be evaluated in the Peripheral Neuropathy Evaluable Population.

3.4.1.4.5.1 NIS-LL Total Score

- Change and percent change from baseline in the NIS-LL total score to each visit (except Month 9 [additional secondary endpoint]
- Peripheral neuropathy response (Appendix 1) at each visit
- Peripheral neuropathy best response through Month 3 visit, Month 6 visit, Month 9 visit, and Month 12 visit, and over course of study

3.4.1.4.5.2 NIS-LL Component Scores

- Change and percent change from baseline in the 3 NIS-LL component scores (sensory function, reflexes, muscle strength) to each visit

3.4.1.4.5.3 Visual Analog Score – Pain Intensity (VASPI)

- Change and percent change from baseline to each visit in the VASPI score (for peripheral neuropathy evaluable subjects with painful neuropathy, defined as a baseline VASPI score >0)

3.4.1.4.6 Hepatic Endpoints

The following endpoints will be evaluated in the Hepatic Evaluable Population.

3.4.1.4.6.1 Hepatic Response

- Hepatic response (Appendix 1) at each visit
- Hepatic best response through Month 3 visit, Month 6 visit, and Month 12 visit, and over course of study
- Change and percent change in ALP to each visit

3.4.1.4.6.2 Liver Size

- Change and percent change from baseline to each visit in liver size (i.e., craniocaudal dimension)

3.4.1.4.7 Additional Time-to-Event Endpoints

- Time to cardiac mortality at any time or cardiac hospitalization (occurring ≥91 days after a subject's first infusion of study drug) as adjudicated by the CEC
- Time to cardiac mortality as adjudicated by the CEC
- Progression-free survival
- Time to hematologic progression
- Time to derived organ progression (Appendix 1) for each organ (cardiac/NT-proBNP, renal, peripheral neuropathy, hepatic) separately and to any organ progression
- Time to first organ response (Appendix 1) for each organ (cardiac/NT-proBNP, renal, peripheral neuropathy, hepatic) separately and to any organ response

3.4.1.4.8 Other Efficacy Endpoints

3.4.1.4.8.1 Cardiac Hospitalizations

- Frequency of cardiac hospitalizations over the course of the study

3.4.1.4.8.2 ECOG Performance Status, NYHA Class, Mayo Clinic Stage, Renal Stage

- ECOG Performance Status, NYHA Class, Mayo Clinic Stage, and Renal Stage at each visit including any changes from baseline

3.4.1.4.8.3 Selected Hematologic and Urine Analyte Endpoints

- Change and percent change from baseline in serum free light chains (sFLCs), serum and 24-hour urine PEP, and serum and urine IFE to each visit
- Hematologic response (Appendix 6) at each visit
- Hematologic best response through Month 3 visit, Month 6 visit, Month 9 visit, and Month 12 visit, and over course of study

3.4.1.4.8.4 Disease-Related Symptoms

- Change from baseline in disease-related symptoms at each visit

3.4.1.4.8.5 Pharmacokinetics

Data on serum NEOD001 concentrations from this study will be pooled with data from similar samples from other studies in a population PK analysis.

3.4.2 Safety Endpoints

- Safety as assessed by vital signs, 12-lead ECGs, routine laboratory assessments, frequency and severity of AEs, and immunogenicity

3.5 Estimated Study Duration

Subject's participation in the study will begin with a 28-day Screening period; if they are assessed as eligible for enrollment, they will be randomized and will receive study drug intravenously every 28 days. Subjects will remain on study until study completion, which will occur when approximately 156 primary endpoint events have been reached. Therefore, subjects who enroll at the beginning of the study may remain on study for a longer period of time (as long as approximately 3.5-4 years) than subjects enrolled closer to the end of the study, who may only be on study for up to approximately 1.5-2 years. At the time of study completion (i.e., once approximately 156 primary endpoint events have been reached), all subjects still on study (i.e., subjects still receiving study drug [NEOD001 or placebo] treatment, subjects who discontinue study drug early but agree to return for assessments after the ETD Visit, and subjects participating in the vital status phone call follow up) may be considered for entry into a separate open-label extension study of NEOD001.

3.6 Definition of Primary Endpoint and End of Study

The study will end when approximately 156 primary endpoint events have occurred and EOT Visits have been completed for all subjects who remain on study at that time. Events are defined as deaths due to any cause, and AL amyloidosis-related cardiac hospitalizations as adjudicated by the CEC.

3.7 Termination of the Clinical Study

If the Investigator, the Sponsor, or the Medical Monitor becomes aware of conditions or events that suggest a possible hazard to subjects if the clinical study continues, then the clinical study may be terminated. The clinical study may also be terminated at the Sponsor's discretion in the absence of such a finding, at any time and for any reason.

Conditions that may warrant termination of the clinical study include, but are not limited to:

- The discovery of an unexpected, relevant, or unacceptable risk to the subjects enrolled in the clinical study
- Failure to enroll subjects at the required rate
- A decision by the Sponsor to suspend the study, or to suspend or discontinue development of the study drug, for any reason

4 SUBJECT SELECTION

4.1 Inclusion Criteria

Subjects must meet ***all*** of the following criteria:

1. Aged ≥ 18 years
2. Newly diagnosed and AL amyloidosis treatment naïve
3. Bone marrow demonstrating clonal plasma cells
4. Confirmed diagnosis of AL amyloidosis by the following:
   - Histochemical diagnosis of amyloidosis determined by polarizing light microscopy of green birefringent material in Congo red-stained tissue specimens **OR** characteristic electron microscopy appearance

     AND

   - Confirmatory immunohistochemistry **OR** mass spectroscopy of AL amyloidosis
5. Confirmed diagnosis of AL amyloidosis by mass spectrometry or immunoelectron microscopy of amyloid material in tissue biopsy if the subject meets any of the following:
   - Is black or African American
   - Is over 75 years of age with concurrent monoclonal gammopathy
   - Has a history of familial amyloidosis and has concurrent monoclonal gammopathy

     OR

   - If the subject meets any of the above 3 conditions and has echocardiographic evidence of amyloidosis, biopsy-proven amyloidosis with a monoclonal gammopathy and no tissue is available for mass spectrometry or immunoelectron microscopy, the subject must have gene sequencing consistent with transthyretin (TTR) wild type (e.g., no TTR mutation present) **AND** must score 0 in technetium-99m-3,3-diphosphono-1,2 propanodicarboxylic acid (^{99m}Tc-DPD; Rapezzi 2011), hydroxymethylenediphosphonate (^{99m}Tc-HMDP; Galat 2015), or pyrophosphate (^{99m}Tc-PYP; Bokhari 2013) scintigraphy
6. Cardiac involvement as defined by ***all*** of the following:
   - Past documented or presently noted clinical signs and symptoms supportive of a diagnosis of heart failure in the setting of a confirmed diagnosis of AL amyloidosis in the absence of an alternative explanation for heart failure
   - Either an endomyocardial biopsy demonstrating AL amyloidosis or an echocardiogram demonstrating a mean left ventricular wall thickness at diastole > 12 mm in the absence of other causes (e.g., severe hypertension, aortic stenosis), which would adequately explain the degree of wall thickening
   - NT-proBNP ≥ 650 pg/mL and ≤ 8500 pg/mL
7. Planned first-line chemotherapy contains bortezomib administered weekly and SC

8. Adequate bone marrow reserve, hepatic function, and renal function, as demonstrated by:
   - Absolute neutrophil count (ANC) $\geq 1.0 \times 10^9$/L
   - Platelet count $\geq 75 \times 10^9$/L
   - Hemoglobin ≥ 9 g/dL
   - Total bilirubin ≤ 2 times the upper limit of normal ($\times$ ULN)
   - Aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase (SGOT) $\leq 3 \times$ ULN
   - Alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase (SGPT) $\leq 3 \times$ ULN
   - Alkaline phosphatase (ALP) $\leq 5 \times$ ULN (***except*** for subjects with hepatomegaly and isozymes specific to liver, rather than bone)
   - Estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73 m^2 as estimated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation
9. Seated systolic blood pressure (BP) 90-180 mmHg
10. Distance walked during each Screening 6MWT is $\geq$ 30 meters and $\leq$ 550 meters
11. Women of childbearing potential (WOCBP) must have two negative pregnancy tests during Screening, the second within 24 hours prior to the first administration of study drug, and must agree to use highly effective physician-approved contraception (Appendix 4) from Screening to 90 days following the last study drug administration
12. Male subjects must be surgically sterile or must agree to use highly effective physician-approved contraception (Appendix 4) from Screening to 90 days following the last study drug administration
13. Ability to understand and willingness to sign an informed consent form prior to initiation of any study procedures

4.2 Exclusion Criteria

Subjects must meet ***none*** of the following criteria:

1. Non-AL amyloidosis
2. NT-proBNP < 650 pg/mL or > 8,500 pg/mL
3. Meets the International Myeloma Working Group (IMWG) definition of Multiple Myeloma (Appendix 5)

*Note that subjects who meet the IMWG definition of symptomatic multiple myeloma with symptoms attributable only to associated amyloidosis are potentially eligible upon approval of the Sponsor.

4. Subject is eligible for ***and*** plans to undergo ASCT or organ transplant

5. Symptomatic orthostatic hypotension that in the medical judgment of the Investigator would interfere with subject's ability to safely receive treatment or complete study assessments
6. Myocardial infarction, uncontrolled angina, severe uncontrolled ventricular arrhythmias, or ECG evidence of acute ischemia, within 6 months prior to the Month 1-Day 1 Visit
7. Severe valvular stenosis (e.g. aortic or mitral stenosis with a valve area <1.0 cm^2) or severe congenital heart disease
8. ECG evidence of acute ischemia or active conduction system abnormalities ***with the exception*** of any of the following:
    - First degree AV-block
    - Second degree AV-block Type 1 (Mobitz Type 1 / Wenckebach type)
    - Right or left bundle branch block
    - Atrial fibrillation with a controlled ventricular rate (uncontrolled [i.e., >110 bpm] ventricular rate is not allowed [determined by an average of three beats in Lead II or three representative beats if Lead II is not representative of the overall EKG])
9. Peripheral neuropathy assessed as National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Grade 2 with pain, Grade 3, or Grade 4
10. Subject is receiving oral or IV antibiotics, antifungals or antivirals within 1 week of Month 1-Day 1 with the exception of prophylactic oral agents
11. Prior treatment with hematopoietic growth factors, transfusions of blood or blood products within 1 week of Month 1-Day 1
12. Prior radiotherapy within 4 weeks of Month 1-Day 1
13. Major surgery within 4 weeks of Month 1-Day 1 or planned major surgery during the study
14. Active malignancy ***with the exception*** of any of the following:
    - Adequately treated basal cell carcinoma, squamous cell carcinoma, or *in situ* cervical cancer
    - Adequately treated Stage I cancer from which the subject is currently in remission and has been in remission for 2 years
    - Low-risk prostate cancer with Gleason score < 7 and prostate specific antigen < 10 ng/mL
    - Any other cancer from which the subject has been disease-free for ≥ 2 years
15. History of severe allergy to any of the components of NEOD001 such as histidine/L histidine hydrochloride monohydrate, trehalose dehydrate, or polysorbate 20 or history of Grade ≥ 3 infusion-related AEs or hypersensitivity to another monoclonal antibody, or known hypersensitivity to diphenhydramine (or an equivalent H1 antihistamine) or acetaminophen (or its equivalent, paracetamol)
16. Known or history of uncontrolled, active HIV, hepatitis B or hepatitis C infection

17. Prior treatment with plasma cell-directed chemotherapy, NEOD001, 11-1F4, anti-serum amyloid P antibody, doxycycline for amyloid, or other investigational treatment directed at amyloid
18. Treatment with another investigational agent within 30 days of Month 1-Day 1
19. Women who are pregnant or lactating
20. Any condition which could interfere with, or the treatment for which might interfere with, the conduct of the study or which would, in the opinion of the Investigator, unacceptably increase the subject's risk by participating in the study
21. Subject is under legal custodianship
22. History of epilepsy or seizure disorder ***with the exception of*** childhood febrile seizures
23. Waldenström's macroglobulinemia and/or immunoglobulin M (IgM) monoclonal gammopathy

5 SUBJECT SCREENING AND RANDOMIZATION

A 4-digit Subject Screening Number will be assigned via a phone- and web-based registration for each subject who has signed an informed consent. This Screening Number will be utilized for submission of lab samples, Screening ECGs, and other Screening procedures.

After a subject has completed all Screening requirements and meets all of the eligibility criteria, a Patient Registration Form should be submitted within several days prior to Month 1-Day 1 for eligibility review and approval by the Medical Monitor or designee. If approved, randomization will be implemented through a phone call or via the Internet connection to an Interactive Voice and Web Response System (IXRS) utilizing results from Screening assessments. Eligible subjects will be randomized in a 1:1 ratio into one of two arms, NEOD001 24 mg/kg or placebo. The randomization will be stratified by three factors:

- Mayo Clinic Stage (Appendix 2): Stages I and II vs. Stages III and IV
- Renal Stage (Appendix 2): Stage I vs. Stages II and III
- 6MWT distance: < 300 meters vs. ≥ 300 meters

Upon successful randomization, the subject will be assigned a 6-digit Subject ID consisting of the 3-digit site number plus the 3-digit subject number, and the Unblinded Pharmacist or their designee (henceforth collectively referred to as the Unblinded Pharmacy Staff) will be provided access to the treatment assignment. Subject IDs that are assigned to subjects who are randomized but do not receive study drug will not be re-utilized. Each arm of this 2-arm study will consist of approximately 130 subjects for an estimated total of 260 subjects.

Refer to the Study File Notebook for additional details.

6 INVESTIGATIONAL MEDICINAL PRODUCT AND TREATMENT

6.1 Formulation, Packaging, and Labeling of NEOD001

The active study drug, NEOD001, is supplied as a sterile, single-use, lyophilized dosage form in a 20/25 mL vial containing 500 mg/vial NEOD001. After reconstitution with 9.6 mL of sterile water for injection (WFI), the vial will contain 50 mg/mL of NEOD001, 25 mM L-Histidine, 230 mM Trehalose, and 0.02% Polysorbate 20.

At a minimum, the label for each vial shipped to a clinical site will provide the following information: batch number/lot number, required storage conditions, directions for use, and any region-specific caution statements, e.g. "New Drug - Limited by United States Federal Law to Investigational Use."

6.2 Shipping, Storage, and Handling of NEOD001

NEOD001 will be shipped to clinical sites in individual cartons (one vial per carton). Upon receipt, a study staff member will place the study drug in a refrigerator at a temperature ranging from 2 to 8°C in a secure, locked location. Access to the study drug should be strictly limited to the Unblinded Pharmacy Staff. Neither the Investigator nor any member of the study staff will distribute any of the study supplies to any person who is not participating in this study.

If a study staff member becomes aware that the study drug has not been properly handled (e.g., physical damage to carton/vial, temperature outside the 2ºC to 8ºC range in transit, or not stored at 2ºC to 8ºC in the clinic), follow the procedure outlined in the Pharmacy Manual or immediately contact the Unblinded Monitor (contact information available in the Study File Notebook). In such an event, study drug should be quarantined in a 2 to 8°C refrigerator and must not be administered to any subject until the drug has been approved for use.

It is expected that the site staff will maintain refrigerator temperature logs in the investigational product storage area, recording the temperature at least once each working day.

See the Pharmacy Manual for further details about shipping, storage, and handling of NEOD001.

6.3 Placebo

A matching placebo will not be provided for this study. Subjects who are randomized to the placebo arm will be administered a 250 mL IV bag of 0.9% saline, which will look identical to the NEOD001 infusion bag.

6.4 Accountability and Return of Study Drug Supplies

The study drug will be dispensed at the discretion of the Investigator under the direction of the Unblinded Pharmacy Staff, in accordance with the conditions specified in this protocol. It is the Unblinded Pharmacy Staff's responsibility to ensure that accurate records of study drug disposition and return are maintained.

6.5 Dosage, Administration, and Schedule

6.5.1 Study Drug

Study drug consists of IV NEOD001 or placebo. The NEOD001 dose is 24 mg/kg; however, the maximum dose administered is not to exceed 2500 mg. Therefore, subjects with a weight of 104.2 kg or greater will receive the maximum dose of 2500 mg. The subject's weight during Screening may be used for calculation of the first dose. Subsequent doses may be calculated based on the current weight at that visit or by using the baseline weight, based on the site's institutional guidelines. A change of ±10% from the weight being used for dosing should trigger recalculation of the dose based on the new weight.

Each vial of 500 mg of NEOD001 will be reconstituted with 9.6 mL sterile WFI to a concentration of 50 mg/mL resulting in a buffered, isotonic, preservative-free solution with a total extractable volume of 10 mL. Study drug will be prepared in a 250-mL IV bag of 0.9% saline. The equivalent volume of reconstituted NEOD001 will be withdrawn prior to transferring the drug solution into the IV bag, such that the total IV bag volume will be 250 mL. Each vial of NEOD001 is single-use – if there is residual drug in a vial after treating a subject, it should not be used for another subject and must be destroyed. Refer to the Pharmacy Manual for complete information on preparing and administering the study drug.

Subjects who are randomized to the placebo arm will be administered a 250 mL IV bag of 0.9% saline, which will look identical to the NEOD001 infusion bag.

The Unblinded Pharmacy Staff at each site will be responsible for preparing the study drug; all other study team members, including the Sponsor and site monitor, must remain blinded to study drug assignment. The Unblinded Pharmacy Staff will obtain the treatment assignment information from the IXRS, and will then prepare and reconstitute the study drug, providing the prepared IV bag to the Investigator for administration. The Unblinded Pharmacy Staff will maintain the records for drug accountability for audits or inspections. An Unblinded Monitor will be assigned as the Sponsor's designee to perform drug accountability and as such, will be the Unblinded Pharmacy Staff's primary point of contact for any study drug-related issues.

The study drug should only be administered in settings where emergency resuscitative equipment and personnel trained in the management of anaphylaxis are immediately available to treat systemic reactions under the direct supervision of a physician.

The study drug will be administered once every 28 days from the time the subject is randomized until the EOT/Early Treatment Discontinuation (ETD) Visit, as an initial 120 (±10) minute IV infusion on Month 1-Day 1. If the subject tolerates the initial administration without infusion-related AEs, subsequent infusions may be administered over 60 (±10) minutes. If there is concern about infusing 250 mL over 60 (±10) minutes in any specific subject, the length of the infusion may be extended over a longer period of time as clinically indicated. If it is anticipated that the infusion will extend beyond 4 hours, the reconstituted and diluted study drug should be split into multiple bags to ensure that no amount of reconstituted study drug will be at room temperature for longer than 4 hours (i.e., from the time of reconstitution of the vial to end of the infusion of a bag). The additional bag(s) should remain refrigerated until ready for use. The volume contained in the administration tubing should be completely flushed using approximately

30 mL of 0.9% Sodium Chloride Injection (USP) after administration of study drug. The infusion line should NOT be used for blood draws.

Every effort must be made to ensure doses are given 28 days from the previous dose. If logistic considerations intervene, a minimum of 21 days between doses is required. All subjects will be closely monitored for 90 (±10) minutes after completion of the study drug infusion. The Investigator may increase this standard monitoring time if deemed appropriate or per local standards. In the event of any clinical concerns or suspicious signs or symptoms after the infusion, the subject will remain under observation for as long as the Investigator deems it appropriate.

6.5.2 Study Drug Premedication

All subjects will be premedicated with 25 mg diphenhydramine (or an equivalent dose of a H1 antihistamine) and 650 mg acetaminophen (or an equivalent paracetamol dose) within 30-90 minutes prior to study drug administration.

6.5.3 Standard of Care Chemotherapy

All subjects will receive concomitant standard of care chemotherapy. The initial first-line chemotherapy regimen must include bortezomib, which must be administered SC on a weekly basis. Subsequent chemotherapy regimens may be prescribed as per standard of care at the Investigator's discretion. Bortezomib should be administered according to the approved prescribing information and local institutional practices. Antiviral prophylaxis is required. When chemotherapy is administered on same day as study drug, the chemotherapy must be administered ***after*** the 90 (±10)-minute post-study drug infusion observation period.

The number of cycles of first-line chemotherapy that is administered is at the discretion of the Investigator; however, commonly accepted treatment practice suggests that a change in plasma cell-directed chemotherapy may occur in any of the following circumstances:

In subjects who are at high risk for complications due to Mayo Stage III or IV (Appendix 2): a change in therapy should be considered if they fail to attain at least a hematologic partial response by 6 weeks or a very good partial response by 3 months.

- In subjects who are Mayo Stage I or II (Appendix 2): a change in therapy should be considered if they fail to attain at least a hematologic partial response by 3 months or a very good partial response by 6 months.
- Withdrawal of consent
- Unacceptable toxicity
- Investigator decision

The Investigator may prescribe subsequent chemotherapy at his/her discretion as per standard of care. Particular care must be taken to accurately report chemotherapy administration, including missed or delayed doses, and dose reductions. The Sponsor does not intend to provide reimbursement for standard of care chemotherapy.

In the event that bortezomib doses are missed, the chemotherapy cycles may become misaligned with the monthly study drug dosing. In this case, the weekly visits during Months 1 through 3 should continue as described above in order to closely monitor subjects' health during the initial months of concomitant chemotherapy. Throughout the study, monthly doses of study drug should not be delayed or skipped due to adjustments that are made to chemotherapy dosing. Study drug dosing adjustments are described in Section 6.6.

6.6 Dosage Adjustments

6.6.1 Withholding of Study Drug

Subjects with symptomatic orthostatic hypotension which in the medical judgment of the Investigator would interfere with subject's ability to safely receive treatment will have study drug withheld until the next scheduled monthly administration, but should still have all other study visit assessments completed. Subjects who have had study drug withheld for two consecutive scheduled monthly treatments and who require study drug to be withheld during the subsequent, third consecutive scheduled monthly treatment visit will have study drug permanently discontinued and have an ETD Visit per Section 7.1.5.

Throughout the study, monthly doses of study drug should not be delayed or skipped due to adjustments that are made to chemotherapy dosing.

6.6.2 Management of Suspected Infusion-Related/Hypersensitivity Adverse Events

In the event of a suspected infusion-related and/or hypersensitivity adverse event (AE), the infusion should be immediately discontinued and appropriate supportive therapy should be administered per institutional practice, which may include epinephrine, IV fluids, corticosteroids, vasopressors, oxygen, bronchodilators, antihistamines or acetaminophen/paracetamol. Subjects should be evaluated and carefully monitored until there is complete resolution of the AE (i.e., all hypersensitivity signs and symptoms have resolved). In addition to the institution's recommended assessments, blood samples should be obtained in the event of a suspected infusion-related and/or hypersensitivity AE for assessment of the following: tryptase, complements C_3 and C_4, PK, and anti-NEOD001 antibody levels.

For subjects with a Grade 2 infusion-related AE, if it is appropriate to restart the infusion, then this should be done at 50% of the original rate (i.e., if the initial infusion is administered over 120 minutes, the new rate should be based on administering 250 mL over at least 180 minutes). If the subject is to receive additional infusions in subsequent weeks, then the rate of these infusions should be discussed with and agreed upon prospectively by the Investigator and the Medical Monitor.

If a subject experiences a Grade 3 infusion-related and/or hypersensitivity AE, the infusion should not be restarted. The decision to continue dosing this subject at their next scheduled

administration should be discussed with the Medical Monitor. If the decision is made to proceed with dosing, the dose will be reduced by 50%, in addition to a 50% reduction of the original infusion rate (i.e., 250 mL over at least 180 minutes). In addition, maximal premedication must be administered according to institutional practice and should include an H1 blocker, an H2 blocker, an antipyretic such as acetaminophen/paracetamol and a steroid (e.g., 25-50 mg hydrocortisone IV). Subjects who have an infusion-related and/or hypersensitivity AE at the subsequent scheduled study drug administration must have study drug permanently discontinued and have an ETD Visit per Section 7.1.5.

Subjects who experience a Grade 4 infusion-related and/or hypersensitivity AE must have study drug permanently discontinued and have an ETD Visit per Section 7.1.5.

6.6.3 Dose Reductions

Dose reductions may be allowed in the event that AEs are observed that are believed to be related to study drug, and which in consultation between the Investigator and the Medical Monitor, may be managed by a 50% reduction in dose. The duration of the dose reduction will be at the Investigator's discretion.

6.7 Treatment Compliance

Treatment compliance is assured as study drug will be administered at the study site. Any changes in volume or rate of administration will be recorded on the eCRF, along with reasons why treatment was adjusted or not administered, if applicable.

6.8 Concomitant Therapy

Concomitant medication includes any drug (prescription or over-the-counter) or biological product (such as vaccines, blood or blood components) including herbal remedies or preparations. All medications that are taken by a subject within the 28 days prior to the Month 1-Day 1 Visit through the EOT/ETD Visit, and any changes to concomitant medications during the study will be recorded on the appropriate eCRF.

6.8.1 Allowed Concomitant Therapy

- All supportive concomitant therapy
- Medications such as anti-emetics required for prophylaxis of emesis for the subsequent chemotherapy are allowed, but should be administered ***after*** the post-infusion ECG has been completed
- Radiation therapy for the removal of local amyloid deposits
- Steroids are allowed for the treatment of AL amyloidosis during the study.

6.8.2 Prohibited Concomitant Therapy

- Other investigational agents (e.g., drugs not approved for any indication)
- Myeloablative chemotherapy with ASCT
- Organ transplant
- Doxycycline
- Steroids are not allowed PRIOR to study entry for the treatment of AL amyloidosis

7 STUDY PROCEDURES

7.1 Study Visits and Assessments

7.1.1 First Screening Visit: Day -28 to Day -1

Screening will take place within the 28 days prior to the first administration of study drug on Month 1-Day 1. The Screening period may be extended upon approval by the Medical Monitor. Individual test results that do not meet eligibility requirements may be repeated, with the exception of 6MWT; full rescreening is allowed once per subject.

Subjects should have bone marrow demonstrating clonal plasma cells within 90 days prior to Screening Day -28.

Two pre-treatment 6MWTs are required before the first administration of study drug. The first Screening 6MWT is required to be performed between Days -28 and -5, at least 4 days prior to the second Screening 6MWT, which should be performed within 2 days prior to Month 1-Day 1 (i.e., on Day -2 or Day -1). Although the entire Screening period does not need to be utilized, a minimum of 5 days must be allowed to accommodate the required 4-day interval between the two Screening 6MWTs. Subjects should plan to be able to return to the same clinical site for each 6MWT from first Screening through Month 9.

Written informed consent must be obtained before any study-specific screening evaluations are performed and should be documented in the subject's medical chart.

The following will be performed between Days -28 and -1 prior to the Month 1-Day 1 Visit, unless otherwise noted:

- Obtain written informed consent
- Review inclusion and exclusion criteria to assess eligibility
- Obtain comprehensive cardiac, hematologic and oncologic medical history; additionally for all other conditions obtain relevant medical history for the past 5 years (including all major hospitalizations and surgeries), as well as the subject's current medical status
- Confirmation of AL amyloidosis by mass spectrometry tissue typing, immunoelectron microscopy, gene sequencing, and/or ^{99m}Tc scintigraphy must be completed, and results obtained prior to randomization, for subjects who meet Inclusion Criterion #5
- Functional Assessment of Cancer Therapy – Gynecologic Oncology Group Neurotoxicity Subscale (FACT-GOG NTX) - should be performed prior to any other study assessments on the day it is administered
- Echocardiogram - To be eligible for the additional cardiac imaging analysis, the subject must have had a 4-chamber view, 2-dimensional echocardiogram with Doppler. If an echocardiogram has been conducted within 90 days prior to Screening Day -28, it does not need to be repeated during Screening and the previous result can be used for eligibility.

- CT imaging of the abdomen for liver measurement for subjects with liver involvement based on ALP >1.5 × ULN (Section 7.6) (*Exception:* not required in Germany). The dimension that is measured at Screening (i.e., craniocaudal) should be consistently measured for all subsequent assessments for the same subject. If CT imaging of the abdomen for liver measurement has been conducted within 60 days prior to Screening Day -28 and it meets acquisition guidelines, it does not need to be repeated during Screening and the previous result can be used for eligibility.
- 12-lead ECG performed in triplicate
- Complete physical exam (PE) including height (Screening only), weight, and examination of general appearance; head, ears, eyes, nose, and throat; neck; skin; cardiovascular system; respiratory system; gastrointestinal system; and nervous system. The following should be assessed: macroglossia, submandibular nodes/fullness, adenopathy, ecchymoses, liver/spleen size (palpable +/-), ascites (+/-), and edema (which should be quantified on a scale of 0-4).
- ECOG PS (Appendix 13)
- NYHA class (Appendix 14)
- Determine if a subject has AL amyloidosis disease-related peripheral neuropathy prior to administration of study drug and administer the following to **all** subjects:
    - NIS-LL (Section 7.4 and Appendix 10)
    - VASPI (Section 7.4 and Appendix 11)
- Central Laboratory Assessments – Collect samples prior to 6MWT, if being performed on the same day:
    - Hematology: complete blood count (CBC) with differential, hemoglobin (Hgb), hematocrit (Hct), and platelet count
    - Chemistry: sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine, creatinine clearance, glucose, ALT, AST, ALP, total bilirubin, direct bilirubin, lactate dehydrogenase (LDH), eGFR, total protein, albumin, calcium, phosphate, and magnesium (and isozymes for subjects with ALP > 5 × ULN)
    - Amylase
    - Troponin T
    - NT-proBNP
    - sFLCs
    - Serum pregnancy test for women of childbearing potential (WOCBP); note that women with tubal ligations are considered to be of childbearing potential but women who are surgically sterile (hysterectomy) or post-menopausal ≥ 2 years are ***not*** considered to be of childbearing potential
    - Serum immunofixation electrophoresis (IFE) and protein electrophoresis (PEP)
    - Urinalysis

- 24-hour urine collection (see Section 7.3) for:
  - Urine protein excretion
  - Urine IFE and PEP

- First Screening 6MWT – must be performed between Days -28 and -5, at least 4 days prior to the second Screening 6MWT, which should be performed within 2 days prior to Month 1-Day 1 (i.e., on Day -2 or Day -1); collect BP and HR pre- and post-6MWT administration
- Vital signs, including BP, heart rate (HR), respiratory rate (RR), and temperature – after the subject has been at rest for ≥ 5 minutes
- Record all medications and therapy beginning with Day -28
- Assess for AEs after written informed consent is obtained

7.1.2 Second Screening Visit: Day -2 or Day -1

The following assessments will be conducted on Day -2 or Day -1 (i.e., 1-2 days prior to dosing on Month 1-Day 1):

- Administer questionnaires in the following order, prior to conducting any other assessments on the day they are administered:
  - SF-36v2 Questionnaire (Appendix 7)
  - KCCQ (Appendix 8)
  - FACT-GOG NTX (Section 7.4 and Appendix 9)
- Central Laboratory Assessments – Collect samples prior to 6MWT, if being performed on the same day:
  - Hematology: CBC with differential, Hgb, Hct, and platelet count
  - Chemistry: sodium, potassium, chloride, bicarbonate, BUN, creatinine, creatinine clearance, glucose, ALT, AST, ALP, total bilirubin, direct bilirubin, LDH, eGFR, total protein, albumin, calcium, phosphate, and magnesium
  - Amylase
  - PT/INR and PTT
  - Additional coagulation samples per Appendix 12
  - Complements C_3 and C_4
  - Troponin T
  - NT-proBNP
  - Tryptase
  - sFLCs
  - Urinalysis

- 24-hour urine collection (see Section 7.3) for urine protein excretion

- Second Screening 6MWT; collect BP and HR pre- and post-6MWT administration
- Ensure all medications and therapy beginning with Day -28 have been recorded
- Assess for AEs as of the first Screening visit

7.1.3 Randomization

If the subject meets all eligibility criteria after completion of Screening assessments, randomization will occur per Section 5. After the subject is randomized, Month 1-Day 1 assessments will be completed and treatment will be initiated.

7.1.4 Treatment Visits

Subjects will receive study drug as an IV infusion every 28 days. Assessment and visit windows are described in the Schedule of Events (Table 1) and in the sections below; the study drug dosing window is described in Section 6.5.1. The pre-dose assessments for each visit may be performed within the 2 days prior to the visit.

Although central laboratory assessments will be performed each month for study analysis, local laboratory assessments, including hematology and chemistry, will be performed for subject management. Results will be reviewed prior to dosing and prior to in-clinic bortezomib administration, to confirm that continued dosing is appropriate.

Subjects who present with symptomatic orthostatic hypotension, which in the medical judgment of the Investigator would interfere with the subject's ability to safely receive treatment, will have the study drug withheld. If the study drug is withheld and subsequently rescheduled, central laboratory assessments required for that visit will need to be repeated if they were drawn more than 7 days prior to the rescheduled dosing date. However, a symptom-directed PE and vital signs need to be repeated prior to each dosing. Subjects who have had study drug withheld for more than two consecutive scheduled treatments (i.e., if a third consecutive infusion needs to be withheld) will be withdrawn from the study.

Additional anti-NEOD001 antibody and PK samples should be collected if significant toxicity is observed (e.g., an infusion reaction in the clinic, anaphylaxis, etc.) and if possible, should be collected while the acute symptoms persist.

If the subject discontinues study drug treatment prior to the end of the study, refer to Section 8.2.

7.1.4.1 Month 1-Day 1

The subject must return to the study site for the following procedures:

Prior to Study Drug Infusion:

- FACT-GOG NTX (Section 7.4 and Appendix 9) – prior to any other study assessments on the day it is administered

- Symptom-directed PE should be as clinically indicated and also include weight and assessment of macroglossia, submandibular nodes/fullness, adenopathy, ecchymoses, liver/spleen size (palpable +/-), ascites (+/-), and edema (which should be quantified on a scale of 0-4)
- ECOG PS (Appendix 13)
- NYHA class (Appendix 14)
- NIS-LL (Section 7.4 and Appendix 10)
- VASPI (Section 7.4 and Appendix 11)
- Local Laboratory Assessment:
  - Serum Pregnancy Test for WOCBP within 24 hours prior to Month 1-Day 1 study drug administration; test results must be obtained prior to dosing and must be negative
- Bioanalytical Laboratory Assessments – any time on Month 1-Day 1, prior to the start of the infusion:
  - Pre-dose PK sample
  - Pre-dose anti-NEOD001 antibody sample
  - Pre-dose serum sample for archiving (only for those subjects who have consented to the collection and archiving of their samples for future correlative testing)
- Administer premedication within 30-90 minutes prior to the start of the infusion:
  - 25 mg diphenhydramine or an equivalent dose of a H1 antihistamine
  - 650 mg acetaminophen or an equivalent paracetamol dose
- 12-lead ECG performed in triplicate – within 30 minutes prior to infusion
- Vital signs including BP, HR, RR, and temperature – within the 30 minutes prior to dosing after premedications have been administered and subject has been at rest for ≥ 5 minutes. Vital signs should be assessed in the same position at each assessment (i.e., pre-dose, during infusion, and after the infusion); if the subject will be supine during the infusion, then all of the vital signs should be assessed in the supine position.

Study Drug Administration:

- The initial dose of study drug will be delivered over 120 (±10) minutes (Section 6.5.1)
- Vital signs, including BP, HR, RR, and temperature – halfway through the infusion (i.e., approximately 60 minutes after the start of the infusion)

Assessments After Infusion:

- Bioanalytical Laboratory Assessments – PK samples are to be collected at the following time points and should take priority over collection of vital signs for this time point:

- Immediately at the End of Infusion (EOI) (+5 minutes), which includes completion of the saline flush
- 0.5 hour (±5 minutes) post-EOI
- 1 hour (±10 minutes) post-EOI

- Vital signs, including BP, HR, RR, and temperature – in the same position as assessed pre-dose and during the infusion, at the following time points:
  - Immediately at the EOI (+ 10 minutes), which includes completion of the saline flush
  - 0.5 hour (±10 minutes) post-EOI
  - 1 hour (±10 minutes) post-EOI
- 12-lead ECG performed in triplicate 1 hour (±15 minutes) after the EOI; medications given for prophylaxis chemotherapy-induced side effects should not be administered prior to completion of the post-infusion ECG
- Closely monitor subject for 90 (±10) minutes following completion of the study drug infusion per Section 6.5.1
- Administer Cycle 1-Day 1 bortezomib, antiviral prophylaxis, and other scheduled chemotherapy following the post-study drug infusion observation period
- Assessment of AEs
- Record all changes to concomitant medications and therapy

7.1.4.2 Month 1-Days 8, 15, 22 (±2 Days)

The subject must return to the study site for the following procedures:

Prior to Chemotherapy Administration:

- FACT-GOG NTX (Section 7.4 and Appendix 9) – prior to any other study assessments on the day it is administered
- Local Laboratory Assessments:
  - Perform pre-dose local laboratory assessments, including hematology and chemistry, and review results prior to dosing
- Central Laboratory Assessments:
  - Hematology: CBC with differential, Hgb, Hct, and platelet count
  - Chemistry: sodium, potassium, chloride, bicarbonate, BUN, creatinine, creatinine clearance, glucose, ALT, AST, ALP, total bilirubin, direct bilirubin, LDH, eGFR, total protein, albumin, calcium, phosphate, and magnesium
- Bioanalytical Laboratory Assessment – ***Month 1-Day 15 only***:
  - PK sample

- Vital signs, including BP, HR, RR, and temperature – after the subject has been at rest for ≥ 5 minutes

Chemotherapy Administration:

- Administer bortezomib, antiviral prophylaxis, and other scheduled chemotherapy
- Assessment of AEs
- Record all changes to concomitant medications and therapy

7.1.4.3 Month 2-Day 1 (±2 Days)

- The subject must return to the study site for the following procedures:

Prior to Study Drug Infusion:

- Administer questionnaires in the following order, prior to conducting any other assessments on the day they are administered:
  - SF-36v2 Questionnaire (Appendix 7)
  - KCCQ (Appendix 8)
  - FACT-GOG NTX (Section 7.4 and Appendix 9)
- 12-lead ECG performed in triplicate – within 30 minutes prior to infusion
- Symptom-directed PE should be as clinically indicated and also include weight and assessment of macroglossia, submandibular nodes/fullness, adenopathy, ecchymoses, liver/spleen size (palpable +/-), ascites (+/-), and edema (which should be quantified on a scale of 0-4)
- ECOG PS (Appendix 13)
- NYHA class (Appendix 14)
- NIS-LL (Section 7.4 and Appendix 10)
- VASPI (Section 7.4 and Appendix 11)
- Local Laboratory Assessments:
  - Perform local laboratory assessments, including hematology and chemistry, and review results prior to dosing
  - WOCBP: Serum pregnancy test
- Central Laboratory Assessments:
  - Hematology: CBC with differential, Hgb, Hct, and platelet count
  - Chemistry: sodium, potassium, chloride, bicarbonate, BUN, creatinine, creatinine clearance, glucose, ALT, AST, ALP, total bilirubin, direct bilirubin, LDH, eGFR, total protein, albumin, calcium, phosphate, and magnesium

- Amylase
- PT/INR and PTT
- Troponin T
- NT-proBNP
- sFLCs
- Urinalysis

- Bioanalytical Laboratory Assessments – any time on Month 2-Day 1, prior to the start of the infusion:
  - Pre-dose PK sample
  - Pre-dose anti-NEOD001 antibody sample
  - Pre-dose serum sample for archiving (only for those subjects who have consented to the collection and archiving of their samples for future correlative testing)
- Administer premedication within 30-90 minutes prior to the start of the infusion:
  - 25 mg diphenhydramine or an equivalent dose of a H1 antihistamine
  - 650 mg acetaminophen or an equivalent paracetamol dose
- Vital signs, including BP, HR, RR, and temperature – after the subject has been at rest for ≥ 5 minutes, within the 30 minutes prior to dosing, after premedication has been administered.

Study Drug Administration

- The dose of study drug may be delivered over 60 (±10) minutes if the Month 1-Day 1 infusion was well tolerated without infusion-related AEs (Section 6.5.1)

Assessments After Infusion:

- Bioanalytical Laboratory Assessments – PK samples are to be collected at the following time points; the PK sample collection should take priority over collection of vital signs for this time point:
  - Immediately at the EOI (+5 minutes), which includes completion of the saline flush
  - 1 hour (±10 minutes) post-EOI
- Vital signs, including BP, HR, RR, and temperature – in the same position as those assessed pre-dose and during the infusion, at the following time points:
  - Immediately at the EOI (+10 minutes), which includes completion of the saline flush
  - 1 hour (±10 minutes) post-EOI
- Closely monitor subject for 90 (±10) minutes following completion of the study drug infusion per Section 6.5.1

- Administer Cycle 2-Day 1 bortezomib, antiviral prophylaxis, and other scheduled chemotherapy following the post-study drug infusion observation period
- Assessment of AEs
- Record all changes to concomitant medications and therapy

7.1.4.4 Month 2-Days 8, 15, 22 (±2 days)

If the subject had significant toxicities associated with previous chemotherapy administrations, then the subject should return to the study site for the following procedures and Cycle 2-Day 8 and/or Cycle 2-Day 22 bortezomib administration. If there were no significant toxicities associated with previous chemotherapy administration, then Cycle 2-Day 8 and/or Cycle 2-Day 22 chemotherapy may be administered by the subject's local physician, at the Investigator's discretion, and a Homecare visit performed. The subject must return to the study site for Cycle 2-Day 15 bortezomib administration and assessments, regardless of previous tolerability.

Prior to Chemotherapy Administration:

The following assessments will be performed whether the visit is conducted at the study site or at the subject's local physician's clinic. If the visit is performed at the subject's local physician's clinic, a Prothena-sponsored Homecare visit will take place either within 1 day prior to or pre-dose on the same day as bortezomib administration to administer the FACT-GOG NTX, to perform vital signs and to collect central laboratory assessments. If bortezomib is administered on a Monday, then it is acceptable for the Homecare visit to take place on the previous Friday.

- FACT-GOG NTX (Section 7.4 and Appendix 9) – prior to any other study assessments on the day it is administered
- Vital signs, including BP, HR, RR, and temperature – after the subject has been at rest for ≥ 5 minutes
- Central Laboratory Assessments:
  - Hematology: CBC with differential, Hgb, Hct, and platelet count
  - Chemistry: sodium, potassium, chloride, bicarbonate, BUN, creatinine, creatinine clearance, glucose, ALT, AST, ALP, total bilirubin, direct bilirubin, LDH, eGFR, total protein, albumin, calcium, phosphate, and magnesium

The following assessments will only be performed if the subject returns to the study site for the visit:

- Local Laboratory Assessments:
  - Perform local laboratory assessments, including hematology and chemistry, and review results prior to dosing
- Assessment of AEs

- Record all changes to concomitant medications and therapy

Chemotherapy Administration (Investigator or local physician):

- Administer bortezomib, antiviral prophylaxis, and other scheduled chemotherapy

7.1.4.5 Month 3-Day 1 (±2 Days)

The postbaseline 6MWT may be administered on the same day as study drug administration as long as the NT-proBNP sample is drawn before conducting the 6MWT and the 6MWT is completed before initiation of the study drug infusion. Questionnaires and collection of central laboratory samples are to be performed ***prior*** to the 6MWT, if being performed on the same day.

The subject must return to the study site for the following procedures:

Prior to Study Drug Infusion:

- Administer questionnaires in the following order, prior to conducting any other assessments on the day they are administered:
  - SF-36v2 Questionnaire (Appendix 7)
  - KCCQ (Appendix 8)
  - FACT-GOG NTX (Section 7.4 and Appendix 9)
- 12-lead ECG performed in triplicate - within 30 minutes prior to infusion
- Symptom-directed PE should be as clinically indicated and also include weight and assessment of macroglossia, submandibular nodes/fullness, adenopathy, ecchymoses, liver/spleen size (palpable +/-), ascites (+/-), and edema (which should be quantified on a scale of 0-4)
- ECOG PS (Appendix 13)
- NYHA class (Appendix 14)
- NIS-LL (Section 7.4 and Appendix 10)
- VASPI (Section 7.4 and Appendix 11)
- Local Laboratory Assessments:
  - Perform local laboratory assessments, including hematology and chemistry, and review results prior to dosing
  - WOCBP: Serum pregnancy test
- Central Laboratory Assessments – Collect samples prior to 6MWT, if being performed on the same day:
  - Hematology: CBC with differential, Hgb, Hct, and platelet count

- Chemistry: sodium, potassium, chloride, bicarbonate, BUN, creatinine, creatinine clearance, glucose, ALT, AST, ALP, total bilirubin, direct bilirubin, LDH, eGFR, total protein, albumin, calcium, phosphate, and magnesium
- Amylase
- PT/INR and PTT
- Complements C_3 and C_4
- Troponin T
- NT-proBNP
- sFLCs
- Serum IFE and PEP
- Urinalysis
- 24-hour urine collection (see Section 7.3) for:
  - Urine protein excretion
  - Urine IFE and PEP

- 6MWT; collect BP and HR pre- and post-6MWT administration
- Bioanalytical Laboratory Assessments – any time on Month 3-Day 1, prior to the start of the infusion:
  - Pre-dose PK sample
  - Pre-dose anti-NEOD001 antibody sample
  - Pre-dose serum sample for archiving (only for those subjects who have consented to the collection and archiving of their samples for future correlative testing)
- Administer premedication within 30-90 minutes prior to the start of the infusion:
  - 25 mg diphenhydramine or an equivalent dose of a H1 antihistamine
  - 650 mg acetaminophen or an equivalent paracetamol dose
- Vital signs, including BP, HR, RR, and temperature – within 30 minutes before dosing

Study Drug Administration:

- The dose of study drug may be delivered over 60 (±10) minutes if the previous infusions were well tolerated without infusion-related AEs (Section 6.5.1)

Assessments After Infusion:

- Vital signs, including BP, HR, RR and temperature – in the same position as those assessed pre-dose, at the following time points:
  - Immediately at the EOI (+10 minutes), which includes completion of the saline flush
  - 1 hour (±10 minutes) post-EOI

- Closely monitor subject for 90 (±10) minutes following completion of the study drug infusion per Section 6.5.1
- Administer bortezomib, antiviral prophylaxis, and other scheduled chemotherapy following the post-study drug infusion observation period
- Assessment of AEs
- Record all changes to concomitant medications and therapy

7.1.4.6 Month 3-Days 8, 15, and 22 (±2 days)

If the subject had significant toxicities associated with Cycles 1 or 2 chemotherapy administrations, then the subject should return to the study site for the following procedures and Cycle 3-Days 8, 15, and 22 bortezomib administration. If there were no significant toxicities associated with previous chemotherapy administrations, Cycle 3-Days 8, 15, and 22 chemotherapy may be administered by the subject's local physician, at the Investigator's discretion, and a Homecare visit performed within 1 day prior to or on the same day as bortezomib administration to conduct the following pre-chemotherapy assessments. If bortezomib is administered on a Monday, then it is acceptable for the Homecare visit to take place on the previous Friday.

Prior to Chemotherapy Administration:

The following assessments will be performed whether the visit is conducted at the study site or at the subject's local physician's clinic:

- FACT-GOG NTX (Section 7.4 and Appendix 9) – prior to any other study assessments on the day it is administered
- Vital signs, including BP, HR, RR and temperature – after the subject has been at rest for ≥ 5 minutes
- Central Laboratory Assessments:
  - Hematology: CBC with differential, Hgb, Hct, and platelet count
  - Chemistry: sodium, potassium, chloride, bicarbonate, BUN, creatinine, creatinine clearance, glucose, ALT, AST, ALP, total bilirubin, direct bilirubin, LDH, eGFR, total protein, albumin, calcium, phosphate, and magnesium
- Bioanalytical Laboratory Assessment– ***Month 3-Day 8 only***:
  - PK sample

The following assessments will only be performed if the subject returns to the study site for this visit:

- Local Laboratory Assessments:

- Perform local laboratory assessments, including hematology and chemistry, and review results prior to dosing

- Assessment of AEs

- Record all changes to concomitant medications and therapy

Chemotherapy Administration (Investigator or local physician):

- Administer bortezomib, antiviral prophylaxis, and other scheduled chemotherapy

7.1.4.7 Every Third Month-Day 1 (±5 Days): Month 6-Day 1, Month 9-Day 1, Month 12-Day 1, etc.

The postbaseline 6MWT may be administered on the same day as study drug administration as long as the NT-proBNP sample is drawn before conducting the 6MWT and the 6MWT is completed before initiation of the study drug infusion. Questionnaires and collection of central laboratory samples are to be performed ***prior*** to the 6MWT, if being performed on the same day.

The subject must return to the study site for the following procedures:

Prior to Study Drug Infusion:

- Administer questionnaires in the following order, ***prior to conducting any other assessments on the day they are administered***:
  - SF-36v2 Questionnaire (Appendix 7)
  - KCCQ (Appendix 8)
  - FACT-GOG NTX (Appendix 9) – if applicable per Table 2

- Echocardiogram – ***every sixth month only (i.e., Month 6, Month 12, etc.)***; may be completed within 10 days prior to Day 1. To be eligible for the additional cardiac imaging analysis, the subject must have a 4-chamber view, 2-dimensional echocardiogram with Doppler.

- For subjects with liver involvement at Screening (*Exception:* not required in Germany): perform *scheduled* CT imaging of the abdomen for liver measurement every sixth month and/or *unscheduled* CT imaging at any other month per Section 7.6; imaging may be completed within the 10 days prior to Day 1. The dimension that was measured at Screening (i.e., craniocaudal) should be consistently measured for all subsequent assessments for the same subject.

- 12-lead ECG performed in triplicate - within 30 minutes prior to infusion

- Symptom-directed PE should be as clinically indicated and also include weight and assessment of macroglossia, submandibular nodes/fullness, adenopathy, ecchymoses, liver/spleen size (palpable +/-), ascites (+/-), and edema (which should be quantified on a scale of 0-4)

- ECOG PS (Appendix 13)

- NYHA class (Appendix 14)
- NIS-LL (Section 7.4 and Appendix 10) – if applicable per Table 2
- VASPI (Section 7.4 and Appendix 11) – if applicable per Table 2
- Local Laboratory Assessments:
  - If administering chemotherapy during the visit: Perform local laboratory assessments, including hematology and chemistry, and review results prior to dosing with chemotherapy
  - WOCBP: Serum pregnancy test
- Central Laboratory Assessments – ***Collect samples prior to 6MWT, if being performed on the same day***:
  - Hematology: CBC with differential, Hgb, Hct, and platelet count
  - Chemistry: sodium, potassium, chloride, bicarbonate, BUN, creatinine, creatinine clearance, glucose, ALT, AST, ALP, total bilirubin, direct bilirubin, LDH, eGFR, total protein, albumin, calcium, phosphate, and magnesium
  - Amylase
  - PT/INR and PTT
  - Complements C_3 and C_4
  - Troponin T
  - NT-proBNP
  - sFLCs
  - Serum IFE and PEP: Perform monthly. If a subject's first on-study hematologic complete response was assessed at the previous visit, perform serum IFE/PEP (and 24-hour urine IFE/PEP) at least 28 days after the initial assessment of response to confirm response.
  - Urinalysis
  - 24-hour urine collection (see Section 7.3) for:
    - Urine protein excretion – ***odd-numbered months only***
    - Urine IFE and PEP - If a subject's first on-study hematologic complete response was assessed at the previous visit, perform 24-hour urine IFE/PEP (and serum IFE/PEP) at least 28 days after the initial assessment of response to confirm response. Repeat every odd-numbered month (to correspond with 24-hour urine protein excretion collection) to assess for continuing response or progression. If the initial response confirmation needs to occur on an even-numbered month, perform an additional 24-hour urine collection.
- 6MWT; collect BP and HR pre- and post-6MWT administration

- Bioanalytical Laboratory Assessments – any time on Day 1, prior to the start of the infusion:
  - Pre-dose PK sample
  - Pre-dose anti-NEOD001 antibody sample
  - Pre-dose serum sample for archiving (only for those subjects who have consented to the collection and archiving of their samples for future correlative testing)
- Administer premedication within 30-90 minutes prior to the start of the infusion:
  - 25 mg diphenhydramine or an equivalent dose of a H1 antihistamine
  - 650 mg acetaminophen or an equivalent paracetamol dose
- Vital signs, including BP, HR, RR and temperature – within the 30 minutes prior to dosing, after premedication has been administered

Study Drug Administration:

- The dose of study drug may be delivered over 60 (±10) minutes if previous infusions have been well tolerated without infusion-related AEs (Section 6.5.1)

Assessments After Infusion:

- Bioanalytical Laboratory Assessments – PK samples are to be collected post-infusion at the following time points at ***Month 6-Day 1 and Month 12-Day 1***:
  - EOI (+5 minutes)
  - 0.5 hour (±5 minutes)
  - 1 hour (±10 minutes) post-EOI
- Vital signs, including BP, HR, RR and temperature – assessed in the same position as assessed pre-dose, at the following time points:
  - Immediately at the EOI (+10 minutes), which includes completion of the saline flush
  - 1 hour (±10 minutes) post-EOI
- Closely monitor subject for 90 (±10) minutes following completion of the study drug infusion per Section 6.5.1
- If standard of care chemotherapy is being administered, it may be administered following the post-study drug infusion observation period, and the review of local laboratory tests
- Assessment of AEs
- Record all changes to concomitant medications and therapy

7.1.4.8 All Other Months-Day 1 (±5 Days): Month 4-Day 1, Month 5-Day 1, Month 7-Day 1, Month 8-Day 1, etc.

The following assessments will be done on Day 1 of all other months (e.g., Months 4, 5, 7, 8, 10, 11, 13, etc.), unless otherwise noted:

Prior to Study Drug Infusion:

- For subjects with liver involvement at Screening (*Exception:* not required in Germany): perform *unscheduled* CT imaging of the abdomen for liver measurement, if applicable per Section 7.6
- Symptom-directed PE should be as clinically indicated and also include weight and assessment of macroglossia, submandibular nodes/fullness, adenopathy, ecchymoses, liver/spleen size (palpable +/-), ascites (+/-), and edema (which should be quantified on a scale of 0-4)
- ECOG PS (Appendix 13)
- NYHA class (Appendix 14)
- FACT-GOG NTX (Appendix 9) - if applicable per Table 2
- NIS-LL (Section 7.4 and Appendix 10) - if applicable per Table 2
- VASPI (Section 7.4 and Appendix 11) - if applicable per Table 2
- Local Laboratory Assessments:
  - If administering chemotherapy during this visit: Perform local laboratory assessments, including hematology and chemistry, and review results prior to dosing with chemotherapy
  - WOCBP: serum pregnancy test
- Central Laboratory Assessments:
  - Hematology: CBC with differential, Hgb, Hct, and platelet count
  - Chemistry: sodium, potassium, chloride, bicarbonate, BUN, creatinine, creatinine clearance, glucose, ALT, AST, ALP, total bilirubin, direct bilirubin, LDH, eGFR, total protein, albumin, calcium, phosphate, and magnesium
  - Amylase
  - PT/INR and PTT
  - Troponin T
  - NT-proBNP
  - sFLCs
  - Serum IFE and PEP: Perform monthly. If a subject's first on-study hematologic complete response was assessed at the previous visit, perform serum IFE/PEP (and

24-hour urine IFE/PEP) at least 28 days after the initial assessment of response to confirm response.

- Urinalysis
- 24-hour urine collection (see Section 7.3) for:
  - Urine protein excretion – ***odd-numbered months only***
  - Urine IFE and PEP - If a subject's first on-study hematologic complete response was assessed at the previous visit, perform 24-hour urine IFE/PEP (serum IFE/PEP) at least 28 days after the initial assessment of response to confirm response. Repeat every odd-numbered month (to correspond with 24-hour urine protein excretion collection) to assess for continuing response or progression. If the initial response confirmation needs to occur on an even-numbered month, perform an additional 24-hour urine collection.

- Bioanalytical Laboratory Assessments – any time on Day 1, prior to the start of the infusion:
  - Pre-dose PK sample
  - Pre-dose anti-NEOD001 antibody sample
  - Pre-dose serum sample for archiving (only for those subjects who have consented to the collection and archiving of their samples for future correlative testing)
- Administer premedication within 30-90 minutes prior to the start of the infusion:
  - 25 mg diphenhydramine or an equivalent dose of a H1 antihistamine
  - 650 mg acetaminophen or an equivalent paracetamol dose
- 12-lead ECG performed in triplicate - within 30 minutes prior to infusion
- Vital signs, including BP, HR, RR and temperature – within the 30 minutes prior to dosing, after premedication has been administered.

Study Drug Administration:

- The dose of study drug may be delivered over 60 (±10) minutes if previous infusions have been well tolerated without infusion-related AEs (Section 6.5.1)

Assessments After Infusion:

- Vital signs including BP, HR, RR and temperature – in the same position as assessed pre-dose, at the following time points:
  - Immediately at the EOI (+10 minutes), which includes completion of the saline flush
  - 1 hour (±10 minutes) post-EOI
- Closely monitor subject for 90 (±10) minutes following completion of the study drug infusion per Section 6.5.1
- If standard of care chemotherapy is being administered, it may be administered following the post-study drug infusion observation period, and the review of local laboratory tests

- Assessment of AEs
- Record all changes to concomitant medications and therapy

7.1.5 Concomitant Chemotherapy Visits

The first cycle of first-line, bortezomib-containing chemotherapy should be initiated on Month 1-Day 1, following administration of study drug and completion of the post-study drug observation period. Month 1-Day 1 is equivalent to Cycle 1-Day 1 of chemotherapy. Bortezomib should be given SC weekly on Days 1, 8, 15, and 22 according to the approved prescribing information and local institutional practices. Antiviral prophylaxis is required.

The subject must be closely monitored during at least the first 3 cycles of the first-line, bortezomib-containing chemotherapy regimen. ***During the first cycle of chemotherapy (i.e., Month 1 of the study), the subject must return to the study site for each administration of bortezomib and for assessments prior to each administration.*** In addition, subjects must receive Cycle 2-Day 1, Cycle 2-Day 15, and Cycle 3-Day 1 (i.e., Month 2-Day 1, Month 2-Day 15, and Month 3-Day 1, respectively) of bortezomib, along with any other chemotherapy, ***at the study site***.

During the second and third cycles, Cycle 2-Day 1, Cycle 2-Day 15, and Cycle 3-Day 1 will correspond to the Month 2-Day 1, Month 2-Day 15, and Month 3-Day 1 visits, respectively, during which visits, bortezomib, along with any other chemotherapy, will be administered ***at the study site*** and assessments will be performed prior to each administration. For chemotherapy on Cycle 2-Days 8 and 22, as well as Cycle 3-Days 8, 15, and 22, the subject should return to the study site for bortezomib administration and assessments ***if***, in the opinion of the Investigator, the subject is ***experiencing any significant toxicity*** that appears to exceed the anticipated side effects of the chemotherapy. At the Investigator's discretion, if the subject is ***not*** experiencing any unanticipated or significant toxicity, the subject may be administered bortezomib by their local physician, rather than by the Investigator.

In the event that bortezomib doses are missed, the chemotherapy cycles may become misaligned with the monthly study drug dosing. In this case, the weekly visits during Months 1 through 3 should continue as described above in order to closely monitor subjects' health during the initial months of concomitant chemotherapy. Throughout the study, monthly doses of study drug should not be delayed or skipped due to adjustments that are made to chemotherapy dosing. Study drug dosing adjustments are described in Section 6.6.

When bortezomib administration takes place at the subject's local physician's office, the FACT-GOG NTX assessment, vital signs, and central laboratory sample collection must be performed by a Prothena-sponsored healthcare professional within 1 day prior to or pre-dose on the same day as each administration of bortezomib. If bortezomib is administered on a Monday, then it is acceptable for the Homecare visit to take place on the previous Friday.

The number of cycles of first-line chemotherapy that is administered is at the discretion of the Investigator, and subsequent chemotherapy regimens may be prescribed as per standard of care at the Investigator's discretion. The Sponsor does not intend to provide reimbursement for

standard of care chemotherapy. Refer to Section 6.5.3 for guidance regarding cycles of chemotherapy beyond Month 3.

7.1.6 End of Treatment (EOT)/Early Treatment Discontinuation (ETD) (28-35 days post-final dose)

After approximately 156 primary endpoint events have occurred, the study will conclude and all subjects will have an EOT Visit. Subjects who discontinue study drug before the EOT should have an ETD Visit after they decide to end their treatment. The EOT/ETD Visit should be completed 28-35 days after the subject's final administration of study drug. Subjects who are willing to participate in additional visits after the ETD Visit should have assessments every third month per Appendix 3 (see also Section 8.2).

- Administer questionnaires in the following order, ***prior to conducting any other assessments on the day they are administered***:
  - SF-36v2 Questionnaire (Appendix 7)
  - KCCQ (Appendix 8)
  - FACT-GOG NTX (Section 7.4 and Appendix 9)
- Echocardiogram – unless it has been performed within the 60 days prior to the EOT/ETD Visit. To be eligible for the additional cardiac imaging analysis, the subject must have a 4-chamber view, 2-dimensional echocardiogram with Doppler.
- For subjects with liver involvement at Screening (*Exception:* not required in Germany): Perform CT imaging of the abdomen for liver measurement per Section 7.6, in any of the following situations:
  - If not done within the previous 60 days
  - If a ≥50% reduction from baseline in ALP is newly observed
  - To confirm a hepatic response (i.e., reduction in liver size) ≥ 28 days after the assessment of response

  If the initial occurrence of response based on liver size is assessed at the EOT/ETD Visit, then *unscheduled* imaging should be scheduled ≥ 28 days after that imaging was completed to confirm the assessment of response.
- 12-lead ECG performed in triplicate
- Complete PE including weight and examination of general appearance; head, ears, eyes, nose, and throat; neck; skin; cardiovascular system; respiratory system; gastrointestinal system; and nervous system. The following should be assessed: macroglossia, submandibular nodes/fullness, adenopathy, ecchymoses, liver/spleen size (palpable +/-), ascites (+/-), and edema (which should be quantified on a scale of 0 4).
- ECOG PS (Appendix 13)
- NYHA class (Appendix 14)

- NIS-LL (Section 7.4 and Appendix 10)
- VASPI (Section 7.4 and Appendix 11)
- Central Laboratory Assessments - ***Collect samples prior to 6MWT, if being performed on the same day:***
    - Hematology: CBC with differential, Hgb, Hct, and platelet count
    - Chemistry: sodium, potassium, chloride, bicarbonate, BUN, creatinine, creatinine clearance, glucose, ALT, AST, ALP, total bilirubin, direct bilirubin, LDH, eGFR, total protein, albumin, calcium, phosphate, and magnesium
    - Amylase
    - PT/INR and PTT
    - Additional coagulation samples, per Appendix 12
    - Complements C_3 and C_4
    - Troponin T
    - NT-proBNP
    - sFLCs
    - WOCBP: Serum pregnancy test
    - Serum IFE and PEP
    - Urinalysis
    - 24-hour urine collection (see Section 7.3) for:
        - Urine protein excretion
        - Urine IFE and PEP
- 6MWT; collect BP and HR pre- and post-6MWT administration
- Bioanalytical Laboratory Assessments:
    - PK sample
    - Anti-NEOD001 antibody blood sample
    - Serum sample for archiving (only for those subjects who have consented to the collection and archiving of their samples for future correlative testing)
- Vital signs, including BP, HR, RR, and temperature – after the subject has been at rest for ≥ 5 minutes
- Assessment of AEs
- Record all changes to concomitant medications and therapy

7.1.7 90-day Postdose Pregnancy Test

For WOCBP only: Obtain a local laboratory serum pregnancy test 90 (±5) days after the last administration of study drug.

7.1.8 Telephone Follow-Up Every Three Months

Follow-up phone calls should be made to randomized subjects (or their caregivers) who received a dose of study drug and are no longer receiving study drug every 3 months, beginning approximately 3 months from the subject's last visit. The subject's health status, as well as details of any hospitalizations will be collected accordingly in the study database to ensure adequate capture of primary endpoint events. New SAEs reported to the Investigator during this period will be reported to the Sponsor or its designee only if, in the judgment of the Investigator, the SAE is associated with any protocol intervention (i.e., related to study procedure or previous study drug exposure).

7.2 Order of Assessments

At each study visit, there are certain assessments that must be performed in a prescribed order, as follows:

- **Questionnaires:** At visits where one or more questionnaires are to be administered, the following order occurs ***prior*** to the performance of any other study assessments on the day they are administered:

  1. SF-36v2
  2. KCCQ
  3. FACT-GOG NTX

- **6MWT:** The postbaseline 6MWT may be administered on the same day as study drug administration as long as the NT-proBNP sample is drawn before conducting the 6MWT and the 6MWT is completed before initiation of the study drug infusion. Questionnaires and collection of central laboratory samples must be performed ***prior*** to administering the 6MWT, if being performed on the same day.

- **Chemotherapy:** Blood samples for local laboratory assessments must be collected per institutional practice ***prior*** to administration of chemotherapy. Within 3 days ***prior*** to the first day of a new regimen of chemotherapy, conduct an unscheduled central laboratory collection, including hematology, chemistry, and coagulation factors. If standard of care chemotherapy is administered on the same day as study drug, the chemotherapy must be administered ***after*** the 90 (±10)-minute post-study drug infusion observation period.

- **ECGs:** Medications given for prophylaxis chemotherapy-induced side effects should not be administered prior to completion of the post-infusion ECG.

- **Vital Signs:** Pre-dose vital sign assessments should be performed within the 30 minutes ***prior*** to dosing, ***after*** administration of study drug premedication. PK sample collection should take priority over collection of vital signs.

7.3 Laboratory Evaluations

A central laboratory will be used for analysis of hematology, chemistry, amylase, coagulation, NT-proBNP, troponin T, sFLCs, serum IFE/PEP, urinalysis, and 24-hour urine collection for urine IFE/PEP and urine protein excretion. Central and local pregnancy testing will be conducted as shown in Table 1.

Local laboratory results (e.g., hematology, chemistry) will be obtained for subject management when necessary for obtaining results on a more immediate basis. Local laboratory results should also be obtained and reviewed for a safety assessment prior to each administration of chemotherapy. Results from these local laboratory tests will not be collected in the eCRFs or the clinical database.

Citrated plasma samples may be collected and frozen for potential analysis of coagulation indices at a later date. These analyses may include but may not be limited to the indices listed in Appendix 12.

The 24-hour urine protein excretion and 24-hour urine IFE/PEP tests will be performed using the same 24-hour urine collection sample, when required at the same visit. Details regarding the 24-hour urine sample collection are provided in the Laboratory Manual.

In addition, a bioanalytical laboratory will be used for the analysis of PK and anti-NEOD001 antibody samples, as well as for the storage of serum samples for future correlative testing. Serum samples will be collected and archived at the bioanalytical laboratory for those subjects who have consented to the collection and use of their samples for future correlative studies. Samples will be stored for up to 5 years after completion of the study, after which point any remaining samples will be destroyed. Approximately 146 mL of blood will be collected from each subject during the first year of participation in the study for bioanalytical testing. Each month thereafter, 10 mL of blood will be collected from each subject for bioanalytical assessments.

One or more laboratories will be used for mass spectrometry of tissue samples, immunoelectron microscopy, gene sequencing, and/or ^{99m}Tc scintigraphy, which are required for a subset of subjects who meet Inclusion Criterion #5 (Section 4.1).

Details for the processing of laboratory specimens are provided in the Laboratory Manual.

7.4 Peripheral Neuropathy Assessment

In addition to assessing peripheral neuropathy adverse events using NCI-CTCAE grading as shown in Appendix 9, the following three assessments will be utilized to assess peripheral neuropathy:

- The FACT-GOG NTX (Appendix 9) assesses subject-reported neurotoxicity symptoms and concerns that evaluate Activities of Daily Living (ADL) with an 11-item scale with a range of possible scores of 0 to 44. The FACT-GOG NTX should be performed after the SF-36v2 and KCCQ (if being performed on the same day) and prior to any other study assessments on the day it is administered.

- The NIS-LL (Appendix 10) assesses reflexes, sensation, and motor strength to determine a peripheral neuropathy score, with a range of possible scores of 0 to 88.
- The VASPI (sample tool in Appendix 11) assesses a subject's level of pain related to peripheral neuropathy.

Peripheral neuropathy assessments will be performed as shown in Table 2. After Month 3, subjects who do not meet the criteria listed in the "Months 4-12" and "Months 13+" columns do not need to have the peripheral neuropathy assessments conducted until their EOT/ETD Visit.

Table 2: Peripheral Neuropathy Assessments

Assessment	Screening	Months 1-3	Months 4-12	Months 13+	EOT/ETD
FACT-GOG NTX (Appendix 9)	**All Subjects:** Once between Days -28 and -1 and again on Day -2 or Day -1	**All Subjects:** Weekly (Day 1, 8[a], 15[a], and 22[a] Visits)	• **Subjects who had positive scores at Screening and/or Month 3:** Months 6, 9, and 12 (Day 1 Visit) • **Subjects who are receiving identified concomitant medication[b]:** Monthly (Day 1 Visit) • **Subjects who had negative scores at Screening and Month 3 and new PN signs and symptoms develop:** Monthly (Day 1 Visit)	• **Subjects who had positive scores at Screening and/or Month 3:** Every sixth month (e.g., Months 18, 24 [Day 1 Visit]) • **Subjects who are receiving identified concomitant medication[b]:** Monthly (Day 1 Visit) • **Subjects who had negative scores at Screening and Month 3 and new PN signs and symptoms develop:** Monthly (Day 1 Visit)	**All Subjects**
NIS-LL (Appendix 10) **and VASPI** (Appendix 11)	**All Subjects:** Once between Days -28 and -1	**All Subjects:** Monthly (Day 1 Visit)	• **Subjects who had positive scores at Screening and/or Month 3:** Months 6, 9, and 12 (Day 1 Visit) • **Subjects who are receiving identified concomitant medication[b]:** Monthly[a] (Day 1 Visit) until completion of concomitant medication & then at Months 6, 9, and 12 (Day 1 Visit) or whatever remains of these months • **Subjects who had negative scores at Screening and Month 3 and new PN signs and symptoms develop:** At the next scheduled visit and then at Months 6, 9, and 12 (Day 1 Visit) or whatever remains of these months	• **Subjects who had positive scores at Screening and/or Month 3:** Every sixth month (e.g., Months 18, 24 [Day 1 Visit]) • **Subjects who are receiving identified concomitant medication[b]:** Monthly (Day 1 Visit) until completion of concomitant medication & then every sixth month (e.g., Months 18, 24 [Day 1 Visit]) • **Subjects who had negative scores at Screening and Month 3 and new PN signs and symptoms develop:** At the next scheduled visit and then every third month (e.g., Months 15, 18 [Day 1 Visit])	**All Subjects**

EOT/ETD = End of Treatment/Early Treatment Discontinuation; FACT-GOG NTX = Functional Assessment of Cancer Therapy – Gynecologic Oncology Group Neurotoxicity Subscale; NIS-LL = Neuropathy Impairment Score – Lower Limbs; PN = peripheral neuropathy; VASPI = Visual Analog Scale – Pain Intensity.

a Subjects who have discontinued study drug prior to the end of the study but are willing to return for visits will be assessed every third month (i.e., Months 3, 6, 9, and 12 or whatever remains of these visits) per Appendix 3.

b Bortezomib, another proteasome inhibitor, or other drug with the propensity to cause peripheral neuropathy.

Note: After Month 3, subjects who do not meet the criteria listed in the "Months 4-12" and "Months 13+" columns do not need to have the peripheral neuropathy assessments conducted until the EOT/ETD Visit.

7.5 6-Minute Walk Test

The 6MWT will be assessed twice during Screening, every third month, and at the EOT/ETD Visit (per Table 1). The postbaseline 6MWT may be administered on the same day that study drug is administered, if the 6MWT is completed before initiation of the study drug infusion. At least 4 days are required between the two Screening 6MWTs; therefore, the first Screening 6MWT must be performed between Day -28 and Day -5 and the second Screening 6MWT should be performed within 2 days ***prior*** to Month 1-Day 1 (i.e., on Day -2 or Day -1). Subjects should plan to be able to return to the same clinical site for each 6MWT from first Screening through Month 9.

Questionnaires and collection of central clinical laboratory samples must be performed ***prior*** to administering the 6MWT, if being performed on the same day.

As part of the 6MWT, BP and HR will be collected pre- and post-6MWT administration.

If the subject discontinues study drug prior to the Month 9 Visit, ***every effort should be made for the subject to return to the study site at the Month 9 time point for completion of all of the Month 9-Day 1 assessments, in particular, the 6MWT***.

Details regarding the requirements for proper administration of the 6MWT are described in a separate manual.

7.6 Liver Imaging

CT imaging of the abdomen for liver measurement will be conducted as follows (*Exception:* subjects in Germany are not required to have study-specific liver imaging; any liver imaging performed for these subjects will be at the discretion of the Investigator and will be considered standard of care):

- Perform Screening CT imaging if a subject has an ALP >1.5 × ULN (Note: If CT imaging has been conducted within 60 days prior to Screening Day -28 and it meets acquisition guidelines, it does not need to be repeated during Screening and the previous result can be used for eligibility)
- Perform CT imaging every sixth month (i.e., Months 6, 12, 18, etc.), within the 10 days prior to Day 1
- When there is a ≥50% reduction from baseline in ALP, perform *unscheduled* CT imaging within the 10 days prior to Day 1 of the applicable month
    - If the 50% reduction from baseline in ALP is maintained, yet no hepatic response based on liver measurement (i.e., ≥ 2 cm reduction in liver size from baseline radiographically) is observed, repeat CT imaging 3 months later to determine if response or progression is observed
- When there is a ≥ 2 cm reduction in liver size from baseline radiographically (Appendix 1) repeat CT imaging ≥ 28 days later to confirm the reduced liver size, and then revert back to the usual imaging schedule of every sixth month (i.e., Months 6, 12, 18, etc.)

- If no response or progression is observed, then the CT imaging schedule will continue every sixth month (i.e., Months 6, 12, 18, etc.)
- If CT imaging was performed within the 30 days of the next scheduled visit, that scan can be skipped until the following scheduled visit
- If imaging was completed within the 60 days prior to the EOT/ETD Visit, it does not need to be repeated **unless**:
  - a ≥ 50% reduction from baseline in ALP is newly observed **OR**
  - imaging is required for confirmation of a response observed at the previous assessment
- If the initial occurrence of response based on liver size is assessed at the EOT/ETD Visit, then *unscheduled* CT imaging should be scheduled ≥ 28 days after that imaging was completed to confirm the assessment of response

The dimension that was measured at Screening (i.e., craniocaudal) should be consistently measured for all subsequent assessments for the same subject. CT imaging should be done as per the imaging acquisition guidelines provided by the central imaging laboratory. Measurements will be performed by the central imaging laboratory and provided to the site.

7.7 Monitoring Anti-NEOD001 Antibodies During the Study

Serum anti-NEOD001 antibody levels will be measured on Day 1 of each month and at the EOT/ETD Visit. Additional serum samples to test for anti-NEOD001 antibodies should be collected if significant toxicity is observed (e.g., an infusion reaction in the clinic, anaphylaxis) and if possible, should be collected while the acute symptoms persist. Anti-NEOD001 antibody levels will be correlated with NEOD001 exposure level to assess potential dose concentration related associations when anti-NEOD001 antibody and corresponding PK data are available.

8 EMERGENCY UNBLINDING OF STUDY DRUG, EARLY DISCONTINUATION, OR TERMINATION FROM STUDY

8.1 Emergency Unblinding

The Investigator has the ability to break the blind for a specific subject in the event of an immediate medical emergency, where knowledge of the subject's treatment (NEOD001 or placebo) must be known in order to provide adequate medical treatment. In these situations, the breaking of the blind must be reported to the Sponsor within 24 hours. The procedure for the unblinding of a specific subject using the IXRS is provided in the Study File Notebook.

Any other requests to reveal a subject's treatment must be requested of, and approved by, the Medical Monitor.

8.2 Early Treatment Discontinuation

If the subject discontinues study drug prior to the end of the study, but is willing to continue to participate in study visits, the subject should have an ETD Visit within 28-35 days after his/her final administration of study drug (per Table 1 and Section 7.1.6) and then have assessments every third month per Appendix 3. ***The most important visit is the Month 9-Day 1 Visit, so if a subject is unwilling to continue visits every third month, every effort should be made for the subject to return and complete the Month 9-Day 1 Visit on schedule.*** All visits after the ETD Visit should occur on schedule, that is, at the time when their visit would have occurred had they remained on study drug.

If the subject discontinues study drug prior to the end of the study and is not willing to continue to participate in study visits, the subject should return for an ETD Visit 28-35 days after his/her final administration of study drug (per Table 1 and Section 7.1.6). If a subject fails to return for the scheduled visit, a documented effort must be made to determine the reason. If the subject cannot be reached by phone after two attempts, a certified letter will be sent to the subject (or the subject's legally authorized representative, if appropriate) requesting contact with the Investigator. This information will be recorded in the study records.

Reasons for early discontinuation from study drug treatment may include, but are not limited to:

- A suspected NEOD001-related immunologic reaction – collect additional serum samples, if possible, during the period following the treatment stoppage to allow for the determination of the persistence of anti-NEOD001 antibodies. At a minimum, samples should be collected at the ETD Visit and at the every third month visits through Month 12, if the subject agrees to return to the clinic.
- Occurrence of an AE or clinically significant laboratory abnormality that, in the opinion of the Investigator, warrants the subject's permanent discontinuation from study drug treatment; the Medical Monitor should be notified as soon as possible of any discontinuation of study drug due to an AE
- Suspected or confirmed pregnancy or nursing during study treatment period. Female subjects who has a positive pregnancy test at the ETD Visit must be followed to term or until termination of the pregnancy (Section 9.8).

At any point in the study, if a subject who was randomized and received a dose of study drug is unwilling to return to the study site for further visits but is willing to discuss his/her health status by phone, follow-up phone calls should be made to the subject or their caregiver, per Section 7.1.8.

8.3 Early Termination from the Study

Subject participation in this study will continue until the end of the study (i.e., after approximately 156 primary endpoint events have occurred). Early termination occurs if the subject fails to complete the entire study and is no longer participating in study visits. Subjects may withdraw their consent to participate in this study at any time without prejudice. The Investigator must withdraw from the study any subject who requests to be withdrawn. A subject's participation in the study may be discontinued at any time at the discretion of the Investigator in accordance with his/her clinical judgment. The Sponsor should be notified in a timely manner of all subject discontinuations.

Early termination from the study may occur if:

- Subject needs to receive any of the prohibited concomitant therapies listed in Section 6.8.2
- In the opinion of the Investigator, the subject cannot safely participate in the procedures required by the protocol
- Subject withdraws consent
- Subject is unwilling or unable to comply with the study requirements
- Subject is lost to follow-up
- Prothena reserves the right to discontinue the study at any time for any reason, including but not limited to, clinical or administrative reasons, or to discontinue participation of an individual Investigator or site for any reason, including but not limited to, poor enrollment or noncompliance.

Vital status will be collected within legal and ethical boundaries for all randomized subjects receiving at least one dose of study drug and will be searched in public sources. During the study close-out period, survival status will be collected within legal and ethical boundaries for all randomized subjects who withdrew participation from the study. If vital status is determined, the subject will not be considered lost to follow-up.

8.4 Replacement of Subjects

Randomized subjects who drop out of the study for any reason will not be replaced.

9 ADVERSE EVENTS/SERIOUS ADVERSE EVENTS AND REPORTING

Adverse events, both reported and observed, will be recorded in the source documents and on the appropriate eCRF page from the time initial eligibility is established during Screening (upon signature of the informed consent form) until the EOT/ETD Visit or for 28 days after the last dose, whichever is later. New SAEs (per definition in Section 9.1) occurring beyond the EOT/ETD Visit or >28 days after the last administration of study drug, whichever is later, will be reported to the Sponsor or its designee only if, in the judgment of the Investigator, the SAE is associated with any protocol intervention (i.e., related to study procedure or previous study drug exposure).

9.1 Definitions

Consistent with the current regulatory guidance provided by the US Code of Federal Regulations (CFR) and the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practices, AEs and SAEs are defined below.

AE Definition: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, syndrome, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. The AE may involve any organ or system and can be represented by the new onset, or the deterioration, of a disease, a syndrome, a symptom, or a physical sign, as well as by findings and results of instrumental examinations and laboratory tests. Any medically relevant and untoward change, including frequency or pattern changes for a fluctuating condition (e.g., migraine), occurring during the reporting period is considered an AE. All such occurrences must be recorded and reported to the Sponsor, or the Sponsor's designee, accordingly, whether or not they appear causally related to the study medication.

Examples include:

- The emergence of any signs and symptoms that were not present at baseline (an event present at baseline that has not changed is not considered an AE)
- Pre-existing conditions that are marked by a worsening from the subject's baseline/entry status (i.e., an increase in severity or frequency of the pre-existing abnormality or disorder)
- Reactions to study drug, abuse of drug, withdrawal phenomena, sensitivity, or toxicity to study drug
- Apparently unrelated illnesses
- Injuries or accidents
- Extensions or exacerbations or symptomatology, subjective events reported by the subject, or new clinically significant abnormalities in clinical laboratory tests, physiological tests or PE

SAE Definition: Any AE occurring at any dose that results in any of the following outcomes is an SAE:

- Death
- Life threatening
- Inpatient hospitalization, or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Important medical events

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and/or may require medical or surgical intervention to prevent one of the outcomes listed in the definition of SAEs. Examples of such events are:

- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

An SAE may also include any other event that the Investigator or Medical Monitor judges to be serious, or that suggests a significant hazard, contraindication, side effect, or precaution.

Important Note: The concepts of AEs and SAEs represent regulatory instruments used to evaluate and monitor the safety of clinical trial subjects. Therefore, these terms only apply in light of their regulatory definition. The term "serious," in a regulatory sense, does not necessarily mean "severe." All AEs (serious and non-serious) reported during a study will be taken into account when analyzing the study data and establishing the safety profile of the investigational drug.

Death: Death, in and of itself, is not an AE; it is only an outcome. The cause of death is the AE. Therefore, the Investigator should make every effort to obtain and document the cause of death for all subjects who die during the study. If, despite all efforts, the cause of death remains unknown, the SAE should be documented as an "unspecified fatal event."

Life-threatening AE: Any AE that places the subject, in the view of the Investigator, at ***immediate*** risk of death from the event as it occurred. This does not include an event that, had it occurred in a more severe form, might have caused death.

Hospitalization: Hospitalization is defined by the Sponsor as a full admission to the hospital for diagnosis and treatment. This includes prolongation of an existing inpatient hospitalization. Examples of visits to a hospital facility that do ***not*** meet the serious criteria for hospitalization include:

- Emergency room visits that do not result in a full hospital admission or that last for a period of less than 24 hours
- Outpatient surgery
- Preplanned or elective procedures
- Protocol procedures

A pre-scheduled elective procedure or a routinely scheduled treatment is not to be considered an SAE, even if the subject is hospitalized, provided the site stipulates that:

- The condition requiring the pre-scheduled elective procedure or routinely scheduled treatment was present before and did not worsen or progress between the subject's consent to participate in the clinical trial and the time of the procedure or treatment
- The pre-scheduled elective procedure or routinely scheduled treatment is the sole reason for admission and intervention

An untoward medical event occurring during the pre-scheduled elective procedure or routinely scheduled treatment should be recorded as an AE or an SAE, as appropriate.

Disability: A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.

9.2 Recording of Adverse Events

Subjects should be instructed to report to the study staff any AE that they experience, even those that may not be related to the study drug, and to discuss potential treatment. Subjects should be instructed to call the appropriate emergency response telephone number (911 if within the US) if they experience an AE that requires immediate attention or could, if untreated, have potentially serious consequences.

At each visit, the Investigator will prompt the subject with non-leading questions to determine if any AEs were experienced since the last visit. The Investigator must follow all AEs until the events have resolved or until the condition has stabilized and no further medical follow-up is warranted.

It is the responsibility of the Investigator to document all AEs that occur during the reporting period. Pre-existing conditions (noted before Screening) should not be reported as AEs unless they worsen (i.e., become more severe or more frequent) after beginning participation in the study (upon signing the informed consent form).

Whenever feasible, AEs should be documented as medical diagnoses and a unifying diagnosis should be provided. For example, symptoms including fever, productive cough, opacity in the left lower lobe of the lung on x-ray would be reported as a single AE of pneumonia. Otherwise, if reported AEs do not appear clearly inter-related, individual signs or symptoms may be reported as separate AEs. Information recorded on the appropriate page of the eCRF will include

the description of the AE, the date and time of onset and resolution (if applicable), severity, seriousness, relationship to the study drug, action taken, and the outcome.

When an AE resulting from disease progression meets the requirements to be considered serious the SAE verbatim term should be reported as the sign/symptom that best describes the event rather than as disease progression. For example, a subject presents with worsening shortness of breath due to a pleural effusion resulting from disease progression. The event term should be reported as "pleural effusion" instead of as disease progression.

9.3 Assessment of AEs: Severity

AEs will be assessed according to the NCI-CTCAE version 4.0. AEs that do not have a corresponding NCI-CTCAE term will be assessed according to their impact on the participant's ability to perform daily activities as listed below.

The severity of each AE should be characterized and then classified into one of five clearly defined categories as follows:

- Grade 1 (Mild): the AE does not interfere in a significant manner with the subject's normal functioning level; it may be an annoyance
- Grade 2 (Moderate): the AE produces some impairment of functioning, but is not hazardous to health; it is uncomfortable or an embarrassment
- Grade 3 (Severe): the AE produces significant impairment of functioning or incapacitation and is a definite hazard to the subject's health
- Grade 4 (Life threatening): Life threatening or disabling
- Grade 5 (Fatal): Causes death of the participant

These five categories are based on the Investigator's clinical judgment, which in turn depends on consideration of various factors such as the subject's reports, the Investigator's observations, and the Investigator's prior experience. The severity of the AE should be recorded in the appropriate section of the eCRF. The evaluation of severity is distinguished from the evaluation of "seriousness." A severe event might not meet the criteria for seriousness and a serious event might be evaluated as mild. For example, a subject might have a **severe** headache that does not require hospitalization and is consequently **not serious**; or a subject might have a **mild** myocardial infarction that requires hospitalization and is, therefore, **serious**.

9.4 Assessment of AEs: Relationship to Study Drug

The causality of each adverse event should be assessed and classified by the Investigator as "related" or "not related." An event is considered related if there is "a reasonable possibility" that the event may have been caused by the product under investigation (i.e., there are facts, evidence, or arguments to suggest possible causation).

Guidelines for "Related" Events

- There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out
- There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
- There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the study drug). However, the influence of other factors may have contributed to the event (e.g., the subject's clinical condition, other concomitant events).

Guidelines for "Not related" Events

- There is little evidence to suggest there is a causal relationship. There is another reasonable explanation for the event.
- An adverse event will be considered "not related" to the use of the product if any of the following tests are met:
    - An unreasonable temporal relationship between administration of the product and the onset on the AE (e.g., the event occurred either before, or too long after administration of the product for it to be considered product-related)
    - A causal relationship between the product and the AE is biologically implausible (e.g., death as a passenger in an automobile accident)
    - A clearly more likely alternative explanation for the AE is present (e.g., typical adverse reaction to a concomitant drug and/or typical disease-related event)

Consider the Following When Assessing Causality

- Temporal associations between the agent and the event
- Effect of dechallenge and/or rechallenge
- Compatibility with known class effect
    - The likelihood the AE can be attributed to the use of concomitant drugs, in particular chemotherapeutic agents used in treating the subject's underlying PCD (see the current prescribing information for chemotherapeutic products used as standard of care; refer to Appendix 15)
- Pre-existing risk factors
- A plausible mechanism
- Concurrent illnesses

9.5 Assessment of AEs: Outcome

Recovered/Resolved:	The event has improved or recuperated.
Recovered/Resolved with Sequelae:	The subject recuperated but retained pathological conditions resulting from the prior disease or injury.
Recovering/Resolving:	Event is improving.
Not Recovered/Not Resolved:	Event has not improved or recuperated.
Fatal:	The termination of life as a result of an AE.
Unknown:	Not known, not observed, not recorded, or refused.

(Source: Clinical Data Interchange Standards Consortium [CDISC] in collaboration with the National Cancer Institute's Enterprise Vocabulary Services.)

9.6 Reporting of Serious Adverse Events

It is the responsibility of the Principal Investigator to report SAEs to the Sponsor or its designee. Any SAE that occurs at any time during the study (Screening until the EOT/ETD Visit or for 28 days after the last dose of study drug, whichever is later) whether or not related to study drug, must be reported within 24 hours of discovery to the Sponsor or its designee. New SAEs occurring beyond the EOT/ETD Visit or >28 days after the last administration of study drug, whichever is later, will be reported to the Sponsor or its designee only if, in the judgment of the Investigator, the SAE is associated with any protocol intervention (i.e., related to study procedure or previous study drug exposure). Do **not** delay in the reporting of an SAE in order to obtain additional information. Any additional information, if collected, can be reported to the Sponsor as a follow-up to the initial report. The SAE report should include the subject identification number or other appropriate terminology and the narrative should be comprehensive, including a chronology and assessment of the event. The SAE report should also include the Investigator's assessment of the relationship of the event to the use of study drug. This assessment can be changed as more information becomes available.

The Investigator is encouraged to discuss with the Medical Monitor any AEs for which the assessment of seriousness is unclear or questionable. Contact information for the Medical Monitor is found in the Study Manual.

9.7 Follow-up of Adverse Events

All AEs experienced by a subject, regardless of the suspected causality, will be followed until the event has resolved, until the Investigator and/or the Medical Monitor deems the event to be chronic or stable, until there is a satisfactory explanation for the changes observed, or until the subject is lost to follow-up.

9.8 Pregnancy

The Sponsor has a responsibility to monitor the outcome of all pregnancies reported during the clinical study. Although pregnancy is not considered an SAE, an abnormal outcome of pregnancy is an SAE. Therefore, the Pregnancy Form should be used to report to the Sponsor the pregnancy of a female subject, or the pregnancy of the female partner of a male subject.

Each pregnancy must be reported by the Investigator to the Sponsor within 24 hours after becoming aware of the pregnancy. The Investigator must follow-up and document the course and the outcome of all pregnancies even if the subject was withdrawn from the clinical study or if the clinical study has ended. Pregnancies must be followed until birth, termination of the pregnancy, or loss of the subject to follow-up.

9.9 Urgent Safety Measures

The Sponsor is required to follow global regulations including EU regulations which state that the appropriate regulatory bodies, including IRBs/ECs/REBs, be notified according to their respective regulations of any new event resulting in the Sponsor and Investigator taking urgent safety measures to protect subjects against any immediate hazards.

The reporting period for these events, which may require the implementation of urgent safety measures, is the period from the time the ICF is signed through the completion of the EOT/ETD Visit or for 28 days after the last dose of study drug, whichever is later. Investigators are required to report any events which may require the implementation of urgent safety measures to Sponsor within 24 hours. Examples of situations that may require urgent safety measures include the following:

- Immediate need to revise the study drug administration (e.g., modified dose amount or frequency not defined in protocol)
- Change in the study which has a significant impact on the scientific value of the clinical trial
- Detrimental study conduct or management
- Discovery that the quality or safety of the study drug does not meet established safety requirements

10 STATISTICAL CONSIDERATIONS

A statistical analysis plan (SAP), providing details about the specific planned analyses and hypothesis tests, will be prepared and approved by the Sponsor and its designees prior to study database lock and unblinding of double blind subject treatment assignments.

10.1 Analysis Populations

The Intent to Treat (ITT) Population will include all randomized subjects with AL amyloidosis who receive any amount of study drug (NEOD001 or placebo). The ITT Population will be the primary population used for efficacy analyses. The Safety Population will include all subjects with AL amyloidosis who receive any amount of study drug (NEOD001 or placebo). The Safety Population will be the primary population used for safety analyses.

Additional analysis populations may be defined in the SAP.

Efficacy Subset Populations:

The Renal Evaluable Population will include subjects who had renal involvement (i.e., proteinuria >0.5 g/24 hours [measured by 24-hour urine total protein excretion]) at baseline and at least 1 postbaseline assessment of proteinuria.

The Peripheral Neuropathy Evaluable Population will include subjects who had peripheral nerve involvement at baseline (only if the subject had ascending sensorimotor neuropathy at screening due to AL amyloidosis etiologies answered as yes) and had a baseline NIS-LL total score of 2 or greater and at least 1 postbaseline peripheral neuropathy assessment.

The Hepatic Evaluable Population will include subjects who had hepatic involvement defined as one of the following: 1) >1.5 × ULN alkaline phosphatase at baseline and at least 1 postbaseline assessment of alkaline phosphatase or 2) baseline total liver size (i.e., craniocaudal dimension) >15 cm and at least 1 postbaseline assessment total liver size.

10.2 General Considerations

Subject disposition will be summarized for all screened subjects and will include the number of subjects screened, the number screened but not randomized with reasons for screen failure, the number randomized, the number randomized and not treated, the number in each subject population for analysis, the number who withdraw from study prior to completing the study and reason(s) for withdrawal, and the number who discontinued treatment early and reason(s) for discontinuation of treatment. The demographic and baseline characteristics will be presented by treatment group and overall for the ITT and Safety populations. Duration of study drug exposure will be summarized using descriptive statistics by treatment group for the Safety Population.

Continuous variables will be summarized by the number of subjects, mean, standard deviation (SD), standard error of the mean (SEM), median, 25th quartile (Q1), 75th quartile (Q3), minimum, and maximum values. Categorical variables will be summarized using frequency counts and percentages.

10.3 Efficacy Analyses

10.3.1 Primary Analysis

The primary endpoint is time to all-cause mortality or cardiac hospitalization as adjudicated by the CEC (Section 3.4.1 and Section 11.2).

For all-cause mortality, all deaths occurring after the first infusion of study drug (i.e., Study Day 1) through the study's last subject last visit (LSLV) will be included. Cardiac hospitalization occurring ≥91 days after a subject's first infusion of study drug through LSLV will be included. All primary endpoint events will be adjudicated. Each subject will be counted only once in the primary analysis, based on their first adjudicated occurrence of an endpoint event.

In addition, each component of the primary efficacy endpoint will be evaluated separately.

The distribution of the primary endpoint of time to all-cause death or cardiac hospitalization in the two treatment groups will be summarized using the Kaplan-Meier method. The two treatment groups will be compared using a two-sided stratified (by the randomization stratification factors) log-rank test at the alpha=0.05 level of significance.

10.3.2 Key Secondary Efficacy Analyses

If the primary analysis is statistically significant ($p<0.05$) in favor of NEOD001, the following key secondary endpoints will be analyzed using a fixed-sequence testing procedure in the order specified below to control the overall level of significance:

- Change from baseline to Month 9 in the PCS score of the SF-36v2
- Change from baseline to Month 9 in the 6MWT distance (meters)
- NT-proBNP (cardiac) best response from baseline through Month 9

For each of these endpoints, the treatment groups will be compared using a two-sided test at the alpha=0.05 level of significance. However, once a nonsignificant result ($p>0.05$) occurs, the results of all subsequent analyses will be considered nominal, descriptive, and exploratory rather than confirmatory.

The SF-36v2 PCS score change from baseline at Month 9 will be analyzed using a restricted maximum likelihood (REML) based mixed-effect model for repeated measures (MMRM) model including fixed effects for randomization strata, treatment group, categorical time point, and the treatment group × time point interaction, and with the baseline value included as a covariate. The unstructured covariance model will be used. The 6MWT distance (meters) change from baseline at Month 9 will be analyzed using a rank ANCOVA model including fixed effects for randomization strata and treatment group, with the ranked baseline value included as a covariate. The Hodges-Lehman estimate of the median treatment difference with associated 95% CI will be presented. The NT-proBNP (cardiac) best response rates in the 2 treatment groups will be compared using the Cochran-Mantel-Haenszel (CMH) test stratified by the randomization stratification factors.

10.3.3 Additional Secondary Efficacy Analyses

For the Renal Evaluable Population, renal best response will be analyzed in the same manner described for NT-proBNP (cardiac) best response. For the Peripheral Neuropathy Evaluable Population, the change from baseline in NIS-LL total score will be analyzed in the same manner described for the SF-36v2 PCS score. For the Hepatic Evaluable Population, hepatic best response will be analyzed in the same manner described for NT-proBNP (cardiac) best response.

10.3.4 Exploratory Efficacy Analyses

Endpoints that are defined as time-to-event variables will be analyzed in the same manner as the primary endpoint. Quantitative exploratory endpoints will be analyzed in the same manner described for the SF-36v2 PCS score. Exploratory endpoints that are defined as proportions will be analyzed in the same manner described for NT-proBNP (cardiac) best response. All exploratory analyses will be carried out using two-sided tests at the alpha=0.05 level of significance.

10.3.5 Handling of Missing Data

Every effort must be made to avoid missing data. For all time-to-event endpoints, subjects with no data after randomization will be censored on Day 1 (first day of study drug dosing). As a sensitivity analysis, subjects with no data after randomization will be considered to have an event on Day 1 (first day of study drug dosing).

Missing data for quantitative endpoints will not be imputed; all available data from each subject will be included in the linear mixed model analysis. Additional approaches for sensitivity analyses of the effects of missing data for primary, secondary, and exploratory endpoints may be provided in the SAP.

For proportion endpoints, missing data will be replaced by the least favorable response.

10.3.6 Subgroup Analyses

The primary and key secondary efficacy endpoints will be analyzed for subject subgroups using the ITT Population including the interaction between treatment group and the subgroup. In addition, select safety analyses will also be analyzed for subject subgroups using the Safety Population. Subgroups will be defined based on baseline values and only if there is a sufficient number of subjects in each category of the subgroup (e.g., >5 subjects per treatment group). Baseline subgroups of interest are as follows:

- Age (<65, ≥65 years; <75, ≥75 years)
- Sex (males, females)
- Race (White, Non-White [Black or African American, Asian, Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native])
- Geographic Region (North America, Rest of World)
- IWRS Stratification Factor Mayo Clinic Stage (I/II vs. III/IV)
- Baseline NYHA Class (I/II vs. III/IV)

- IWRS Stratification Factor Renal Stage (I vs. II/III)
- IWRS Stratification Factor 6MWT distance (<300 meters vs. ≥300 meters)
- Baseline NT-proBNP (<1800 pg/mL vs. ≥1800 pg/mL)

10.4 Safety Analyses

Safety data, including AEs, and clinical laboratory observations will be summarized by treatment group using the Safety Population. A comparison of safety will be made between the two arms of the study.

10.4.1 Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities. Summary tables of TEAEs will be provided. The incidence of TEAEs will be tabulated by system organ class and preferred term for each treatment group, and by severity and relationship to treatment. Tables of TEAEs leading to study drug discontinuation and SAEs will be provided. TEAEs are defined as those AEs or SAEs that occur from the initiation of the first study drug infusion through the 28-day period following the last dose of study drug.

10.4.2 Clinical Laboratory Evaluations

Descriptive statistics summarizing central laboratory data will be presented for all study visits. Changes from baseline to each study visit will also be summarized by treatment group. In addition, mean change from baseline will be summarized for the maximum and minimum post-treatment values and for the values at the EOT/ETD Visit.

The number and percent of subjects with a lab value with CTCAE Grade ≥3 and the number and percent of subjects with a CTCAE shift of ≥2 grades will be presented.

10.4.3 Additional Safety Analysis

Additional safety assessments include vital signs and ECGs. Descriptive statistics of the vital sign and ECG parameters will be presented by treatment group and study visit, as well as the change from baseline at each visit.

10.5 Pharmacokinetic Analyses

Serum NEOD001 concentrations and elapsed time from the preceding NEOD001 dose will be listed. Serum NEOD001 concentrations from this study will be pooled with data from similar samples from other NEOD001 studies in a population PK analysis. There will be no PK analyses for this protocol.

10.6 Immunogenicity

Serum anti-NEOD001 antibody titers will be listed and, if sufficient data exist, summarized by treatment group. Serum anti-NEOD001 antibody titers may be correlated with serum NEOD001 concentrations and select safety endpoints, if sufficient data exist.

An electrochemiluminescent (ECL) assay format will be used to detect serum anti-NEOD001 antibodies in the study.

10.7 Interim Analysis

No interim analyses are planned for this study.

10.8 Determination of Sample Size

For the endpoint of time to all-cause mortality or cardiac hospitalization, the assumed 18-month event rate in the control arm is 60%, based on Kumar 2012. The 18-month event rate in the active arm is assumed to be 42%, a relative reduction of 30%. These assumptions correspond to a hazard ratio of 0.594. For a two-arm study with 1:1 randomization, and based on the use of a two-sided test at the alpha=0.05 level of significance, a total of 156 events (both arms combined) are required for 90% power. The study is designed to have 90% power in accordance with common practice for the design of confirmatory trials. Assuming an accrual period of 24 months, and a treatment/follow-up period of 18 months (i.e., a total study duration of 42 months), a total sample size of approximately 236 subjects will be required to attain 156 events.

11 STUDY COMMITTEES

11.1 Data Monitoring Committee (DMC)

The primary objective of the independent DMC is to safeguard the interests of subjects in the study and to help ensure the integrity and credibility of the study. The DMC abides by the principles set forth in the Food and Drug Administration (FDA) Guidance for Clinical Trial Sponsors, Establishment and Operation of Clinical Trial Data Monitoring Committees. The DMC is composed of individuals external to the study organizers, Sponsors, and Investigators and operates under the DMC's written Charter that includes standard operating guidelines. The DMC will conduct reviews of accumulating data from the study on a regular basis and will advise the Sponsor regarding the continuing safety of trial subjects and those yet to be recruited to the trial, as well as the continuing validity and scientific merit of the trial. It is possible that the DMC may advise the Sponsor to stop the study based on its review of the accruing data that indicate clear harm to subjects participating in the study. A DMC Charter will be drafted to provide the guidelines for its operations and monitoring plans.

The DMC members will review safety reports on a monthly basis. After the first 20 subjects have completed 3 cycles of randomized treatment, the DMC will conduct a review to confirm the safety and tolerability of the administration of NEOD001 and concomitant chemotherapy. This will include review of aggregated data to assess SAEs. The DMC will meet at least twice a year starting when the first subject is exposed to study medication, and continuing until the study is terminated and the database is locked and finalized.

11.2 Clinical Events Committee (CEC)

An independent CEC, previously referred to as the Cardiovascular Adjudication Committee (CAC), blinded to treatment groups, will provide independent central adjudication of all deaths and hospitalizations. The CEC will define in its Manual of Procedures (MOP) cardiac events for use in the primary and secondary outcome analyses. The members of this committee will be experts in cardiac event adjudication and will be responsible for determining if hospitalizations meet the adjudication standard to be considered as a primary endpoint. The members of the CEC will not directly participate in this trial, nor will they participate as a member of the DMC.

Any potential endpoint event (i.e., death or hospitalization) must be reported to the Sponsor or designee within 24 hours after the site staff learns of the clinical event. Study sites should collect the required documents, including the relevant completed endpoint eCRFs and the requested source documentation for submission to the CEC in a timely fashion for adjudication of the event.

Further details regarding endpoint event submission guidelines, the CEC responsibilities, and the process of adjudication are described in the CEC MOP.

11.3 Hepatic Response Committee

Hepatic responses according to consensus criteria (Comenzo 2012) may be subject to independent review by a Hepatic Response Committee.

12 DATA RECORDING, RETENTION, AND MONITORING

12.1 Case Report Forms

The clinical sites participating in this study are required to submit clinical data for each enrolled subject via an electronic data capture (EDC) system, using an eCRF. Site personnel will be trained on the EDC system before receiving access to it. The Sponsor or its designee is responsible for maintaining a record of all system users. The participants of the study will not be identified by name on any study documents to be collected by the Sponsor.

All clinical information requested in this protocol will be recorded on the eCRFs provided by the Sponsor or their designee (or via other data collection methods, e.g., electronic laboratory data transfer). The Principal Investigator is responsible for reviewing all eCRFs for their subjects, verifying them for accuracy, and approving them via an electronic signature. Copies of the completed eCRFs, saved to disk in pdf format, will be sent to the Investigator's site at the completion of the study.

12.2 Availability and Retention of Records

The Investigator must make study data accessible to the study monitor, other authorized representatives of the Sponsor, and Regulatory Agency inspectors upon request. A file for each subject must be maintained that includes the signed Informed Consent Form (ICF) and the Investigator's copies of all source documentation related to that subject. The Investigator must ensure the reliability and availability of source documents from which the information on the eCRF was derived.

Investigators are required to maintain all study documentation, including documents created or modified in electronic format, for at least 15 years following the completion of the study. ICFs and adequate records for the receipt and disposition of all study drug must be retained for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated, or if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA and other applicable Regulatory Authorities are notified, unless a longer period is required by applicable law or regulation. The Investigator must not discard any records unless given written authorization by the Sponsor.

Subject identity information will be maintained for 15 years unless applicable law or regulation requires a longer period.

12.3 Quality Control and Quality Assurance

Sponsor representatives and regulatory authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the study (e.g., eCRFs and other pertinent data), provided that subject confidentiality is respected.

The study monitor is responsible for inspecting the eCRFs at regular intervals throughout the study to verify the following: adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research.

The monitor should have access to subject medical records and other study-related records needed to verify the entries on the eCRFs. The Investigator must agree to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

In accordance with ICH Good Clinical Practice (GCP) and Sponsor's (or designee's) audit plans, this study may be selected for an audit. Inspection of site facilities (e.g., pharmacy, drug storage areas, laboratories, etc.) and review of study-related records may occur in order to evaluate the trial conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

12.4 Subject Confidentiality

The Investigator must ensure that each subject's anonymity is maintained as described below. On the eCRFs or other documents submitted to the Sponsor or its designee, subjects must be identified by no more than their initials, date of birth, and a Subject Identification Number. Documents that are not for submission to the Sponsor (e.g., signed ICFs) should be kept in strict confidence by the Investigator in compliance with applicable regulations and ICH GCP Guidelines. The Investigator and institution must permit authorized representatives of the Sponsor, of regulatory agencies, and the IRB/EC direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are needed for the evaluation of the study. The Investigator is obligated to inform the subject in the ICF that the above named representatives may review study-related records from subjects.

13 ETHICAL AND LEGAL ISSUES

13.1 Ethical Conduct of the Study

The Investigator and Sponsor will ensure that this study is conducted in full compliance with the "Declaration of Helsinki" ICH guidelines, the CFR and/or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject.

13.2 Regulatory Approval

The Sponsor/designee will make the appropriate applications to the Regulatory Authority in each participating country for regulatory approval of the study and, if necessary, approval to import Investigational Product. The study will not start in a given region until the required regulatory approvals have been obtained in the appropriate jurisdiction.

13.3 Independent Review Board / Ethics Committee (EC) Approval

The Investigator at the site is responsible for obtaining Institutional Review board/Ethics Committee (IRB/EC) approval for the final protocol, the Sponsor or designee-approved ICF, and any materials provided to or used to recruit subjects. Written approval of these documents must be obtained from the IRB/EC before any subject may be enrolled at the site.

The Investigator is also responsible for the following interactions with the IRB/EC:

- Obtaining IRB/EC approval for any protocol amendments and ICF revisions before implementing the changes
- Providing the IRB/EC with any required information before or during the study
- Submitting progress reports to the IRB/EC, as required during the conduct of the study, requesting re-review and approval of the study, as needed, and for providing copies of all IRB/EC re-approvals and relevant communication to the Sponsor or its designee
- Notifying the IRB/EC of all serious and unexpected AEs related to the study medication reported by the Sponsor or its designee, as required by local regulations

13.4 Subject Informed Consent

The Sponsor or its designee must review and approve the draft ICF and any amended ICFs prepared by the Investigator prior to submission to the IRB/EC for approval. An IRB/EC-approved copy of the ICF and all amendments will be forwarded to Prothena.

The ICF documents the study-specific information the Investigator provides to the subject and the subject's agreement to participate. Among other things, the Investigator will fully explain in layman's terms the nature of the study, along with the aims, methods, potential risks, and any discomfort participation in the study may entail. The subject must voluntarily, personally sign and date the ICF before any study-related procedures are performed. The original and any

amended, signed and dated ICF(s) must be retained in the subject's file at the study site and a copy of the signed ICF must be provided to the subject.

13.5 Subject Compensation for Adverse Effects on Health

The Sponsor or its designee will adhere to local regulations regarding clinical trial compensation guidelines to subjects whose health is adversely affected by taking part in the study.

13.6 Protocol Amendments and Study Termination

The Sponsor or its designee may amend the protocol as needed to ensure that the clinical investigation is being conducted as intended. The Sponsor or its designee will initiate protocol amendments in writing if any change significantly affects the safety of subjects, the scope of the investigation, or the scientific quality of the study. Protocol changes must be submitted to the IRB/EC as a protocol amendment. If necessary, the ICF will be revised to reflect the changes in the amendment and will be submitted to the IRB/EC for review and approval. A copy of the amendment signature page must be signed by the Investigator and returned to the Sponsor or its designee. Written documentation of IRB/EC approval is required before the amendment is implemented.

Both the Sponsor and the Investigator reserve the right to terminate the study, according to the study contract. The Investigator should notify the IRB/EC in writing of the trial's completion or early termination and send a copy of the notification to the Sponsor and/or their designee.

13.7 Finance, Insurance and Indemnity

A study center will not initiate study participation until a fully executed Clinical Study Agreement is in place between the study center and the Sponsor. All details associated with finance, insurance and indemnity will be delineated in the Clinical Study Agreement.

14 PUBLICATION

All publication rights are delineated in the Clinical Study Agreement.

15 REFERENCES

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16 APPENDICES

APPENDIX 1: ORGAN RESPONSE AND PROGRESSION CRITERIA

Organ	Response	Progression
Heart/Cardiac[1]	NT-proBNP response (> 30% and > 300 ng/L decrease in patients with baseline NT-proBNP ≥ 650 ng/L) or NYHA class response (≥ 2 class decrease in subjects with baseline NYHA class III or IV)	NT-proBNP progression (> 30% and > 300 ng/L increase)[2]
Kidney/Renal[3]	≥ 30% decrease in proteinuria or drop of proteinuria below 0.5 g/24 hours in the absence of renal progression	≥ 25% decrease in eGFR
Peripheral Nerve[4]	NIS-LL increase from baseline of <2 points	NIS-LL increase from baseline of ≥ 2 points
Liver/Hepatic[1]	50% decrease in abnormal ALP value OR ≥ 2 cm reduction in liver size radiographically	≥ 50% increase in ALP above lowest value

ALP = alkaline phosphatase; eGFR = estimated glomerular filtration rate (as estimated by the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation); NIS-LL = Neuropathy Impairment Score–Lower Limbs; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association.

1 Modified from Table 2 in Comenzo 2012. In addition to the progression criteria listed above, Investigators will use their best clinical judgment in circumstances that do not meet the specifically referenced criteria above in assessing the progression. A repeated assessment at an interval that is determined by the investigator is required to confirm the progression.

2 Patients with progressively worsening renal function cannot be scored for NT-proBNP progression.

3 Palladini 2014.

4 Coelho 2012.

APPENDIX 2: STRATIFICATION DETAILS

Stratification Details for Mayo Staging Criteria

Test	Value	Score
NT-proBNP	< 1,800 pg/mL	0
	≥1,800 pg/mL	1
Troponin-T	≤0.03 ng/mL[1]	0
	>0.03 ng/mL[1]	1
dFLC	<18 mg/dL	0
	≥18 mg/dL	1
	Total Score	0 = Mayo Stage I 1 = Mayo Stage II 2 = Mayo Stage III 3 = Mayo Stage IV

1 Modified from the value of 0.025 ng/mL cited in Kumar et al, to 0.03 ng/mL, which is the lowest validated determination for this commercially available test.

Source: Kumar 2012.

Stratification Details for Renal Staging

Test	Value	Score
Proteinuria	≤5 g/24 hours	0
	>5g/24 hours	1
eGFR	≥50 mL/min/1.73 m^2	0
	<50 mL/min/1.73 m^2	1
	Total Score	0 = Renal Stage I 1 = Renal Stage II 2 = Renal Stage III

eGFR = estimated glomerular filtration rate.

Source: Palladini 2014.

APPENDIX 3: Schedule Of Events For Subjects Who Discontinue Study Drug Early but Agree to Return For Assessments After the ETD Visit

Assessments	Months 3, 6, 9, 12 Day 1 (±5)[1]	Every Third Month After Month 12[2] (e.g., Months 15, 18, 21) Day 1 (±5)	Every 3 Months after Last Visit
SF-36v2 Health Survey[3]	X		
KCCQ[3]	X		
FACT-GOG NTX[3,4]	Per Section 7.4 & Table 2		
Echocardiogram	Months 6 and 12[5]		
Liver Imaging (CT)	Months 6 and 12[6]		
12-lead Triplicate ECG[7]	X		
Symptom-Directed PE[8]	X		
ECOG PS & NYHA Class	X		
NIS-LL[9]	Per Section 7.4 & Table 2		
VASPI[10]	Per Section 7.4 & Table 2		
Local Laboratory			
Serum Pregnancy (WOCBP)	X[11]		
Central Laboratory[12]			
Hematology & Chemistry	X		
Amylase	X		
Coagulation[13]	X		
Complements C_3, C_4	X		
Troponin T	X		
NT-proBNP	X		
Serum Free Light Chains (sFLCs)	X		
Serum IFE/PEP	X[14]		
Urinalysis	X		
24-hour Urine Collection for:			
Urine Protein Excretion[15]	Months 3 and 9		
Urine IFE/PEP[15]	Months 3 and 9[16]		
6-Minute Walk Test (6MWT)	X	X[17]	
Bioanalytical Laboratory			
Anti-NEOD001 Antibody Sample[18]	X		
Vital Signs	X[19]	X[17]	
Adverse Event Assessment	X[20]	X[17, 20]	
Concomitant Medications	X	X[17]	
Health Status & Hospitalizations	X[21]	X[17, 21]	X[17, 20, 21]
Vital Status Phone Call			X[22]

BP = blood pressure; CT = computed tomography; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; ETD = Early Treatment Discontinuation; FACT-GOG NTX = Functional Assessment of Cancer Therapy – Gynecologic Oncology Group Neurotoxicity Subscale; HR = heart rate; IFE = immunofixation electrophoresis; KCCQ = Kansas City Cardiomyopathy Questionnaire; NGAL = neutrophil gelatinase-associated lipocalin; NIS-LL = Neuropathy Impairment Score – Lower Limbs; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; PE = physical exam; PEP = protein electrophoresis; RBP = retinol-binding protein; RR = respiratory rate; 6MWT = 6-minute walk test; SF-36v2 = Short Form-36 Version 2; VASPI = Visual Analog Scale – Pain Intensity; WOCBP = women of childbearing potential.

1. If a subject discontinues study drug prior to the end of the study, but is willing to continue to participate in study visits, the subject should have an ETD Visit within 28-35 days after the last study drug administration (per Table 1 and Section 7.1.6) and then have assessments performed every third month (i.e., Months 3, 6, 9, and 12, or whatever remains of these visits). ***The most important visit is the Month 9-Day 1 Visit, so if a subject is unwilling to continue visits every third month, every effort should be made for the subject to return and complete the Month 9-Day 1 Visit on schedule.*** All visits after the ETD Visit should occur on schedule, that is, at the time when the visit would have occurred had the subject remained on study drug.
2. If subject is willing to return to the study site, otherwise, subjects will receive vital status phone calls per Footnote 22.
3. Administer questionnaires in the following order prior to the performance of any other study assessments on the day they are administered: SF-36v2 (Appendix 7), KCCQ (Appendix 8), and FACT-GOG NTX (Appendix 9).
4. Administer the FACT-GOG NTX (Appendix 9) per Table 2.
5. Perform echocardiograms within 10 days prior to Day 1 of Months 6 and 12. To be eligible for the additional cardiac imaging analysis, the subject must have had a 4-chamber view, 2-dimensional echocardiogram with Doppler.
6. For subjects with liver involvement at Screening (*Exception*: not required in Germany), perform *scheduled* repeat CT imaging of the abdomen for liver measurement at Months 6 and 12 and *unscheduled* repeat CT imaging as needed per Section 7.6.
7. ECG to be performed in triplicate.
8. Symptom-directed PE should be as clinically indicated and also include weight, and assessment of macroglossia, submandibular nodes/fullness, adenopathy, ecchymoses, liver/spleen size (palpable +/-), ascites (+/-), and edema (which should be quantified on a scale of 0-4).
9. Administer NIS-LL (Appendix 10) per Table 2.
10. Administer VASPI (Appendix 11) per Table 2.
11. Obtain local laboratory serum pregnancy test 90 (±5) days after the last study drug administration.
12. Collect central laboratory samples before 6MWT, if being performed on the same day.
13. Collect PT/INF and PTT at each time point. As clinically indicated, collect citrated plasma samples for freezing and for potential analysis of coagulation indices at a later date; these analyses may include, but may not be limited to, the indices listed in Appendix 12.
14. Perform serum IFE/PEP at each visit. If a subject's first on-study hematologic complete response was assessed at the previous visit, perform serum IFE/PEP (and 24-hour urine IFE/PEP) at least 28 days after the initial assessment of response to confirm response.
15. The 24-hour urine protein excretion and 24-hour urine IFE/PEP tests will be performed using the same 24-hour urine collection sample, when required at the same visit.
16. If a subject's first on-study hematologic complete response was assessed at the previous visit, perform 24-hour urine IFE/PEP (and serum IFE/PEP) at least 28 days after the initial assessment of response to confirm response. Repeat every odd-numbered month (i.e., Months 3 and 9 to correspond with 24-hour urine protein excretion collection) to assess for continuing response or progression. If the initial response confirmation needs to occur on an even-numbered month, perform an additional 24-hour urine collection.
17. After Month 12, if the subject is willing to return to the study site, perform or collect the following every third month (e.g., Months 15, 18, 21): 6MWT (which includes BP and HR pre- and post-6MWT administration), adverse events, concomitant medications, overall health status, as well as details of any hospitalizations.
18. Collect if an earlier sample established the presence of anti-NEOD001 antibodies or if a subject discontinued treatment due to a suspected immunologic reaction.
19. Collect BP, HR, RR, and temperature any time during visit.
20. New SAEs occurring beyond the EOT/ETD Visit or >28 days after the last administration of study drug, whichever is later, will be reported to the Sponsor or its designee only if, in the judgement of the Investigator, the SAE is associated with any protocol intervention (i.e., related to study procedure or previous study drug exposure).
21. All hospitalizations and deaths occurring during this period need to be reported to the Sponsor or its designee.
22. Conduct a vital status phone call per Section 7.1.8 approximately 3 months after the subject's last visit and approximately every 3 months thereafter.

APPENDIX 4: EXAMPLES OF HIGHLY EFFECTIVE CONTRACEPTION METHODS

Contraception methods that can achieve a failure rate of <1% per year when used consistently and correctly are considered to be highly effective. Such methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[1]:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation[1]:
  - Oral
  - Injectable
  - Implantable[2]
- Intrauterine device (IUD)[2]
- Intrauterine hormone-releasing system (IUS)[2]
- Bilateral tubal occlusion[2]
- Vasectomized partner[2,3]
- Sexual abstinence[4]

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[1] *Hormonal contraception may be susceptible to interaction with the Investigational Medicinal Product (IMP), which may reduce the efficacy of the contraception method.*
[2] *Contraception methods that in the context of this guidance are considered to have low user dependency.*
[3] *Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.*
[4] *In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.*

Source: Clinical Trial Facilitation Group (CTFG): Recommendations related to contraception and pregnancy testing in clinical trials (Final Version 15Sep2014). Available from: http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf. Accessed 02Aug2015.

APPENDIX 5: REVISED INTERNATIONAL MYELOMA WORKING GROUP DIAGNOSTIC CRITERIA FOR MULTIPLE MYELOMA

Definition of Multiple Myeloma

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

Myeloma defining events:

- Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
    - Hypercalcaemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal (ULN) or >2.75 mmol/L (>11 mg/dL)
    - Renal insufficiency: creatinine clearance <40 mL per min† or serum creatinine >177 μmol/L (>2 mg/dL)
    - Anemia: hemoglobin value of >20 g/L below the lower limit of normal, or a hemoglobin value <100 g/L
    - Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT‡
- Any one or more of the following biomarkers of malignancy:
    - Clonal bone marrow plasma cell percentage* ≥60%
    - Involved:uninvolved serum free light chain ratio§ ≥100
    - >1 focal lesions on magnetic resonance imaging (MRI) studies¶

PET-CT=^{18}F-fluorodeoxyglucose PET with CT. *Clonality should be established by showing κ/λ-light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and core biopsy, the highest value should be used. †Measured or estimated by validated equations. ‡If bone marrow has less than 10% clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement. §These values are based on the serum Freelite assay (The Binding Site Group, Birmingham, UK). The involved free light chain must be ≥100 mg/L. ¶Each focal lesion must be 5 mm or more in size.

Source: Rajkumar 2014.

APPENDIX 6: HEMATOLOGIC RESPONSE AND PROGRESSION CRITERIA

Response Subcategory	Response Criteria
Complete Response (CR)	• Normalization of free light chain levels and ratio, negative serum and urine immunofixation
Very Good Partial Response (VGPR)*	• Reduction in the dFLC to <40 mg/L (<4.0 mg/dL)
Partial Response (PR)*	• A greater than 50% reduction in the dFLC
No Response (NR)	• Less than a PR
Progression	• From CR: any detectable monoclonal protein or abnormal free light chain ratio (light chain must double)
	• From 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) or free light chain increase of 50% to > 10 mg/dL (100 mg/L)

dFLC = difference between involved and uninvolved free light chains.
*Only applicable for subjects with dFLC > 50 mg/L (5 mg/dL) at study entry.
Source: Comenzo 2012.

APPENDIX 7: SHORT FORM-36 QUESTIONNAIRE (SF-36V2)

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Thank you for completing this survey!

For each of the following questions, please select the one box that best describes your answer.

In general, would you say your health is:

Excellent
Very good
Good
Fair
Poor

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

Much better now than one year ago
Somewhat better now than one year ago
About the same as one year ago
Somewhat worse now than one year ago
Much worse now than one year ago

The following question is about activities you might do during a typical day. Does your health now limit you in vigorous activities, such as running, lifting heavy objects, participating in strenuous sports? If so, how much? Yes, limited a lot Yes, limited a little No, not limited at all
The following question is about activities you might do during a typical day. Does your health now limit you in moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf? If so, how much? Yes, limited a lot Yes, limited a little No, not limited at all
The following question is about activities you might do during a typical day. Does your health now limit you in lifting or carrying groceries? If so, how much? Yes, limited a lot Yes, limited a little No, not limited at all
The following question is about activities you might do during a typical day. Does your health now limit you in climbing several flights of stairs? If so, how much? Yes, limited a lot Yes, limited a little No, not limited at all

The following question is about activities you might do during a typical day. Does your health now limit you in climbing one flight of stairs? If so, how much? Yes, limited a lot Yes, limited a little No, not limited at all
The following question is about activities you might do during a typical day. Does your health now limit you in bending, kneeling, or stooping? If so, how much? Yes, limited a lot Yes, limited a little No, not limited at all
The following question is about activities you might do during a typical day. Does your health now limit you in walking more than a mile? If so, how much? Yes, limited a lot Yes, limited a little No, not limited at all
The following question is about activities you might do during a typical day. Does your health now limit you in walking several hundred yards? If so, how much? Yes, limited a lot Yes, limited a little No, not limited at all

The following question is about activities you might do during a typical day. Does your health now limit you in walking one hundred yards? If so, how much? Yes, limited a lot Yes, limited a little No, not limited at all
The following question is about activities you might do during a typical day. Does your health now limit you in bathing or dressing yourself? If so, how much? Yes, limited a lot Yes, limited a little No, not limited at all
During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities? Cut down on the amount of time you spent on work or other activities as a result of your physical health All of the time Most of the time Some of the time A little of the time None of the time
During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities? Accomplished less than you would like as a result of your physical health All of the time Most of the time Some of the time A little of the time None of the time

During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities? Were limited in the kind of work or other activities as a result of your physical health All of the time Most of the time Some of the time A little of the time None of the time
During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities? Had difficulty performing the work or other activities as a result of your physical health (for example, it took extra effort) All of the time Most of the time Some of the time A little of the time None of the time
During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities? Cut down on the amount of time you spent on work or other activities as a result of any emotional problems (such as feeling depressed or anxious) All of the time Most of the time Some of the time A little of the time None of the time

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

Accomplished less than you would like as a result of any emotional problems (such as feeling depressed or anxious)

All of the time
Most of the time
Some of the time
A little of the time
None of the time

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

Did work or other activities less carefully than usual as a result of any emotional problems (such as feeling depressed or anxious)

All of the time
Most of the time
Some of the time
A little of the time
None of the time

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

Not at all
Slightly
Moderately
Quite a bit
Extremely

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

This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks did you feel full of life?

All of the time
Most of the time
Some of the time
A little of the time
None of the time

This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks have you been very nervous?

All of the time
Most of the time
Some of the time
A little of the time
None of the time

This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks have you felt so down in the dumps that nothing could cheer you up?

All of the time
Most of the time
Some of the time
A little of the time
None of the time

This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks have you felt calm and peaceful?

All of the time
Most of the time
Some of the time
A little of the time
None of the time

This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks did you have a lot of energy?

All of the time
Most of the time
Some of the time
A little of the time
None of the time

This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks have you felt downhearted and depressed?

All of the time
Most of the time
Some of the time
A little of the time
None of the time

This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks did you feel worn out?

All of the time
Most of the time
Some of the time
A little of the time
None of the time

This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks have you been happy?

All of the time
Most of the time
Some of the time
A little of the time
None of the time

This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks did you feel tired?

All of the time
Most of the time
Some of the time
A little of the time
None of the time

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 of the time
None of the time

How TRUE or FALSE is the following statement for you?

I seem to get sick a little easier than other people.

Definitely true
Mostly true
Don't know
Mostly false
Definitely false

How TRUE or FALSE is the following statement for you?

I am as healthy as anybody I know.

Definitely true
Mostly true
Don't know
Mostly false
Definitely false

How TRUE or FALSE is the following statement for you?

I expect my health to get worse.

Definitely true
Mostly true
Don't know
Mostly false
Definitely false

How TRUE or FALSE is the following statement for you?

My health is excellent.

Definitely true
Mostly true
Don't know
Mostly false
Definitely false

APPENDIX 8: KANSAS CITY CARDIOMYOPATHY QUESTIONNAIRE (KCCQ)

SAMPLE

The KC Cardiomyopathy Questionnaire

The following questions refer to your **heart failure** and how it may affect your life. Please read and complete the following questions. There are no right or wrong answers. Please mark the answer that best applies to you.

1. **Heart failure** affects different people in different ways. Some feel shortness of breath while others feel fatigue. Please indicate how much you are limited by **heart failure** (shortness of breath or fatigue) in your ability to do the following activities over the past 2 weeks.

Place an **X** in one box on each line

Activity	Extremely Limited	Quite a bit Limited	Moderately Limited	Slightly Limited	Not at all Limited	Limited for other reasons or did not do the activity
Dressing yourself	☐	☐	☐	☐	☐	☐
Showering/Bathing	☐	☐	☐	☐	☐	☐
Walking 1 block on level ground	☐	☐	☐	☐	☐	☐
Doing yardwork, housework or carrying groceries	☐	☐	☐	☐	☐	☐
Climbing a flight of stairs without stopping	☐	☐	☐	☐	☐	☐
Hurrying or jogging (as if to catch a bus)	☐	☐	☐	☐	☐	☐

2. Compared with 2 weeks ago, have your symptoms of **heart failure** (shortness of breath, fatigue, or ankle swelling) changed?

My symptoms of **heart failure** have become…

Much worse	Slightly worse	Not changed	Slightly better	Much better	I've had no symptoms over the last 2 weeks
☐	☐	☐	☐	☐	☐

Original US English

SAMPLE

3. Over the past 2 weeks, how many times did you have **swelling** in your feet, ankles or legs when you woke up in the morning?

Every morning	3 or more times a week, but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
☐	☐	☐	☐	☐

4. Over the past 2 weeks, how much has **swelling** in your feet, ankles or legs bothered you?

It has been ...

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no swelling**
☐	☐	☐	☐	☐	☐

5. Over the past 2 weeks, on average, how many times has **fatigue** limited your ability to do what you want?

All of the time	Several times per day	At least once a day	3 or more times per week but not every day	1-2 times per week	Less than once a week	Never over the past 2 weeks
☐	☐	☐	☐	☐	☐	☐

6. Over the past 2 weeks, how much has your **fatigue** bothered you?

It has been ...

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no fatigue**
☐	☐	☐	☐	☐	☐

7. Over the past 2 weeks, on average, how many times has **shortness of breath** limited your ability to do what you wanted?

All of the time	Several times per day	At least once a day	3 or more times per week but not every day	1-2 times per week	Less than once a week	Never over the past 2 weeks
☐	☐	☐	☐	☐	☐	☐

Original US English

SAMPLE

8. Over the past 2 weeks, how much has your **shortness of breath** bothered you?

It has been ...

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no shortness of breath**
☐	☐	☐	☐	☐	☐

9. Over the past 2 weeks, on average, how many times have you been forced to sleep sitting up in a chair or with at least 3 pillows to prop you up because of **shortness of breath**?

Every night	3 or more times a week, but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
☐	☐	☐	☐	☐

10. **Heart failure** symptoms can worsen for a number of reasons. How sure are you that you know what to do, or whom to call, if your **heart failure** gets worse?

Not at all sure	**Not very** sure	**Somewhat** sure	**Mostly** sure	**Completely** sure
☐	☐	☐	☐	☐

11. How well do you understand what things you are able to do to keep your **heart failure** symptoms from getting worse? (for example, weighing yourself, eating a low salt diet etc.)

Do not understand at all	Do not understand very well	Somewhat understand	Mostly understand	Completely understand
☐	☐	☐	☐	☐

12. Over the past 2 weeks, how much has your **heart failure** limited your enjoyment of life?

It has **extremely** limited my enjoyment of life	It has limited my enjoyment of life **quite a bit**	It has **moderately** limited my enjoyment of life	It has **slightly** limited my enjoyment of life	It has **not limited** my enjoyment of life at all
☐	☐	☐	☐	☐

13. If you had to spend the rest of your life with your **heart failure** the way it is right now, how would you feel about this?

Not at all satisfied	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
☐	☐	☐	☐	☐

 Original US English

SAMPLE

14. Over the past 2 weeks, how often have you felt discouraged or down in the dumps because of your **heart failure**?

I felt that way **all of the time**	I felt that way **most of the time**	I **occasionally** felt that way	I **rarely** felt that way	I **never** felt that way
☐	☐	☐	☐	☐

15. How much does your **heart failure** affect your lifestyle? Please indicate how your **heart failure** may have limited your participation in the following activities over the past 2 weeks.

Please place an **X** in one box on each line

Activity	**Severely** limited	Limited **quite a bit**	**Moderately** limited	**Slightly** limited	**Did not** limit at all	Does not apply or did not do for other reasons
Hobbies, recreational activities	☐	☐	☐	☐	☐	☐
Working or doing household chores	☐	☐	☐	☐	☐	☐
Visiting family or friends out of your home	☐	☐	☐	☐	☐	☐
Intimate relationships with loved ones	☐	☐	☐	☐	☐	☐

Original US English

APPENDIX 9: FUNCTIONAL ASSESSMENT OF CANCER THERAPY – GYNECOLOGIC ONCOLOGY GROUP NEUROTOXICITY SUBSCALE (FACT-GOG NTX)

Circle or mark one number per line to indicate your response as it applies to the ***past 7 days***:

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
NTX 1	I have numbness or tingling in my hands	0	1	2	3	4
NTX 2	I have numbness or tingling in my feet	0	1	2	3	4
NTX 3	I feel discomfort in my hands	0	1	2	3	4
NTX 4	I feel discomfort in my feet	0	1	2	3	4
NTX 5	I have joint pain or muscle cramps	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
NTX 6	I have trouble hearing	0	1	2	3	4
NTX 7	I get a ringing or buzzing in my ears	0	1	2	3	4
NTX 8	I have trouble buttoning buttons	0	1	2	3	4
NTX 9	I have trouble feeling the shape of small objects when they are in my hand	0	1	2	3	4
An6	I have trouble walking	0	1	2	3	4

Instructions for Healthcare Professionals:
This assessment tool is to help you evaluate peripheral neuropathy in subjects receiving chemotherapy. You may find discussion of subject responses helpful in determining the grade of neuropathy as defined by the NCI-CTCAE listed below; there is no direct correlation between assessment scores and toxicity grades.

NCI-CTCAE for Peripheral Neuropathy and Neuropathic Pain

	Grade				
	1	2	3	4	5
Peripheral motor neuropathy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; assistive device indicated	Life-threatening consequences; urgent intervention indicated	Death
Peripheral sensory neuropathy	Asymptomatic; loss of deep tendon reflexes or paresthesia	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Neuralgia	Mild pain	Moderate symptoms; limiting instrumental ADL	Severe pain; limiting self-care ADL		

ADL = activities of daily living; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Events.
Source: NCI-CTCAE (version 4.03) 2009.

APPENDIX 10: NEUROPATHY IMPAIRMENT SCALE – LOWER LIMBS (NIS-LL)

THE VITAL AMYLOIDOSIS STUDY

Neuropathy Impairment Scale – Lower Limbs (NIS-LL)
for NEOD001-CL002

The NIS-LL is a scoring system graduated from 0 points (the normal finding) to a maximum of 88 points (the absence of all motor, sensory, and reflex activity in the lower extremities). The scale is additive of all deficits (64 potential points for muscle strength, 8 points for reflexes, and 16 points for sensory function) in the lower extremities.

Instructions: Complete each assessment outlined below and assign a score for the right side and for the left side.

Assessment	*Right*	*Left*	*Sum*
Muscle Weakness - Score each assessment as: 0 - normal, 1 - 25% weakened, 2 - 50% weakened, 3 - 75% weakened, 4 - paralysis			
Hip Flexion (iliopsoas)			
Hip Extension (gluteus max.)			
Knee Flexion (biceps femoris)			
Knee Extension (quadriceps)			
Ankle Dorsiflexors (tibialis ant. +)			
Ankle Plantar Flexors (gastroc. soleus)			
Toe Extensors			
Toe Flexors			
Reflexes - Score each assessment as: 0 - normal, 1 – reduced, 2 - absent			
Quadriceps femoris			
Triceps surae/gastroc. soleus			
Sensation: Great Toe (terminal phalanx) - Score each assessment as: 0 - normal, 1 – reduced, 2 - absent			
Touch pressure			
Pinprick			
Vibration			
Joint position			
Total Score:_____			

Source: Dyck PJ, Litchy WJ, Lehman KA, et al. Variables influencing neuropathic endpoints: the Rochester Diabetic Neuropathy Study of Healthy Subjects. *Neurology*. 1995;45(6):1115-21.

Performed by (Print Name): _____

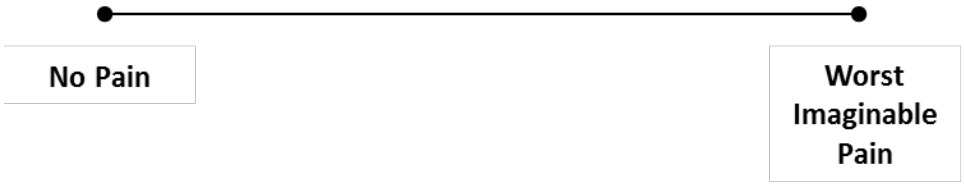
_____ Date: ____/____/____
Signature dd mmm yyyy

SAMPLE

APPENDIX 11: VISUAL ANALOG SCALE – PAIN INTENSITY (VASPI)

VISUAL ANALOG SCALE – PAIN INTENSITY

Over the last week, on average, my lower extremity pain would be described as:



APPENDIX 12: COAGULATION INDICES

For each coagulation time point in Table 1, citrated plasma samples may be collected and frozen for potential analysis of coagulation indices at a later date; these analyses may include, but may not be limited to, the indices listed in the following table:

Antithrombin Activity (ATIII Activity)	Fibrinogen Antigen
Partial Thromboplastin Time Mixing Studies	High-Molecular Weight Kininogen
D-dimer, quantitative	Prekallikrein
Euglobulin Lysis Time	Plasminogen Activator Inhibitor-1 Antigen
Factor II Activity	Plasminogen Activator Inhibitor-1 Activity
Factor V Activity	Plasmin-antiplasmin Complex
Factor VII Activity	Plasminogen Activity
Factor VIII Activity	Protein C Activity
Factor VIII Antigen Quantitation	Protein S Antigen Free
Factor IX Activity	Thrombin Time
Factor X Activity	Tissue Plasminogen Activator Activity
Factor XI Activity	Tissue Plasminogen Activator Antigen
Factor XII Activity	von Willebrand Factor Activity (Ristocetin Cofactor)
Factor XIII Activity	von Willebrand Factor Antigen
Fibrin Monomer	von Willebrand Factor Multimers
Fibrinogen Activity	

APPENDIX 13: EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS

Grade	Eastern Cooperative Oncology Group
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, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Source: Oken 1982.

APPENDIX 14: NEW YORK HEART ASSOCIATION (NYHA) FUNCTIONAL CLASSIFICATION

NYHA Class	Symptoms
I	No symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.

NYHA = New York Heart Association.
Source: American Heart Association 2015.

APPENDIX 15: PACKAGE INSERTS FOR CHEMOTHERAPEUTIC AGENTS COMMONLY PRESCRIBED FOR INDIVIDUALS WITH AL AMYLOIDOSIS

Package Inserts for many chemotherapeutic agents commonly prescribed for individuals with AL amyloidosis and which have been approved by the US Food and Drug Administration (FDA) may be found at the FDA website, Drugs@FDA, at the following link:
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/

The Summary of Product Characteristics for all products approved via the Centralized procedure in the European Union (EU) can be found on the European Medicines Agency (EMA) website as follows:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124

The above website states that EMA does not evaluate all medicines currently in use in Europe. If a specific medicine cannot be found on the website, it may be found on that of the national health authority of a specific EU country. For example, in the United Kingdom, refer to the electronic Medicines Compendium (https://www.medicines.org.uk/emc/about-the-emc).

For countries outside of the US and EU, the package inserts may be found on the website of the country's national health authority, such as:

- Australia: https://www.tga.gov.au/australian-register-therapeutic-goods
- Canada: http://webprod5.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp
- Israel: http://www.old.health.gov.il/units/pharmacy/trufot/index.asp?safa=e