Document Type:	Study Protocol
Official Title:	A Phase 2b, Randomized, Double-blind, Placebo-controlled Study of NEOD001 in Previously Treated Subjects with Light Chain (AL) Amyloidosis who have Persistent Cardiac Dysfunction
NCT Number:	NCT02632786
Document Date:	22 October 2017

This protocol for Study NEOD001-201 was amended three times.

Date of Original Protocol:	06 November 2015
Date of Amendment 1:	28 June 2016
Date of Amendment 2:	25 April 2017
Date of Amendment 3:	22 October 2017

The following key changes were made between amendments:

Overview of Major/Substantial Changes in Amendment 1:

- Corrected and clarified eligibility criteria.
- Clarified study populations, including the Modified Intent-to-Treat population and subjects considered to have AL amyloidosis-related peripheral neuropathy.
- Removed select study procedures to reduce patient burden and clarified various study procedures, including the importance of consistency in administration of the 6-minute walk test.

Overview of Major/Substantial Changes in Amendment 2:

- Added new and modified existing study endpoints.
- Increased the number of subjects
- Removed requirement for monthly collection of additional coagulation indices
- Corrected Inclusion Criterion #7 to align with existing stratification factor
- Updated analysis populations and statistical analyses to align with statistical analysis plan

Overview of Major/Substantial Changes in Amendment 3:

- Modified existing study endpoints based on updates to the statistical analysis plan
- Updated statistical analyses to align with statistical analysis plan

CLINICAL RESEARCH PROTOCOL

Study Title:	A Phase 2b, Randomized, Double-blind, Placebo-controlled Study of NEOD001 in Previously Treated Subjects with Light Chain (AL) Amyloidosis who have Persistent Cardiac Dysfunction
Protocol Number:	NEOD001-201
Investigational Product:	NEOD001
US IND Number:	122,912
EudraCT Number:	2015-004318-14
Indication:	Light Chain (AL) Amyloidosis
Sponsor:	Prothena Therapeutics Limited Adelphi Plaza, Upper George's Street Dún 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]
Development Phase:	2b
Date of Original Protocol:	06 November 2015
Date of Amendment 1:	28 June 2016
Date of Amendment 2:	25 April 2017
Date of Amendment 3:	22 October 2017

Confidential
The information contained in this document and all information provided to you related to NEOD001 is the confidential and proprietary information of Prothena Therapeutics Limited (Prothena). It is intended solely for the recipient clinical investigator(s) and must not be disclosed to any other party. This material may be used only for evaluating or conducting clinical investigations; any other proposed use requires written consent from Prothena.

SPONSOR PROTOCOL APPROVAL PAGE

Protocol Title: A Phase 2b, Randomized, Double-blind, Placebo-controlled Study of NEOD001 in Previously Treated Subjects with Light Chain (AL) Amyloidosis who have Persistent Cardiac Dysfunction

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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]

25 Oct 2017
Date

[redacted]
Chief Medical Officer

INVESTIGATOR SIGNATURE PAGE

Protocol Title: A Phase 2b, Randomized, Double-blind, Placebo-controlled Study of NEOD001 in Previously Treated Subjects with Light Chain (AL) Amyloidosis who have Persistent Cardiac Dysfunction

Protocol Number: NEOD001-201

Sponsor: Prothena Therapeutics Limited

Date of Original Protocol: 06 November 2015

Date of Amendment 1: 28 June 2016

Date of Amendment 2: 25 April 2017

Date of Amendment 3: 22 October 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 your Study Monitor. Please **retain** a copy for your study files.

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PROTOCOL SYNOPSIS

Title	A Phase 2b, Randomized, Double-blind, Placebo-controlled Study of NEOD001 in Previously Treated Subjects with Light Chain (AL) Amyloidosis who have Persistent Cardiac Dysfunction
Phase	2b
Planned Number of Study Centers	Approximately 35 centers globally
Objective	The objective of this study is to determine the efficacy and safety of NEOD001 versus placebo in subjects with AL amyloidosis who have persistent cardiac dysfunction.
Study Design	This is a global, multicenter, Phase 2b, randomized, double-blind, placebo-controlled, two-arm, parallel-group efficacy and safety study of NEOD001 as a single agent administered intravenously in adults with AL amyloidosis who had a hematologic response (Appendix 1) to previous treatment for their amyloidosis (e.g., chemotherapy, autologous stem cell transplant [ASCT]) and have persistent cardiac dysfunction. Subject screening will occur during the 28 days prior to the first administration of study drug (i.e., Month 1-Day 1 Visit). If all eligibility requirements are met, the subject will be enrolled and Screening assessments will be completed. Screening assessments are listed in Table 1. Study visits will occur every 28 days based on scheduling from Month 1-Day 1. A ±5-day window is allowed for visits starting after Month 1. Subjects may receive up to 12 infusions of study drug. Subjects who discontinue study drug before the End of Study (EOS) Visit should have an Early Treatment Discontinuation (ETD) Visit 30 (±5) days after their final administration of study drug.
Number of Subjects and Cohort Specifications	Up to 130 subjects will be enrolled and randomized (1:1) to NEOD001 or placebo. The randomization will be stratified according to: • Hematologic response; that is, complete response/very good partial response (CR/VGPR) vs partial response (PR) to first-line therapy • N-terminal pro-brain natriuretic peptide (NT-proBNP) <1800 pg/mL vs ≥1800 pg/mL

Study Drug, Dose, and Mode of Administration	Study drug consists of NEOD001 24 mg/kg (dose not to exceed 2500 mg) or placebo. Study drug will be administered once every 28 (±5) days; a minimum of 21 days between doses is required. Subjects may receive up to 12 infusions of study drug. Study drug will be administered as an initial 120 (±10)-minute intravenous (IV) infusion. If, in the opinion of the Investigator, 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 5.3. In the case of a suspected systemic infusion-related reaction, follow instructions in Section 5.4.2. 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. Beginning with the third infusion, the Investigator may decrease the monitoring time to no less than 60 minutes, if no infusion-related reactions were observed in the previous infusions and allowed per the IRB/IEC.
Control Group	Normal saline will be used as the placebo control.
Estimated Study and Treatment Duration	Each subject's study duration may be up to 14 months, consisting of a Screening Phase (1 month), Treatment Phase (12 months), and the EOS Visit 30 (±5) days after the last dose. Subjects who complete the study and meet the eligibility criteria will be considered for entry into a separate open-label extension study, during which subjects will receive active treatment and may receive concurrent chemotherapy.
Subject Eligibility Criteria	**Inclusion Criteria** (subjects must meet ***all*** of the following criteria): 1. Age ≥18 years 2. Confirmed diagnosis of systemic 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 electron microscopy **OR** immunohistochemistry **OR** mass spectrometry of AL amyloidosis 3. If the subject meets ***any*** of the following criteria, confirm diagnosis of AL amyloidosis by mass spectrometry **OR** immunoelectron microscopy of amyloid material in tissue biopsy: ○ Is black or African American ○ Is over 75 years of age (at time of diagnosis) 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 et al, 2011), hydroxymethylenediphosphonate (^{99m}Tc-HMDP; Galat et al, 2015), or pyrophosphate (^{99m}Tc-PYP; Bokhari et al, 2013) scintigraphy 4. Cardiac involvement as defined by **BOTH** 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 5. NT-proBNP ≥650 pg/mL and ≤5000 pg/mL (i.e., ≥76.7 pmol/L and ≤590 pmol/L) 6. Received at least one prior systemic chemotherapeutic regimen, which may include stem cell transplant, for AL amyloidosis 7. Achieved at least a partial hematologic response (per Appendix 1) to a first-line therapy resulting in a stable hematologic condition not currently requiring additional active treatment against the plasma cell dyscrasia component of their AL disease 8. Adequate bone marrow reserve, hepatic 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 × upper limit of normal (ULN) ○ Aspartate aminotransferase (AST) ≤3 × ULN ○ Alanine aminotransferase (ALT) ≤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. Systolic blood pressure 90-180 mmHg 10. Distance walked during each of the two Screening 6-minute walk tests (6MWTs) is >100 meters and <600 meters

	11. Women of childbearing potential (WOCBP) must have 2 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 2) 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 2) 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 ***not meet any*** of the following criteria): 1. Diagnosis of non-AL amyloidosis 2. Meets the International Myeloma Working Group (IMWG) definition of Multiple Myeloma (Appendix 3) 3. 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 4. Myocardial infarction, uncontrolled angina, uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia, within 6 months prior to the Month 1-Day 1 Visit 5. Severe valvular stenosis (e.g. aortic or mitral stenosis with a valve area <1.0 cm^2) or severe congenital heart disease 6. Electrocardiographic (ECG) evidence of acute ischemia or active conduction system abnormalities ***with the exception*** of any of the following: o First degree atrioventricular (AV) block o Second degree AV block Type 1 (Mobitz Type 1/ Wenckebach type) o Right or left bundle branch block

	o 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 3 representative beats if Lead II is not representative of the overall ECG]) 7. Has not recovered (i.e., equivalent to a Common Terminology Criteria for Adverse Events [CTCAE] ≥Grade 2) from the clinically significant toxic effects of prior anticancer therapy. ***Exception:*** subjects with prior bortezomib treatment may have CTCAE Grade 2 neuropathy. 8. Received any of the following within the specified time frame prior to the Month 1-Day 1 Visit: o Oral or intravenous antibiotics, antifungals, or antivirals within 1 week, ***with the exception*** of prophylactic oral agents. Note: In the event that a subject requires the chronic use of antivirals, Medical Monitor permission is required for entry into the study. o Hematopoietic growth factors, transfusions of blood or blood products within 1 week o Chemotherapy, radiotherapy, or other plasma cell directed therapy within 6 months o ASCT within 12 months o Major surgery within 4 weeks o Planned major surgery or organ transplant during the study o Any other investigational agent within 4 weeks o Prior treatment with NEOD001, 11-1F4, anti-serum amyloid P [SAP] antibody (***exception:*** allowed as part of established diagnostic procedures such as SAP scintigraphy), or other investigational treatment directed at amyloid o Doxycycline within 6 weeks 9. 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 10. History of Grade ≥3 infusion-related adverse events (AEs) or hypersensitivity to another monoclonal antibody 11. History of severe allergy to any of the components of NEOD001 such as histidine/L-histidine hydrochloride monohydrate, trehalose dehydrate, or polysorbate 20 12. Currently known uncontrolled bacterial, viral, fungal, HIV, hepatitis B, or hepatitis C infection 13. Women who are breastfeeding 14. 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 15. Unable or unwilling to adhere to the study-specified procedures and restrictions 16. Subject is under legal custodianship 17. Waldenström's macroglobulinemia and/or immunoglobulin M (IgM) monoclonal gammopathy
Study Procedures and Assessments	See Schedule of Assessments (Table 1)
Endpoints	*Primary Efficacy Endpoint:* • NT-proBNP best response from baseline through 12 months of treatment *Key Secondary Efficacy Endpoints:* • Change from baseline to 12 months of treatment in the Physical Component Score of the Short Form-36 Version 2 (SF-36v2)

	• Change from baseline to 12 months of treatment in the 6MWT distance (meters) • NT-proBNP Slope over 12 months of treatment *Additional Secondary Efficacy Endpoints:* • Renal evaluable subjects: renal best response from baseline through 12 months of treatment • Peripheral neuropathy evaluable subjects: change from baseline to 12 months of treatment in NIS-LL total score • Hepatic evaluable subjects: hepatic best response from baseline through 12 months of treatment *Exploratory Efficacy Endpoints:* See Section 3.2.4 for a list of exploratory efficacy endpoints *Safety Endpoints:* Safety and tolerability of NEOD001 as assessed by vital signs, 12-lead ECGs, routine clinical laboratory assessments, AEs, and immunogenicity by measurement of anti-NEOD001 antibodies
Statistical Considerations and Methods	*Analysis Populations:* The Intent-to-Treat (ITT) Population will include all randomized subjects who receive any amount of study drug (NEOD001 or placebo). The ITT Population will be the primary population used for efficacy analyses. Treatment assignment will be based on the randomized treatment. The Safety Population will include all subjects who receive any amount of study drug (NEOD001 or placebo). The Safety Population will be the primary population used for safety analyses. Treatment assignment will be based on the randomized treatment. <u>Efficacy Subset Populations:</u> 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 one 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 due to AL amyloidosis etiologies answered as yes) and had a

	baseline NIS-LL total score of 2 or greater and at least one postbaseline NIS-LL total score. The Hepatic Evaluable Population will include subjects who had hepatic involvement defined as >1.5 × ULN alkaline phosphatase at baseline and at least one postbaseline assessment of alkaline phosphatase. *Primary Efficacy Analysis:* The NT-proBNP best response rates in the two arms will be compared using the Cochran-Mantel-Haenszel (CMH) test at the alpha=0.05 (two-sided) level of significance. The analysis will be stratified by the randomization stratification factors. *Key Secondary Efficacy Analyses:* NEOD001 and placebo will be compared on change from baseline in the SF-36v2 Physical Component Summary (PCS) score after 12 months of treatment using a REML-based 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 NEOD001 and placebo distributions of change from baseline in 6MWT distance (meters) after 12 months of treatment will be analyzed using a van Elteren test with stratification by randomization strata. The analysis of NT-proBNP slope will be performed using a general linear mixed effects model to compare the rate of change (i.e., slope) of NT-proBNP over 12 months of treatment between treatment groups. For the primary and key secondary efficacy analyses, the overall 2-sided level of significance will be alpha=0.05. The hypothesis testing of key secondary endpoints will be conducted in a sequential closed testing gate-keeping procedure separately, provided the primary efficacy endpoint comparison is statistically significant at an alpha level 0.05. If this comparison is not statistically significant, then the comparison of key secondary efficacy endpoints will be considered nominal, descriptive, and exploratory. *Additional Secondary Efficacy Analyses:* For the Renal Evaluable Population, renal best response will be analyzed in the same manner described for the primary efficacy endpoint. 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. For the Hepatic Evaluable Population, hepatic best response will be analyzed in the same manner described for the primary efficacy endpoint. *Safety Analyses:* Safety will be assessed through summaries of AEs, changes in laboratory test results, and changes in vital signs. In addition, all SAEs, including deaths, will be listed and summarized separately.
Sample Size Justification	For the primary endpoint, the assumed true rates for NEOD001 vs placebo are 50% and 22.5%, respectively. Based on a two-sample comparison of proportions at the alpha=0.05 level of significance, a total sample size of 100 subjects (50 in the NEOD001 arm, 50 in the placebo arm) will provide >80% power based on a two-sided CMH test. Based on the actual enrolled sample size (N~130), the final power is 91%.
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Table 1 Schedule of Assessments

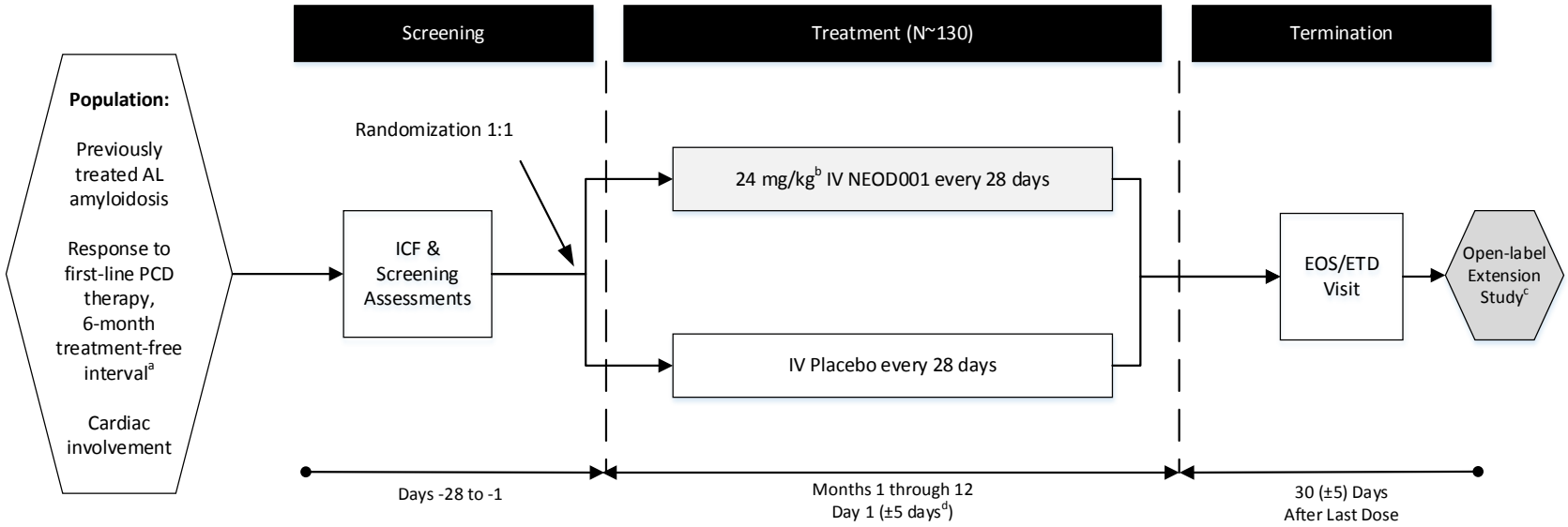
		Screening[1]	Treatment		Termination
	Assessment or Procedure	**Days -28 through -1**	**Month 1 Day 1**	**Months 2 through 12 Day 1 (±5 days)[2]**	**EOS/ETD[3]**
	Written Informed Consent	X			
	Eligibility Review	X			
Clinical	Medical History[4]	X			
	Historical NT-proBNP/BNP[5] Levels	X			
	Prior/Concomitant Medications/Therapy	X	X	X	X
	Adverse Event Assessment[6]	X	X	X	X
	Confirmation of AL Amyloidosis[7]	X			
	Physical Exam[8]	X	X	X	X
	Vital Signs[9]	X	X	X	X
	ECOG PS/NYHA Class[9]	X	X	X	X
	NIS-LL & VASPI[11]	X	X	X (Months 3, 6, 9, 12)	X
	SF-36v2[12]	X		X (Months 3, 6, 9, 12)	X
	KCCQ[13]	X		X (Months 3, 6, 9, 12)	X
	6MWT[14,15]	X, X[16]		X (Months 3, 6, 9, 12)[17]	X
	Echocardiogram[18]	X		X (Month 12)	X
	ECG (12-lead triplicate)	X	X[19]	X (Months 3, 6, 9, 12) [19]	X
Laboratory[24]	Hematology & Chemistry (including amylase and creatine kinase)[20]	X	X	X	X
	Coagulation[21]	X		X	X
	Inflammatory Biomarkers[22,23]		X	X (Month 3)[23]	X
	Troponin T	X		X	X
	NT-proBNP[14]	X	X	X	X
	Pregnancy (WOCBP)[25]	X	X	X	X
	Serum Free Light Chain	X		X (Months 3, 6, 9, 12)	X
	Serum IFE & PEP[26]	X		X (Months 3, 6, 9, 12)	X
	Urinalysis – Dipstick[27]	X	X	X (Months 3, 6, 9, 12)	X
	Urinalysis - Quantitative/Renal Biomarkers[28]	X		X (Months 3, 6, 9, 12)	
	24-hour Urine Collection:				
	Urine IFE & PEP[26]	X		X (Months 3, 6, 9, 12)	X
	Urine Protein Excretion	X		X (Months 3, 6, 9, 12)	X
Other	Serum NEOD001 Sample[23,29]		X	X (Months 3, 6, 9, 12)[23]	X
	Anti-NEOD001 Serum Sample[23,30]		X	X (Months 3, 6, 9, 12)[23]	X
	Archive Sample[31]	X		X (Months 6, 12)	
	Randomization		X		
	Study Drug Infusion[32]		X	X	
	Vital Status Phone Call				X[33]

BNP = B-type natriuretic peptide; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EOI = end of infusion; EOS = End of Study; ETD = Early Treatment Discontinuation; IFE = immunofixation electrophoresis; KCCQ = Kansas City Cardiomyopathy Questionnaire; NIS-LL = neuropathy impairment score – lower limbs; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; PEP = protein electrophoresis; PK = pharmacokinetic; 6MWT = 6-minute walk test; SF-36v2 = Short Form-36v2® Health Survey; VASPI = visual analog scale – pain intensity; WOCBP = women of childbearing potential.

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.
2. Study visits will occur every 28 days based on scheduling from Month 1-Day 1. A ±5-day window is allowed for visits starting after Month 1. The predose assessments for each visit may be performed within the 3 days before the visit unless otherwise specified.
3. Conduct the EOS Visit 30 (±5) days after last administration of study drug. Subjects who discontinue study drug before the end of the study should have an ETD Visit 30 (±5) days after their final administration of study drug, and if willing, have assessments monthly per Appendix 13 (see also Section 4.3). Every effort should be made for the subject to return to the clinic and complete the Month 12-Day 1 Visit on schedule. The assessments shown for EOS/ETD should also be conducted for any unscheduled visit (i.e., a visit not specified by the protocol) as clinically indicated or if deemed necessary.
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. If available, record results of at least 2 prior NT-proBNP or 2 BNP measures from within the previous 6 months; NT-proBNP is preferred, but BNP may be used if it is the institution's historical standard.
6. Adverse events will be collected from the time that the informed consent form is signed through 30 days after the last dose of study drug or last study visit, whichever is later.
7. 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 #3.
8. **Screening and EOS/ETD:** conduct a complete physical examination, including 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. **All other visits:** conduct a directed physical examination, including weight, and the components of the exam will be as clinically indicated. **All visits:** assess macroglossia, submandibular nodes/fullness, adenopathy, ecchymoses, liver/spleen size (palpable +/-), ascites (+/-), and edema (which should be quantified on a scale of 0-4).
9. Vital signs include heart rate (HR), respiratory rate (RR), blood pressure (BP), and body temperature; assess after subject has been at rest ≥5 minutes; within a visit, assess in the same position for all time points. **Month 1:** Within 30 minutes before dosing, 60 (±10) minutes after the start of the infusion, at EOI (+5 minutes), 30 (±5) minutes after EOI, and 60 (±10) minutes after EOI. **All Other Months:** Within 30 minutes before dosing, at EOI (+5 minutes), and 60 (±10) minutes after EOI.
10. See Appendix 7 (ECOG) and Appendix 8 (NYHA).
11. See Appendix 5 (NIS-LL; for all subjects with peripheral neuropathy at Screening) and Appendix 6 (VASPI; for subjects with painful peripheral neuropathy at Screening).
12. See Appendix 9; SF-36v2 should be administered before performing any other study assessments on the same calendar day it is administered.
13. See Appendix 10; administer KCCQ after the SF-36v2, but before conducting any other assessments on the same calendar day it is administered.
14. NT-proBNP should be drawn before conducting 6MWT if being performed on the same calendar day.
15. Collect blood pressure and heart rate pre- and post-6MWT administration. Subject should plan to be able to return to the same clinical site for each 6MWT from first Screening through Month 12.
16. Two pretreatment 6MWTs are required before the first administration of study drug, with a minimum of 4 days in between the two tests. 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).

17. The postbaseline 6MWTs may be administered on the same calendar day that study drug is administered (i.e., Months 3, 6, 9, 12) 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.
18. Perform echocardiogram locally; **Screening:** If an echocardiogram was conducted within 90 days prior to Screening Day -28, it does not need to be repeated during Screening and the previous result may be used for eligibility; however, to be eligible for the additional cardiac imaging analysis, the subject must have had a 4-chamber view, 2-dimensional echocardiogram with Doppler. **Month 12:** may be conducted within 10 days before Day 1; **EOS/ETD:** repeat if not performed within 60 days prior to visit.
19. **Months 1, 3, 6, 9, 12:** perform ECGs centrally within 30 minutes before dosing and within 15 minutes after EOI.
20. Hematology and chemistry per Appendix 11.
21. Collect PT/INR and PTT at each time point. At Screening, EOS/ETD, and 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.
22. Inflammatory biomarkers per Appendix 11.
23. Collect additional samples as clinically indicated, such as when significant toxicity occurs per Section 5.4.2.
24. All laboratory tests to be done centrally, unless otherwise noted. Please refer to Laboratory Manual for details.
25. Pregnancy tests for WOCBP as follows: **Screening:** serum test (central) within 28 days before Month 1-Day 1; **Month 1:** serum test (local) within 24 hours before Month 1-Day 1; **Months 2-12:** serum test (local) preinfusion; **EOS/ETD:** serum test (central); **90 (±5) days after the last study drug administration:** serum test (local).
26. The serum and urine PEP must be conducted before the NEOD001 infusion, if being performed on the same calendar day.
27. Per Appendix 11.
28. Per Appendix 11. It is important that the sample be taken before exercising and at approximately the same time for each collection; therefore, the first morning void is recommended. Urine samples will be collected and frozen for potential analysis at a later date.
29. NEOD001 serum samples (for population PK analysis): collect within 2 hours before infusion and within 4 hours after EOI.
30. Anti-NEOD001 serum samples: collect preinfusion.
31. Archive samples (only subjects who consented to the collection and archiving of their samples for future correlative testing): collect preinfusion.
32. A minimum of 21 days between doses is required. 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. Beginning with the third infusion, the Investigator may decrease the monitoring time to no less than 60 minutes, if no infusion-related reactions were observed in the previous infusions and allowed per the IRB/IEC.
33. For randomized subjects who received at least 1 dose of study drug, conduct vital status telephone call approximately 3 months after last visit and approximately every 3 months thereafter or until subject enrolls in a separate open-label study, death, or for up to 5 years.

Figure 1 NEOD001-201 Study Design



Randomization Stratification:

- Hematologic response; i.e., CR+VGPR vs PR to first-line therapy
- NT-proBNP <1800 pg/mL vs ≥1800 pg/mL

Primary Endpoint:

- NT-proBNP best response from baseline through 12 months of treatment

Key Secondary Endpoints:

- SF-36 PCS change from baseline to 12 months of treatment
- 6MWT distance change from baseline to 12 months of treatment
- NT-proBNP slope over 12 months of treatment

Secondary Endpoints in Efficacy Subset Populations[e]:

- Renal best response from baseline through 12 months of treatment
- NIS-LL Total Score change from baseline to 12 months of treatment
- Hepatic best response from baseline through 12 months of treatment

CR = complete response; EOS/ETD = End of Study/Early Treatment Discontinuation; ICF = informed consent form; IV = intravenous; M12 = Month 12; NT-proBNP = N-terminal pro B-type natriuretic peptide; NIS-LL = Neuropathy Impairment Score-Lower Limbs; PCD = plasma cell dyscrasia; PCS = Physical Component Summary; PR = partial response; SF-36 = Short Form-36; 6MWT = 6 minute walk test; VGPR = very good partial response.
[a] 6 months chemotherapy or 12 months stem cell transplant treatment-free.
[b] Maximum dose not to exceed 2500 mg.
[c] Eligible subjects will receive active treatment and may receive concurrent chemotherapy.
[d] ±5-day window applicable to Months 2-12.
[e] Renal-evaluable subjects, peripheral neuropathy-evaluable subjects, and hepatic-evaluable subjects, respectively.

GLOSSARY OF TERMS

Abbreviation/Acronym	Definition
6MWT	6-minute walk test
^{99m}Tc	Radioisotope of technetium
AA	Amyloid A
ADA(s)	Anti-drug antibody(ies)
ADL	Activities of daily living
AE(s)	Adverse event(s)
AEF	Amyloid-enhancing factor
ALP	Alkaline phosphatase
AL	Amyloid light chain
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ASCT	Autologous stem cell transplant
A-SAA	Acute phase serum amyloid A
AST	Aspartate aminotransferase
AV	Atrioventricular
BNP	B-type natriuretic peptide
BP	Blood pressure
BSA	Bovine serum albumin
BUN	Blood urea nitrogen
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMH	Cochran-Mantel-Haenszel
CR	Complete response
CRP	C-reactive protein
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
D	Aspartic acid

Abbreviation/Acronym	Definition
dFLC	Difference between involved and uninvolved free light chains
E	Glutamic acid
ECG	Electrocardiogram
ECL	Electrochemiluminescent
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EOI	End of infusion
EOS	End of Study
ETD	Early Treatment Discontinuation
FDA	Food and Drug Administration
FLC	Free light chain
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
HR	Heart rate
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Institutional Ethics Committee
IFE	Immunofixation electrophoresis
Ig	Immunoglobulin
IgG1	Immunoglobulin G1
IL-6	Interleukin-6
IMWG	International Myeloma Working Group
INR	International normalized ratio
IRB	Institutional Review Board
ITT	Intent-to-treat

Abbreviation/Acronym	Definition
IV	Intravenous or intravenously
IVSd	Intraventricular septal at diastole
IWRS	Interactive Web Response System
KCCQ	Kansas City Cardiomyopathy Questionnaire
LDH	Lactate dehydrogenase
LPWd	Left posterior wall at diastole
LVEF	Left ventricular ejection fraction
MCS	Mental Component Summary
MMRM	Mixed models for repeated measurements
NGAL	Neutrophil gelatinase-associated lipocalin
NIS-LL	Neuropathy Impairment Score–Lower Limbs
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
PEP	Protein electrophoresis
PK	Pharmacokinetic(s)
PR	Partial response
PS	Performance status
PT	Prothrombin time
PTT	Partial thromboplastin time
RBP	Retinol-binding protein
RR	Respiratory rate
SAA	Serum amyloid A
SAE	Serious adverse event

Abbreviation/Acronym	Definition
SC	Subcutaneous(ly)
SF-36v2	Short Form-36v2® Health Survey
SMC	Safety Monitoring Committee
TEAE(s)	Treatment-emergent adverse event(s)
TRIAD	Transgenic Rapidly Inducible Amyloid Disease
ULN	Upper limit of normal
US(A)	United States (of America)
USP	United States Pharmacopeial Convention
VASPI	Visual Analog Scale – Pain Intensity
VGPR	Very good partial response
WFI	Water for injection
WOCBP	Women of childbearing potential
WT	Wild-type

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. The overall incidence of AL amyloidosis is estimated to be 8.9/million persons/year (CI: 5.1, 12.8) (Kyle et al, 1992; Pinney et al, 2013). NEOD001 was designated as an Orphan Medicinal Product in the European Union on 08 February 2013 for the treatment of AL amyloidosis and in the US on 17 February 2012 for the treatment of AA amyloidosis and AL amyloidosis.

Approximately three-fourths of AL amyloidosis patients present with 1 or 2 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 >2 systems involved (Palladini et al, 2005; Gertz et al, 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 and Dubrey, 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 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 Study Rationale

The pathobiology of AL amyloidosis results from PCD, which causes the overproduction of immunoglobulin light chain, and soluble aggregates and insoluble amyloid that have a profound impact on organ structure and function, leading to the clinical manifestations of the disease. Unlike other hematologic disorders such as multiple myeloma, the morbidity and mortality of AL amyloidosis is related to organ dysfunction rather than the PCD. In all patients with AL amyloidosis, disease outcome is highly dependent on the severity of organ involvement, especially cardiac involvement; and prognosis can be defined by N–terminal pro-brain natriuretic peptide (NT-proBNP). For this study, NT-proBNP was chosen as the primary endpoint because it is a validated cardiac functional biomarker of injury and dysfunction and decreasing NT-proBNP levels predict lower mortality rates (Comenzo et al, 2012). NT-proBNP can also be used for early assessment of cardiac response, allowing treatment modification (Palladini et al, 2014). In the completed Phase 1/2 study of NEOD001 in subjects with AL amyloidosis, monthly infusions of NEOD001 resulted in clinically meaningful reductions in NT-proBNP (Gertz et al, 2016).

Currently, there are no approved treatments for AL amyloidosis and no existing treatments that directly neutralize the toxic soluble aggregates or remove the organ deposited misfolded amyloid that are thought to cause organ dysfunction (Falk and Dubrey, 2010). Current treatment approaches are aimed at reducing or eliminating the PCD, which produces the toxic amyloid (i.e., eliminating or reducing the plasma cells responsible for producing light chains, thereby reducing or halting production of the toxic protein). These include high-dose chemotherapy and ASCT for patients who can tolerate those treatments. Indeed, the incidence of treatment-related mortality following ASCT is high (although variable and treatment center dependent) with the greatest mortality in patients with cardiac involvement (Falk and Dubrey, 2010). Falk and colleagues noted that although complete hematologic responses could be achieved in approximately 40% of treated patients (Falk and Dubrey, 2010), the rate of any organ function improvement or stabilization (“organ response”) after achieving hematologic response from ASCT or chemotherapy regimens is highly variable (Cibeira et al, 2011; Cohen et al, 2007; Michael et al, 2010). This is significant in as much as hematologic response in the absence of organ benefit provides limited if any, clinical benefit to patients with AL amyloidosis (Kaufman et al, 2015) and underscores the fact that the major determinant of morbidity and mortality is end organ damage.

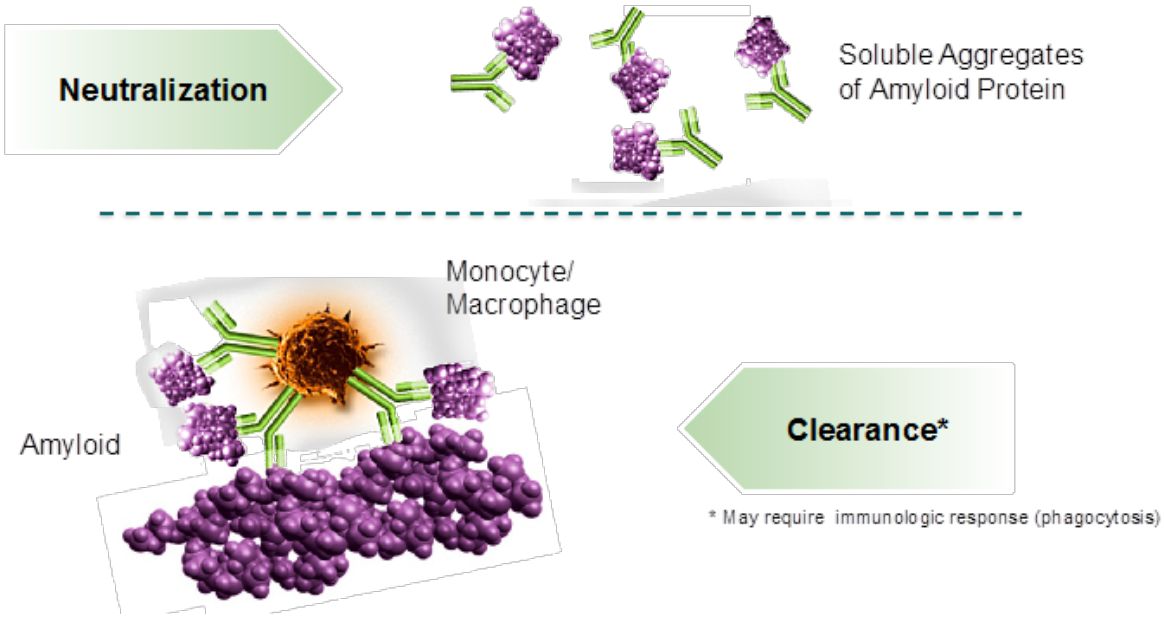
NEOD001 is currently being studied in a double-blind, randomized, placebo-controlled Phase 3 study (The VITAL Amyloidosis Study; Study NEOD001-CL002) in newly diagnosed patients with AL amyloidosis disease receiving chemotherapy to treat the underlying PCD. In addition, Study NEOD001-OLE001, a Phase 2 open-label extension study for subjects who completed 9 months of treatment in the Phase 1/2 Study NEOD001-001, allows subjects to receive NEOD001 and concomitant chemotherapy for treatment of their underlying PCD. Study NEOD001-201 is designed to evaluate the efficacy and safety of NEOD001 as a single agent in AL amyloidosis subjects whose underlying PCD is stable but who still exhibit significant organ impairment.

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. NEOD001 specifically targets misfolded light chain aggregates and amyloid deposits. In the course of specificity characterization of NEOD001, the antibody was found to also react with high affinity and in a conformation-dependent manner with the misfolded light chain found in soluble aggregates and deposited light chain amyloid fibrils, however not with immunoglobulin (Ig) or free non-amyloid light chain in circulation. NEOD001, administered by intravenous (IV) infusion, is proposed for use to target the misfolded light chain protein in subjects with AL amyloidosis. See the current NEOD001 Investigator's Brochure for detailed nonclinical and clinical information.

The proposed mechanism of action for NEOD001 is thought to be two-pronged (Figure 2). 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 2 Proposed Mechanism of Action for NEOD001



Because NEOD001 and 2A4 (the parent murine monoclonal antibody for NEOD001) recognize a conserved epitope in both the AL and serum 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 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.

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. Anti-drug antibody reactions in animal species are not predictive of human responses and, therefore, these effects are not considered to contribute to human risk assessment (Bugelski and Treacy, 2004; Pimm and Smith, 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 (WT) 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

Study NEOD001-001 was a Phase 1/2 open-label, dose escalation study of the IV administration of single-agent NEOD001 in subjects with AL amyloidosis previously treated for their plasma cell dyscrasia (PCD), which enrolled 27 subjects in the Escalation Phase in 7 cohorts (evaluating dose levels from 0.5 mg/kg to 24.0 mg/kg) and enrolled an additional 42 subjects in the Expansion Phase. The most frequently reported treatment-emergent adverse events (TEAEs) overall in Study NEOD001-001 (occurring in ≥20% of subjects [N=69], regardless of relationship to NEOD001) were fatigue, nausea, upper respiratory tract infection, edema peripheral, diarrhea, and anemia. No confirmed anti-NEOD001 antibodies were detected. No dose-limiting toxicities (DLTs) or treatment-related serious TEAEs were reported.

Efficacy data from the completed Study NEOD001-001 were previously reported by Gertz et al. (2016) and final data are summarized herein. Cardiac response was assessed by the clinically relevant cardiac biomarker, NT proBNP, using Comenzo 2012 criteria (Appendix 4). Thirty-six subjects were considered cardiac evaluable (i.e., Screening NT-proBNP ≥650 pg/mL). Among cardiac evaluable subjects, 50% (n=18) met the criteria for cardiac best response and 50% (n=18) met cardiac best response category of stable disease. Renal response was defined according to Palladini 2014 criteria (Appendix 4). Thirty-six subjects were considered renal evaluable (i.e., Screening proteinuria ≥0.5 g/24 hours). Among renal evaluable subjects, 64% (n=23) met the criteria for renal best response and 36% (n=13) met renal best response category of stable disease. Peripheral neuropathy response was defined according to Coelho 2012 criteria (Appendix 4). Eleven subjects (all in the Peripheral Neuropathy Expansion Cohort) were considered peripheral neuropathy evaluable. At Month 10, 82% (n=9) of the peripheral neuropathy evaluable subjects met the criteria for peripheral nerve response (i.e., <2-point increase in Neuropathy Impairment Score–Lower Limbs [NIS-LL] score [88-point scale] from Screening) and 18% (n=2) were progressors. Two of the responders had complete resolution of peripheral neuropathy at Month 10.

Eligible subjects from Study NEOD001-001 enrolled in Study NEOD001-OLE001, an open-label extension study to evaluate the long-term safety and tolerability of NEOD001 in subjects with AL amyloidosis. Subjects receive 24 mg/kg NEOD001 once every 28 days using the infusion duration established for the individual subject in Study NEOD001 001 or over 60 (±10) minutes. As of the data lock point, 11 subjects experienced TEAEs and no treatment-related TEAEs, serious TEAEs, discontinuations due to TEAEs, or deaths were reported.

Study NEOD001-CL002 (VITAL) is an ongoing Phase 3, multicenter, international, randomized, double-blind, placebo-controlled, two-arm efficacy and safety study in subjects with AL amyloidosis. Newly diagnosed subjects with AL amyloidosis are randomized in a 1:1 ratio to received either NEOD001 (24 mg/kg) plus standard of care or placebo plus standard of care, administered once every 28 days as a 1- to 2-hour IV infusion. All subjects are premedicated with 25 mg diphenhydramine (or an equivalent dose of an H1 antihistamine) and 650 mg acetaminophen (or an equivalent dose of paracetamol) within 30 to 90 minutes prior to the start of the infusion. As of the data lock point and including late-breaking events, 68 (52.7%) subjects experienced at least 1 serious TEAE, 2 of which had events considered related to study drug (treatment blinded), 19 (14.7%) subjects had died, none of which were considered by the Investigator to be related to study drug treatment, and 5 (3.9%) subjects had TEAEs that lead to study drug discontinuation.

In an overabundance of caution, premedication is required in Study NEOD001-CL002 because subjects are also receiving standard of care chemotherapy. But, due to the limited number of infusion-related reactions (IRRs) reported to date, premedication will not be routinely administered in the ongoing Studies NEOD001-201, NEOD001-OLE001, and NEOD001-OLE251, unless the Investigator observed an IRR with a prior infusion of study drug in an individual subject.

As of 30 September 2016, 221 subjects had been dosed with a total of 1638 infusions of NEOD001 or placebo in the 4 completed or ongoing studies. In the completed Study NEOD001-001, <1% of infusions administered were associated with IRRs (e.g., rash, hypotension). These IRRs were Common Terminology Criteria for Adverse Events (CTCAE) Grades 1 or 2, nonserious, considered possibly or probably related to study drug, and most resolved within 24 hours. In the ongoing Study NEOD001-CL002 (VITAL), <1% of infusions of study drug (treatment blinded) were associated with infusion-related TEAEs. These TEAEs, experienced by 5 subjects, were Grade 1 or 2, nonserious, and most were considered related to study drug (treatment blinded), and 2 were ongoing at the time of the data lock point. Two events required interruption of the infusion.

Based on the data available to date, NEOD001 has been well tolerated as single-agent therapy in subjects with AL amyloidosis and limited clinically significant safety signals have been identified.

Further details can be found in the latest edition of the NEOD001 Investigator's Brochure.

1.4 Rationale for Study Design and Dose Selection

Since preliminary data have indicated that NEOD001 as a single agent in previously treated subjects appears to improve NT-proBNP (Gertz et al, 2016), a randomized, double-blind, placebo-controlled, two-arm, parallel-group design was selected to evaluate the safety and efficacy of NEOD001 vs placebo in subjects with AL amyloidosis.

2 OBJECTIVES

The objective of this study is to determine the efficacy and safety of NEOD001 versus placebo in subjects with AL amyloidosis who have persistent cardiac dysfunction.

3 STUDY PLAN

3.1 Study Design

This is a global, multicenter, Phase 2b, randomized, double-blind, placebo-controlled, two-arm, parallel-group efficacy and safety study of NEOD001 as a single agent administered intravenously in adults with AL amyloidosis who had a hematologic response (Appendix 1) to previous treatment for their amyloidosis (e.g., chemotherapy, ASCT) and have persistent cardiac dysfunction.

Subject screening will occur during the 28 days prior to the first administration of study drug (i.e., Month 1-Day 1 Visit). If all eligibility requirements are met, the subject will be enrolled and Screening assessments will be completed. Screening assessments are listed in Table 1.

Study visits will occur every 28 days based on scheduling from Month 1-Day 1. A ±5-day window is allowed for visits starting after Month 1. Subjects may receive up to 12 infusions of study drug. Subjects who discontinue study drug before the End of Study (EOS) Visit should have an Early Treatment Discontinuation (ETD) Visit 30 (±5) days after their final administration of study drug (per Section 6.2). If willing, subjects may continue in the study and have monthly assessments, through Month 12, per Appendix 13. Subjects who complete the study and meet the eligibility criteria will be considered for entry into a separate open-label extension study, during which subjects will receive active treatment and may receive concurrent chemotherapy.

3.2 Endpoints

3.2.1 Primary Efficacy Endpoint

- NT-proBNP best response from baseline through 12 months of treatment

3.2.2 Key Secondary Efficacy Endpoints

- Change from baseline to 12 months of treatment in the Physical Component Summary (PCS) score of the Short Form-36 Version 2 (SF-36v2)
- Change from baseline to 12 months of treatment in the 6MWT distance (meters)
- NT-proBNP slope over 12 months of treatment

3.2.3 Additional Secondary Efficacy Endpoints

- Renal evaluable subjects: renal best response from baseline through 12 months of treatment
- Peripheral neuropathy evaluable subjects: change from baseline to 12 months of treatment in NIS-LL total score
- Hepatic evaluable subjects: hepatic best response from baseline through 12 months of treatment

3.2.4 Exploratory Efficacy Endpoints

- Cardiac response, as assessed by NT-proBNP response criteria, at each visit
- Cardiac best response, as assessed by NT-proBNP response criteria, through 3, 6, and 9 months of treatment
- Change and percent change from baseline to each visit in NT-proBNP and troponin T
- 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 diastole
    - LPWd = Left posterior wall at diastole
- Change and percent change from baseline to each visit (except the key secondary endpoint) in the 6MWT distance (meters)
- Change and percent change from baseline to each visit in SF-36v2 PCS score (except the key secondary endpoint), Mental Component Summary (MCS) score, and the 8 subscales
- Change and percent change from baseline to each visit in the Kansas City Cardiomyopathy Questionnaire (KCCQ) subscores and overall summary score
- Renal Evaluable Subjects:
    - Renal response at each visit
    - Renal best response through 3, 6, and 9 months of treatment
    - Change and percent change from baseline to each visit in renal biomarkers (urine albumin/creatinine ratio, urinary neutrophil gelatinase-associated lipocalin [NGAL], and urinary retinol-binding protein [RBP])
    - Change and percent change from baseline to each visit in creatinine, proteinuria, and eGFR
    - Time to eGFR $\leq$15 mL/min/1.73 m^2 (Chronic Kidney Stage 5)
    - Shifts from baseline in Chronic Kidney Stage
    - Time to doubling of creatinine
- Peripheral Neuropathy Evaluable Subjects:

  - Change and percent change from baseline to each visit in the NIS-LL total score (except the additional secondary endpoint)
  - Peripheral neuropathy response at each visit
  - Peripheral neuropathy best response through 3, 6, 9, and 12 months of treatment
  - Change and percent change from baseline to each visit in the 3 NIS-LL component scores (sensory function, reflexes, muscle strength)
  - For peripheral neuropathy evaluable subjects with painful peripheral neuropathy, defined as a baseline VASPI score >0, change and percent change from baseline to each visit in the VASPI score

- Hepatic Evaluable Subjects:
  - Hepatic response at each visit
  - Hepatic best response through 3, 6, and 9 months of treatment
  - Change and percent change from baseline to each visit in ALP
- Time to all-cause mortality (overall survival)
- Progression-free survival
- Duration of response
- Time to derived organ progression for each organ (cardiac/NT-proBNP, renal, peripheral neuropathy, hepatic) separately and to any organ progression
- Time to first organ response for each organ (cardiac/NT-proBNP, renal, peripheral neuropathy, hepatic) separately and to any organ response
- Frequency of cardiac hospitalizations over the course of the study
- ECOG Performance Status, NYHA Class, Mayo Clinic Stage, and Renal Stage at each visit including any changes from baseline
- Change and percent change from baseline to each visit in serum free light chains (FLCs), serum and 24-hour urine PEP, and serum and urine IFE
- Hematologic response at each visit
- Hematologic best response through 3, 6, 9, and 12 months of treatment

- Disease-related symptoms (including macroglossia, submandibular nodes/fullness, adenopathy, ecchymoses, edema, ascites, and liver/spleen size) at each visit and changes from baseline

3.2.5 Safety Endpoints

Safety and tolerability of NEOD001 as assessed by vital signs, 12-lead ECGs, routine laboratory assessments, AEs, and immunogenicity by measurement of anti-NEOD001 antibodies.

3.3 Number of Sites and Subjects

This is a global, multicenter study in approximately 35 centers. Up to 130 subjects will be enrolled and randomized (1:1) to NEOD001 or placebo.

3.4 Randomization and Blinding

3.4.1 Randomization

A subject number will be assigned via a web-based registration for each subject who has signed an informed consent form (ICF). If a subject has completed all Screening requirements and meets all of the eligibility criteria, a Subject Registration Form will be submitted for eligibility review and approval. If approved, randomization will be implemented through an internet connection to an Interactive Web Response System (IWRS) utilizing results from Screening assessments. Up to 130 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 two factors:

- Hematologic response; that is, complete response/very good partial response (CR/VGPR) vs partial response (PR) to first-line therapy

- NT-proBNP <1800 pg/mL vs ≥1800 pg/mL

Upon successful randomization, the Unblinded Pharmacist or their designee (henceforth collectively referred to as the Unblinded Pharmacy Staff) will be provided with the treatment assignment. Numbers assigned to subjects who do not receive study drug will not be re-used.

Refer to the Study Manual for additional details.

3.4.2 Emergency Unblinding

The Investigator has the ability to break the blind for a specific subject in the event of an immediate medical emergency, wherein 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 or its designee within 24 hours. The procedure for the unblinding of a specific subject using the IWRS is provided in the Study Manual.

Any other requests to reveal a subject's treatment must be requested of, and approved in writing by the Sponsor or its designee.

In addition, in the event of any safety concern, the Safety Monitoring Committee (SMC) will have the option to unblind the treatment of any subject. In this situation, only the SMC will have access to the unblinded data.

3.5 Safety Monitoring Committee

An independent Safety Monitoring Committee (SMC), consisting of at least 2 clinicians and a biostatistician not directly involved with the conduct of the trial, will meet to review specified blinded subject data during the conduct of the study. The purpose of these independent data reviews is to assess the totality of the safety data and provide a recommendation to the Sponsor for continuation of dosing or protocol modifications. Details will be provided in the SMC Charter.

3.6 Estimated Study Duration

Each subject's study duration may be up to 14 months, consisting of a Screening Phase (1 month), Treatment Phase (12 months), and the EOS Visit 30 (±5) days after the last dose.

3.7 Definition of End of Study

The study will end when the last subject completes 12 months of study treatment and the 30-day safety follow-up period (i.e., EOS Visit). Subjects who complete the study and meet the eligibility criteria will be considered for entry into a separate open-label extension study, during which subjects will receive active treatment and may receive concurrent chemotherapy.

4 SELECTION, DISCONTINUATION, AND WITHDRAWAL OF SUBJECTS

4.1 Inclusion Criteria

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

1. Age ≥18 years

2. Confirmed diagnosis of systemic 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 electron microscopy **OR** immunohistochemistry **OR** mass spectrometry of AL amyloidosis

3. If the subject meets ***any*** of the following criteria, confirm diagnosis of AL amyloidosis by mass spectrometry or immunoelectron microscopy of amyloid material in tissue biopsy:

   - Is black or African American

   - Is over 75 years of age (at time of diagnosis) 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 et al, 2011), hydroxymethylenediphosphonate (^{99m}Tc-HMDP; Galat et al, 2015), or pyrophosphate (^{99m}Tc-PYP; Bokhari et al, 2013) scintigraphy

4. Cardiac involvement as defined by BOTH 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

5. NT-proBNP ≥650 pg/mL and ≤5000 pg/mL (i.e., ≥76.7 pmol/L and ≤590 pmol/L)

6. Received at least one prior systemic chemotherapeutic regimen, which may include stem cell transplant, for AL amyloidosis

7. Achieved at least a partial hematologic response (per Appendix 1) to a first-line therapy resulting in a stable hematologic condition not currently requiring additional active treatment against the PCD component of their AL disease

8. Adequate bone marrow reserve, hepatic and renal function, as demonstrated by:

    - Absolute neutrophil count (ANC) ≥1.0 x10^9/L
    - Platelet count ≥75 × 10^9/L
    - Hemoglobin ≥9 g/dL
    - Total bilirubin ≤2 × upper limit of normal (ULN)
    - Aspartate aminotransferase (AST) ≤3 × ULN
    - Alanine aminotransferase (ALT) ≤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. Systolic blood pressure (BP) 90-180 mmHg

10. Distance walked during each of the two Screening 6MWTs is >100 meters and <600 meters

11. Women of childbearing potential (WOCBP) must have 2 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 2) 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 2) from Screening to 90 days following the last study drug administration

13. Ability to understand and willingness to sign an ICF prior to initiation of any study procedures

4.2 Exclusion Criteria

Subjects must ***not meet any*** of the following criteria:

1. Diagnosis of non-AL amyloidosis
2. Meets the International Myeloma Working Group (IMWG) definition of Multiple Myeloma (Appendix 3)
3. 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
4. Myocardial infarction, uncontrolled angina, uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia, within 6 months prior to the Month 1-Day 1 Visit
5. Severe valvular stenosis (e.g. aortic or mitral stenosis with a valve area <1.0 cm^2) or severe congenital heart disease
6. ECG evidence of acute ischemia or active conduction system abnormalities ***with the exception*** of any of the following:
    - First degree atrioventricular (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 3 representative beats if Lead II is not representative of the overall ECG])
7. Has not recovered (i.e., equivalent to a CTCAE ≥Grade 2) from the clinically significant toxic effects of prior anticancer therapy. ***Exception:*** subjects with prior bortezomib treatment may have CTCAE Grade 2 neuropathy.
8. Received any of the following within the specified time frame prior to the Month 1-Day 1 Visit:
    - Oral or intravenous antibiotics, antifungals, or antivirals within 1 week, ***with the exception*** of prophylactic oral agents. Note: In the event that a subject requires the chronic use of antivirals, Medical Monitor permission is required for entry into the study.
    - Hematopoietic growth factors, transfusions of blood or blood products within 1 week
    - Chemotherapy, radiotherapy, or other plasma cell directed therapy within 6 months
    - ASCT within 12 months

- Major surgery within 4 weeks
- Planned major surgery or organ transplant during the study
- Any other investigational agent within 4 weeks
- Prior treatment with NEOD001, 11-1F4, anti-SAP antibody (***exception:*** allowed as part of established diagnostic procedures such as SAP scintigraphy), or other investigational treatment directed at amyloid
- Doxycycline within 6 weeks

9. 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
10. History of Grade ≥3 infusion-related AEs or hypersensitivity to another monoclonal antibody
11. History of severe allergy to any of the components of NEOD001 such as histidine/L-histidine hydrochloride monohydrate, trehalose dehydrate, or polysorbate 20
12. Currently known uncontrolled bacterial, viral, fungal, HIV, hepatitis B, or hepatitis C infection
13. Women who are breastfeeding
14. 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
15. Unable or unwilling to adhere to the study-specified procedures and restrictions
16. Subject is under legal custodianship
17. Waldenström's macroglobulinemia and/or immunoglobulin M (IgM) monoclonal gammopathy

4.3 Early Treatment Discontinuation

If the subject discontinues study drug prior to the EOS Visit, they should return for an ETD Visit 30 (±5) days after their final administration of study drug as per Section 6.2. 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 telephone after 2 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.

If the subject discontinues study drug prior to the EOS, but is willing to continue to participate in study visits, the subject should have an ETD Visit 30 (±5) days after his/her final administration of study drug (per Section 6.2) and then have assessments monthly, through Month 12 per Appendix 13. The subject will not have an EOS Visit. The most important visit is the Month 12-Day 1 Visit, so if a subject is unwilling to continue monthly visits, every effort should be made for the subject to return to the clinic and complete the Month 12-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. Following the Month 12-Day 1 Visit, subjects will be followed for vital status per Section 6.4.

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

- Hematologic progression and initiation of chemotherapy is required; chemotherapy regimen should be documented on the appropriate electronic case report form (eCRF).
- Need for organ transplant or major surgery.
- 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 3 months after the ETD Visit, 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 whose pregnancy test is positive at the ETD Visit must be followed to term or until termination of the pregnancy (Section 7.4.2).

At any point in the study, if the subject is unwilling to return to the clinic for further visits but is willing to discuss their health status by phone, follow-up phone calls should be made to the subject or their caregiver every 3 months (Section 6.4).

4.4 Early Termination from the Study

Early termination occurs if the subject fails to complete the entire study, through the EOS Visit. 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 or its designee should be notified in a timely manner of all subject discontinuations. When possible, the tests and evaluations listed for the ETD Visit should be carried out.

Early termination from the study may occur if:

- 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.

4.5 Replacement of Subjects

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

4.6 Termination of the Clinical Study

If the Investigator, the Sponsor or its designee, 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

5 TREATMENT OF SUBJECTS

5.1 Study Drug

Study drug consists of NEOD001 or placebo.

5.1.1 Formulation, Packaging, and Labeling of NEOD001

The active study drug, NEOD001, is supplied as a sterile, 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.

The labelling will comply with applicable regulatory requirements.

5.1.2 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 NEOD001 in a refrigerator at a temperature ranging from 2°C to 8°C in a secure, locked location. Access to the NEOD001 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 NEOD001 has not been properly handled (e.g., physical damage to carton/vial, temperature outside the 2°C to 8°C range in transit, or not stored at 2°C to 8°C in the clinic), follow the procedure outlined in the Pharmacy Manual or immediately contact the Unblinded Monitor (contact information available in the Study Manual). In such an event, NEOD001 should be quarantined in a 2°C 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 Section 5.3 and the Pharmacy Manual for further details about shipping, storage and handling of NEOD001.

5.2 Accountability and Return of Study 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.

5.3 Dosage, Preparation, and Administration

Study drug consists of 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 using the Screening 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 unless thought to be exclusively due to fluid fluctuation (e.g., edema).

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. A separate placebo will not be provided for this study. Subjects who receive placebo will be administered a 250 mL IV bag of 0.9% saline, which will look identical to the NEOD001 infusion bag. Refer to the Pharmacy Manual for complete information on preparing and administering the study drug.

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 IWRS, and will then prepare and reconstitute the study drug, providing it 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.

Study drug will be administered as an initial 120 (±10)-minute IV infusion on Month 1-Day 1. If, in the opinion of the Investigator, the subject tolerates the initial administration, subsequent infusions may be administered over 60 (±10) minutes once every 28 (±5) days; a minimum of 21 days between doses is required. Subjects may receive up to 12 infusions of study drug.

NEOD001 contains no antimicrobial preservatives. Once reconstituted, storage of study drug, inclusive of dilution and administration, should be limited to 24 hours under refrigerated conditions or 4 hours at room temperature. If it is anticipated that the infusion will extend beyond 4 hours, the reconstituted 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.

All subjects will be closely monitored for approximately 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. Beginning with the third infusion, the Investigator may decrease the monitoring time to no less than 60 minutes, if no infusion-related reactions were observed in the previous infusions and allowed per the Institutional Review Board/Institutional Ethics Committee (IRB/IEC).

5.4 Dosage Adjustments

5.4.1 Withholding of Study Drug

Subjects with symptomatic orthostatic hypotension and/or systolic BP <85 mmHg, which in the medical judgment of the Investigator would interfere with subject's ability to safely receive study drug, will have study drug withheld until the next scheduled monthly administration, but should still have all other study visit assessments completed.

5.4.2 Management of Suspected Systemic Infusion-Related/Hypersensitivity Adverse Events

In the event of a suspected systemic infusion-related and/or hypersensitivity AE, the infusion should be immediately discontinued and appropriate supportive therapy should be administered per institutional practice, which may include, but is not limited to, 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 systemic infusion-related and/or hypersensitivity AE for assessment of the following: cytokine levels (IL-6, IL-8, TNF-alpha, and INF-gamma) complements C3, C4, and CH50; C-reactive protein (CRP), serum amyloid A/acute phase serum amyloid A (SAA/A-SAA); tryptase (serial levels: within 30 to 120 minutes of onset AND at 48 to 72 hours); serum NEOD001; and anti-NEOD001 antibody levels.

For subjects with a Grade 2 infusion-related AE, if it is appropriate to restart the infusion, the infusion rate should be decreased by 50% (e.g., if the infusion was previously administered over 60 minutes, the new rate should be based on administering 250 mL over at least 90 minutes). If the subject is to receive additional infusions in subsequent weeks, the rate of these infusions should be discussed with and agreed upon prospectively by the Investigator and the Medical Monitor. In addition, for all subsequent infusions, 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).

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 subsequent dosing, **both** the dose and infusion rate will be reduced by 50% from the original dose (i.e., 12.5 mg/kg in 250 mL) and infusion rate (i.e., over at least 90 minutes [if the previous infusion time was 60 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 6.2.

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 6.2.

5.4.3 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.

5.5 Treatment Compliance

Treatment compliance will be documented in the eCRF by recording the date, time, and whether or not each IV dose of study drug was completely infused, along with reasons why treatment was adjusted or not administered, if applicable.

5.6 Prior and Concomitant Medication/Therapy

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

5.6.1 Allowed (Concomitant)

- Radiation therapy for the treatment of local amyloid deposits
- Calcium channel blockers (if on stable dose)
- Steroids (***exception:*** not allowed for treatment of AL amyloidosis)

5.6.2 Prohibited (Concomitant)

- Chemotherapy
- Other investigational agents (e.g., drugs not approved for any indication)

- Myeloablative chemotherapy with ASCT
- Organ transplant
- Histone deacetylase (HDAC) inhibitors
- Doxycycline use (if required for treatment of infection, contact the Medical Monitor)
- Gadolinium contrast agents are only permitted in exceptional circumstances. If a patient requires the use of gadolinium contrast agents, contact the Medical Monitor.
- Experimental imaging of amyloid

6 STUDY PROCEDURES

6.1 Evaluations by Visit

6.1.1 Screening

With the exception of the assessments to be considered standard of care (e.g., NT-proBNP/BNP, tissue samples, and echocardiograms), a signed ICF must be obtained before any study-specific screening evaluations are performed and should be documented in the subject's medical chart.

Screening evaluations and procedures will be performed within 28 days prior to the first study drug administration on Month 1-Day 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.

The following will be performed within the 28 days prior to the Month 1-Day 1 Visit:

- Signed ICF
- Review inclusion and exclusion criteria to assess eligibility
- Medical History - 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
- If available, record results of at least 2 prior NT-proBNP or 2 prior BNP measures from within the previous 6 months; NT-proBNP is preferred, but BNP may be used if it is the institution's historical standard
- Prior and concomitant medications/therapy
- Assessment of AEs
- Confirmation of AL amyloidosis by mass spectrometry tissue typing, immunoelectron microscopy, gene sequencing, and/or ^{99m}Tc scintigraphy for subjects who meet Inclusion Criterion #3
- Complete physical examination - including height, 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).
- Vital signs – heart rate (HR), BP, respiratory rate (RR), and body temperature after the subject has been at rest for ≥5 minutes
- ECOG PS (Appendix 7)

- NYHA class (Appendix 8)
- NIS-LL (Appendix 5 and Section 6.6.2.5) and VASPI (Appendix 6 and Section 6.6.2.5)
    - Note: NIS-LL is for all subjects with peripheral neuropathy at Screening and the addition of the VASPI is only for subjects with painful peripheral neuropathy at Screening
- SF-36v2 (Appendix 9)
    - Note: Administer SF-36v2 before conducting any other assessments on the same calendar day it is administered
- KCCQ (Appendix 10)
    - Note: Administer KCCQ after the SF-36v2, but before conducting any other assessments on the same calendar day it is administered
- 6MWT (Section 6.6.2.3); collect HR and BP pre- and post-6MWT administration
    - Notes: Two pretreatment 6MWTs are required before the first administration of study drug, with a minimum of 4 days in between the two tests. 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). NT-proBNP should be drawn before conducting 6MWT if being performed on the same calendar day.
- Echocardiogram (perform locally)
    - Note: If an echocardiogram was conducted within 90 days prior to Screening Day -28, it does not need to be repeated during Screening and the previous result may be used for eligibility; however, to be eligible for the additional cardiac imaging analysis, the subject must have had a 4-chamber view, 2-dimensional echocardiogram with Doppler
- 12-lead ECG performed in triplicate (perform centrally)
- Laboratory Assessments (central laboratory, unless otherwise noted):
    - Hematology and chemistry (including amylase and creatine kinase) per Appendix 11
    - PT/INR and PTT
    - Additional coagulation samples per Appendix 12
    - Troponin T
    - NT-proBNP

  - Note: NT-proBNP should be drawn before 6MWT if being performed on the same calendar day

- Serum pregnancy test for WOCBP within 28 days before Month 1-Day 1 study drug administration
  - Note: Women with tubal ligations are considered to be of childbearing potential but women who are surgically sterile (hysterectomy) or postmenopausal ≥2 years are not considered to be of childbearing potential
- Serum free light chains
- Serum immunofixation electrophoresis (IFE) and protein electrophoresis (PEP)
- Urinalysis - dipstick per Appendix 11
- Urinalysis - quantitative analysis/renal biomarkers per Appendix 11
  - Notes: It is important that the sample be taken before exercising and at approximately the same time for each collection; therefore, the first morning void is recommended. Urine samples will be collected and frozen for potential analysis at a later date.
- 24-hour urine collection for:
  - Urine IFE and PEP
  - Urine protein excretion

- Other Assessments (see Laboratory Manual)
  - Archive sample – collect only from those subjects who have consented to the collection and archiving of their samples for future correlative testing

6.1.2 Treatment Visits

Study visits will occur every 28 days based on scheduling from Month 1-Day 1. A ±5-day window is allowed for visits starting after Month 1. Subjects may receive up to 12 infusions of study drug; a minimum of 21 days between doses is required.

The predose assessments for each visit may be performed within the 3 days before the visit unless otherwise specified. Although central laboratory assessments will be performed each month for study analysis, local laboratory assessments may be performed for subject management when necessary for obtaining results on a more immediate basis. Results will be reviewed prior to dosing at each month's Day 1 visit to confirm that continued dosing is appropriate.

Subjects who present with symptomatic orthostatic hypotension and/or systolic BP <85 mmHg, which in the medical judgment of the Investigator would interfere with the 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. If study drug is withheld and subsequently rescheduled, central laboratory assessments required for that visit will need to be repeated if they were drawn >7 days prior to the rescheduled dosing date. However, a symptom-directed physical exam and vital signs need to be repeated prior to each dosing.

6.1.2.1 Month 1-Day 1

Prior to Study Drug Infusion:

The following assessments will be done prior to dosing on Month 1-Day 1:

- Concomitant medications/therapies
- Assessment of AEs
- Directed physical examination - including 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. The components of the physical exam will be as clinically indicated; however, 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).
- Vital signs including HR, BP, RR, and body temperature (per Section 6.6.1.2) – within 30 minutes before dosing, after subject has been at rest ≥5 minutes; assess in same position for all time points
- ECOG PS (Appendix 7)
- NYHA class (Appendix 8)
- NIS-LL (Appendix 5) and VASPI (Appendix 6)
    - Note: NIS-LL is for all subjects with peripheral neuropathy at Screening and the addition of the VASPI is only for subjects with painful peripheral neuropathy at Screening
- 12-lead ECG in triplicate (perform centrally) within 30 minutes before study drug administration
- Laboratory Assessments (central laboratory, unless otherwise noted):
    - Hematology and chemistry (including amylase) per Appendix 11
    - Inflammatory biomarkers per Appendix 11
    - NT-proBNP

  - Serum pregnancy test within 24 hours before study drug administration (local laboratory)
  - Urinalysis - dipstick per Appendix 11

- Other Assessments (see Laboratory Manual)
  - NEOD001 serum sample – within 2 hours before infusion
  - Anti-NEOD001 serum sample

- Randomization – After the subject is randomized, study drug treatment may be initiated
- Ensure subject continues to meet eligibility criteria before administration of study drug

Study Drug Administration:

- Administer study drug IV over 120 (±10) minutes (Section 5.3)
- Vital signs including HR, BP, RR, and body temperature (per Section 6.6.1.2) – assess 60 (±10) minutes after the start of the infusion; assess in same position for all time points

Assessments After Infusion:

- Monitor subjects 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.
- Vital signs including HR, BP, RR, and body temperature (per Section 6.6.1.2) after subject has been at rest ≥5 minutes; assess in same position for all time points:
  - At the end of infusion (EOI) (+5 minutes)
  - 30 (±5) minutes after EOI
  - 60 (±10) minutes after EOI
- 12-lead ECG in triplicate (perform centrally):
  - Within 15 minutes after EOI
- Other Assessments (see Laboratory Manual):
  - NEOD001 serum sample within 4 hours after EOI

- Collect additional blood samples if a significant toxicity is observed (e.g., a systemic infusion-related reaction, anaphylaxis, hypersensitivity reaction; Section 5.4.2) and if possible, samples should be collected while the acute symptoms persist

- Discharge subject from clinic if no immediate safety concerns and/or hypersensitivities are present after the postdose assessments and monitoring period. In the event of any clinical concerns or suspicious signs or symptoms after the infusion, the subject will remain with the Investigator and study staff for further observation until the Investigator deems the subject can safely leave the clinic.

6.1.2.2 Months 2 through 12 – Day 1 (±5 Days)

Prior to Study Drug Infusion:

The following assessments will be done prior to dosing on Day 1:

- Concomitant medications/therapies
- Assessment of AEs
- Directed physical examination - including 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. The components of the physical exam will be as clinically indicated; however, 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).
- Vital signs including HR, BP, RR, and body temperature (per Section 6.6.1.2) – within 30 minutes before dosing, after subject has been at rest ≥5 minutes; assess in same position for all time points
- ECOG PS (Appendix 7)
- NYHA class (Appendix 8)
- NIS-LL (Appendix 5) and VASPI (Appendix 6) – Months 3, 6, 9, 12
  - Note: NIS-LL is for all subjects with peripheral neuropathy at Screening and the addition of the VASPI is only for subjects with painful peripheral neuropathy at Screening
- SF-36v2 (Appendix 9) – Months 3, 6, 9, 12
  - Note: administer SF-36v2 before performing any other study assessments on the same calendar day it is administered
- KCCQ (Appendix 10) – Months 3, 6, 9, 12

  - Note: Administer after the SF-36v2, but prior to conducting any other assessments on the same calendar day it is administered

- 6MWT (Section 6.6.2.3) and collect HR and BP pre- and post-6MWT administration – Months 3, 6, 9, 12

  - Notes: NT-proBNP should be drawn before conducting 6MWT if being performed on the same calendar day. If the 6MWT is conducted on the same calendar day as the study drug infusion, the 6MWT must be completed before initiation of the infusion

- Echocardiogram (perform locally) – Month 12 only

  - Notes: May be conducted within 10 days before Day 1. To be eligible for the additional cardiac imaging analysis, the subject must have a 4-chamber view, 2-dimensional echocardiogram with Doppler.

- 12-lead ECG in triplicate (perform centrally) – within 30 minutes before dosing – Months 3, 6, 9, 12

- Laboratory Assessments (central laboratory, unless otherwise noted):

  - Hematology and chemistry (including amylase and creatine kinase) per Appendix 11

  - PT/INR and PTT

  - Additional coagulation samples if clinically indicated, per Appendix 12

  - Inflammatory biomarkers per Appendix 11 – Month 3

  - Troponin T

  - NT-proBNP

    - Note: NT-proBNP should be drawn before conducting 6MWT if being performed on the same calendar day (i.e., at Months 3, 6, 9, 12)

  - Serum pregnancy test (WOCBP only; local laboratory)

  - Serum free light chain – Months 3, 6, 9, 12

  - Serum IFE and PEP – Months 3, 6, 9, 12

  - Urinalysis - dipstick per Appendix 11 – Months 3, 6, 9, 12

  - Urinalysis - quantitative analysis/renal biomarkers per Appendix 11 – Months 3, 6, 9, 12

  - Notes: It is important that the sample be taken before exercising and at approximately the same time for each collection; therefore, the first morning void is recommended. Urine samples will be collected and frozen for potential analysis at a later date.

- 24-hour urine collection at Months 3, 6, 9, 12 for:
  - Urine IFE and PEP
  - Urine protein excretion

- Other Assessments (see Laboratory Manual):
  - NEOD001 serum sample – within 2 hours before infusion – Months 3, 6, 9, 12
  - Anti-NEOD001 serum sample – Months 3, 6, 9, 12
  - Archive sample – Months 6 and 12

Study Drug Administration:

Subjects with symptomatic orthostatic hypotension and/or systolic BP <85 mmHg, which in the medical judgment of the Investigator would interfere with subject's ability to safely receive treatment, will have study drug withheld.

- Administer study drug IV over 60 (±10) minutes if the prior infusions were well tolerated (Section 5.3). If needed, see Section 5.4 for dose adjustment instructions.
- Collect additional blood samples per Section 5.4.2 if a significant toxicity is observed (e.g., a suspected systemic infusion-related reaction, anaphylaxis, hypersensitivity reaction) and if possible, samples should be collected while the acute symptoms persist

Assessments After Infusion:

- Monitor subjects 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. Beginning with the third infusion, the Investigator may decrease the monitoring time to no less than 60 minutes, if no infusion-related reactions were observed in the previous infusions and allowed per the IRB/IEC.
- Vital signs including HR, BP, RR, and body temperature (per Section 6.6.1.2) – after subject has been at rest ≥5 minutes; assess in same position for all time points:
  - At EOI (+5 minutes)
  - 60 (±10) minutes after EOI

- 12-lead ECG in triplicate (perform centrally) – Months 3, 6, 9, 12:
  - Within 15 minutes after EOI
- NEOD001 serum sample – Months 3, 6, 9, 12:
  - Within 4 hours after EOI
- Discharge subject from clinic if no immediate safety concerns and/or hypersensitivities are present after the postdose assessments and monitoring period. In the event of any clinical concerns or suspicious signs or symptoms after the infusion, the subject will remain with the Investigator and study staff for further observation until the Investigator deems the subject can safely leave the clinic.

6.2 End of Study/Early Treatment Discontinuation (EOS/ETD): 30 (±5) Days AFTER Final Dose

A final visit should occur 30 (±5) days after the final administration of study drug. The assessments shown for EOS/ETD should also be conducted for any unscheduled visit (i.e., a visit not specified by the protocol) as clinically indicated or if deemed necessary.

- Concomitant medications/therapy
- Assessment of AEs
- Complete physical examination - 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).
- Vital signs including HR, BP, RR, and body temperature (per Section 6.6.1.2) - after subject has been at rest ≥5 minutes
- ECOG PS (Appendix 7)
- NYHA class (Appendix 8)
- NIS-LL (Appendix 5) and VASPI (Appendix 6)
  - Note: NIS-LL is for all subjects with peripheral neuropathy at Screening and the addition of the VASPI is only for subjects with painful peripheral neuropathy at Screening
- SF-36v2 (Appendix 9)
  - Note: Administer SF-36v2 before conducting any other assessments on the same calendar day it is administered

- KCCQ (Appendix 10)
    - Note: Administer after the SF-36v2, but prior to conducting any other assessments on the same calendar day it is administered
- 6MWT (Section 6.6.2.3); collect HR and BP pre- and post-6MWT administration
    - Note: NT-proBNP should be drawn before conducting 6MWT if being performed on the same calendar day
- Echocardiogram – perform (locally) if not done within 60 days prior to visit
    - Note: To be eligible for the additional cardiac imaging analysis, the subject must have a 4-chamber view, 2-dimensional echocardiogram with Doppler
- 12-lead ECG performed in triplicate (perform centrally)
- Laboratory Assessments (central laboratory, unless otherwise noted):
    - Hematology and chemistry (including amylase and creatine kinase) per Appendix 11
    - PT/INR and PTT
    - Additional coagulation samples per Appendix 12
    - Inflammatory biomarkers per Appendix 11
    - Troponin T
    - NT-proBNP
        - Note: NT-proBNP should be drawn before conducting 6MWT if being performed on the same calendar day
    - Serum pregnancy test (WOCBP only)
    - Serum free light chains
    - Serum IFE and PEP
    - Urinalysis - dipstick per Appendix 11
    - 24-hour urine collection for:
        - Urine IFE and PEP
        - Urine protein excretion
- Other Assessments (see Laboratory Manual):

- NEOD001 serum sample
- Anti-NEOD001 serum sample

6.3 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.

6.4 Vital Status Follow-Up Phone Call

For randomized subjects who received at least 1 dose of study drug, conduct vital status telephone call approximately 3 months after last visit and approximately every 3 months thereafter or until subject enrolls in a separate open-label study, death, or for up to 5 years.

6.5 Order of Assessments of Specific Tests

SF-36v2:

Whenever the SF-36v2 is required, it should be administered prior to any other visit assessments on the calendar day it is administered.

KCCQ:

Administer the KCCQ after the SF-36v2, but prior to conducting any other assessments on the calendar day it is administered.

6MWT:

Questionnaires and clinical laboratory samples, including NT-proBNP, should be drawn prior to administering the 6MWT, if being performed on the same calendar day. The postbaseline 6MWTs must be completed before the study drug infusion is initiated, if being performed on the same calendar day.

ECGs and Vitals:

When ECGs are scheduled to be performed at the same time point as vital signs (e.g., within 30 minutes before dosing), the ECG should be completed before the blood pressure and HR measurements.

ECGs and PK Sampling:

When ECGs are scheduled to be performed at the same visit as PK blood collection, the ECG should be done before the PK blood collection.

Concomitant Medications:

Routine medications should not be administered in the 15 minutes after the completion of the NEOD001 infusion.

6.6 Methods of Assessment

6.6.1 Safety

6.6.1.1 Clinical Laboratory Evaluations

A central laboratory will be used for this study for analysis of hematology, chemistry (including amylase), coagulation, inflammatory biomarkers, cardiac biomarkers, serum free light chains, serum IFE/PEP, urinalyses, 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 may be obtained at the Investigator's discretion for subject management when necessary for obtaining results on a more immediate basis. Results will be reviewed prior to dosing at each month's Day 1 visit to confirm that continued dosing is appropriate. Results from local laboratory tests will not be collected in the eCRFs or the clinical database.

Citrated plasma samples will 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.

Urine samples will be collected and frozen for potential analysis of renal biomarkers at a later date (see Appendix 11). It is important that the sample be taken before exercising and at approximately the same time for each collection; therefore, the first morning void is recommended.

The 24-hour urine IFE/PEP and 24-hour urine protein excretion 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 will be provided in the Laboratory Manual.

A bioanalytical laboratory will be used for the analysis of NEOD001 and anti-NEOD001 samples, as well as for the storage of serum samples for future correlative testing (Sections 6.6.3 and 6.6.4).

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 subjects who meet Inclusion Criterion #3.

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

6.6.1.2 Vital Signs

Predose vital signs should be assessed within 30 minutes before dosing. Vital signs should be measured after the subject has been at rest ≥5 minutes. Within a single visit, assess in the same position for all time points.

Heart rate will be measured from the radial pulse counted manually or with an automatic BP monitor over at least 15 seconds and adjusted per minute.

Blood pressure (systolic and diastolic) measurements should be taken from the same arm throughout the study using an automated BP monitor that uses an oscillometric method.

Respiratory rate will be measured over at least 15 seconds and adjusted per minute.

Body temperature can be measured using either oral or tympanic methods, but the method should be consistent throughout the study for a given subject.

Blood pressure and HR are to be collected after ECGs are completed.

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

6.6.1.3 Physical Examination

Any unfavorable changes in physical examination findings considered by the Investigator as clinically significant will be documented in the eCRF as an AE. Physical examinations must be performed by the Investigator or a medically qualified delegate.

A complete physical examination 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. A directed physical examination includes weight and other components, which will be as clinically indicated. At all visits, the following are to 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).

6.6.1.4 Echocardiograms

Echocardiograms will be performed locally. Data from study centers that possess the technical abilities to produce a 4-chamber view from a 2-dimensional echocardiogram with Doppler will be used for the relevant exploratory endpoint analysis. Details will be provided in the Study Manual. Note that the Month 12 echocardiogram may be performed within 10 days before Day 1.

6.6.1.5 12-Lead ECGs

The ECGs will be performed centrally. Measurements will be made in triplicate, 1 to 10 minutes apart and taken after the subject has rested in a supine position for ≥5 minutes. Heart rate, PQ/PR duration, QRS duration, QT duration, and QTcF - Fridericia's correction formula, and the Investigator's overall interpretation will be recorded. When ECGs are scheduled to be performed at the same visit as PK blood collection, the ECG should be done before the PK blood collection.

6.6.2 Efficacy

6.6.2.1 Organ Response (i.e., cardiac, renal, peripheral nerve)

See Appendix 4.

6.6.2.2 Short Form-36v2® Health Survey (SF-36v2)

The SF-36v2 should be administered before any other study assessments are performed on the same calendar day it is administered. See Appendix 9. Details will be provided separately.

6.6.2.3 6-Minute Walk Test (6MWT)

The postbaseline 6MWTs may be administered on the same calendar day that study drug is administered, if the 6MWT is completed before initiation of the study drug infusion. The questionnaires and clinical laboratory samples (central and if applicable, local) should be drawn prior to administering the 6MWT, if being performed on the same calendar day. As part of the 6MWT, BP and HR will be collected pre- and post-6MWT administration. Subjects should plan to be able to return to the same clinical site for each 6MWT from first Screening through Month 12.

If the subject discontinues study drug prior to the Month 12 Visit, ***every effort should be made*** for the subject to return to the clinic at the Month 12 time point for completion of all of the Month 12-Day 1 assessments, in particular, the 6MWT.

Details regarding the requirements for proper administration of the 6MWT are described in the Study Manual.

6.6.2.4 Kansas City Cardiomyopathy Questionnaire (KCCQ)

The KCCQ (Appendix 10) should be administered after the SF-36v2, but prior to conducting any other assessments on the same calendar day it is administered. Details will be provided in the Study Manual.

6.6.2.5 Peripheral Neuropathy Assessment

Peripheral neuropathy will be assessed as follows:

- The Neuropathy Impairment Score in Lower Limbs (NIS-LL; Appendix 5) assesses lower limb reflexes, sensation, and motor strength and will be administered to subjects who have peripheral neuropathy at Screening

- The Visual Analog Scale – Pain Intensity (VASPI; sample tool in Appendix 6) assesses a subject's level of pain related to peripheral neuropathy and will be administered to subjects who have painful peripheral neuropathy at Screening. Details regarding administration of the VASPI are described in the Study Manual.

Peripheral neuropathy and neuropathic pain AEs will be assessed using NCI-CTCAE grading, as shown in Table 2.

Table 2 Common Terminology Criteria for Adverse Events (CTCAE) Grade 1-5 for Peripheral Neuropathy and Neuropathic Pain

	CTCAE 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[a]	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		

Abbreviations: ADL = activities of daily living (e.g., preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.).

a Definition: a disorder characterized by inflammation or degeneration of the peripheral sensory nerves.
Source: National Cancer Institute, 2009.

6.6.3 Pharmacokinetics

All subjects enrolled in the study will undergo sparse sampling for serum NEOD001 according to Table 1 and the Laboratory Manual. Additional samples should be collected if a significant toxicity is observed (per Section 5.4.2). Serum NEOD001 concentrations from this study will be pooled with similar samples from other studies in a population PK analysis. Details will be provided in a separate document. Refer to the Laboratory Manual for additional details.

6.6.4 Immunogenicity

Serum ADA levels will be measured according to Table 1 and the Laboratory Manual. Additional samples should be collected if a significant toxicity is observed (per Section 5.4.2). ADA levels will be correlated with serum NEOD001 concentrations when ADA and corresponding serum NEOD001 concentrations are available.

An electrochemiluminescent (ECL) assay will be used to detect serum anti-NEOD001 antibodies. Any screening positives will be run at increasing dilutions and a titer determined (expressed as the reciprocal of the dilution that generates a positive response). Additionally, all positives will be run in a confirmatory assay to determine the response is specific to NEOD001.

Refer to the Laboratory Manual for additional details.

7 ADVERSE EVENTS/SERIOUS ADVERSE EVENTS AND REPORTING

7.1 Adverse Events—Definition

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can, therefore, be any unfavorable and unintended sign (including a laboratory finding, for example), symptom, syndrome, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Examples include:

- Any treatment-emergent signs and symptoms (events that are marked by a change from the subject's baseline/entry status [e.g., an increase in severity or frequency of preexisting abnormality or disorder])
- All reactions from study drug, abuse of drug, withdrawal phenomena, sensitivity, or toxicity to study drug
- Apparently unrelated illnesses
- Injury or accidents
- Exacerbations of the underlying disease (indication)
- Extensions or exacerbations or symptomatology, subjective events reported by the subject, new clinically significant abnormalities in clinical laboratory, physiological testing, or physical examination

The reporting period for AEs is from the time that the ICF is signed through the last study visit or through 30 days after the last dose of study drug, whichever is later. All AEs, whether or not related to the study drug, must be fully and completely documented on the eCRF and in the subject's medical notes. The following attributes must be assigned: description, dates of onset and resolution, severity, assessment of relatedness to study drug (either related or not related), and action taken. The Investigator may be asked to provide additional follow-up information.

In the event that a subject is withdrawn from the study because of an AE, it must be recorded on the eCRF. The subject should be followed and treated by the Investigator until the AE has resolved, stabilized, or a new chronic baseline has been established.

The Investigator must report all AEs. At each visit the Investigator will ask the subject a nonspecific question (e.g., "Have you noticed anything different since your last visit?") to assess whether any AEs have been experienced since the last report or visit. Adverse events will be identified and documented on the eCRF in appropriate medical terminology. The severity and the relationship to the study drug will be determined and reported on the eCRF (Sections 7.2 and 7.3).

Note that any intermittent or as-needed ("PRN") use of medication (and specifically any newly prescribed medication) during the course of a study may indicate the occurrence of an AE that may need to be recorded on more than one eCRF.

7.2 Adverse Events—Severity Rating

Adverse events will be assessed according to CTCAE version 4.0 (National Cancer Institute, 2009). Adverse events that do not have a corresponding 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):** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

- **Grade 2 (moderate):** Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activity of daily living (e.g., preparing meals, shopping for groceries or clothes, using the telephone, managing money).

- **Grade 3 (severe):** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (e.g., bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).

- **Grade 4 (life threatening):** Life-threatening consequences; urgent intervention indicated.

- **Grade 5 (fatal):** Death related to AE.

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**.

7.3 Adverse Events—Causality Rating

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

- Known effects of concomitant medications

- Preexisting risk factors

- A plausible mechanism

- Concurrent illnesses

7.4 Serious Adverse Events and Unexpected Adverse Events

In addition to the severity rating, each AE is to be classified by the Investigator as "serious" or "not serious." The seriousness of an event is defined according to the applicable regulations and generally refers to the outcome of an event. An SAE is one that meets one or more of the following:

- Is fatal

- Is life-threatening

- Is persistent or significantly incapacitating or causes substantial disruption of the ability to conduct normal life functions
- Requires inpatient hospitalization
- Prolongs existing hospitalization
- Is a congenital anomaly or birth defect
- Is an important medical event that may jeopardize the subject and/or may require medical or surgical intervention to prevent one of the outcomes listed above

Definition of Life-threatening
An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator or Sponsor (and/or designee), its occurrence places the subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Definition of 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 last for a period of <24 hours and do not result in a full hospital admission
- Outpatient surgery
- Preplanned or elective procedures (Section 7.4.1)
- Protocol procedures

The above events would not be reported as SAEs unless the event triggering the hospital visit is an SAE as defined by other SAE criteria such as life-threatening, results in persistent or significant disability/incapacity or as per medical judgment of the Investigator.

Any other event fulfilling the definition of serious that develops as a result of the in-hospital procedure or extends the hospital stay is an SAE.

Definition of Disability

Disability is defined as a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.

Definition of Medically Significant
Important medical events (medically significant events) that may not result in death, be life-threatening or require hospitalization may be considered to be 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 this definition. Examples of such events are a new diagnosis of cancer, intensive treatment in an emergency room or at home for allergic bronchospasm, or convulsions that do not result in hospitalization, or 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.

Definition of Suspected Adverse Reactions
Suspected adverse reaction is considered any AE for which there is a reasonable possibility that the drug caused the AE.

Definition of Unexpected
An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the Investigator Brochure or is not listed at the specificity or severity that has been observed. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the Investigator Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

7.4.1 Elective Procedures and Surgeries

For the purposes of this protocol, the following conventions will apply for SAE reporting of elective procedures, and surgeries:

- A prescheduled 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 prescheduled 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 prescheduled elective procedure or routinely scheduled treatment is the sole reason for admission and intervention
- An untoward medical event occurring during the prescheduled elective procedure or routinely scheduled treatment should be recorded as an AE or a SAE. Any concurrent medications should also be recorded on the eCRF.

7.4.2 Other Reportable Information

In addition, and for the purposes of monitoring, any occurrence of exposure through lactation and any pregnancy (with or without an AE) of a female subject or partner of a male subject should be reported, regardless of seriousness, according to the directions in Section 7.4.4. Any subject who becomes pregnant during the study must be withdrawn from study drug treatment, and will be followed to term.

7.4.3 Disease Progression and Death

Disease progression (including progression of hematologic condition and/or organ dysfunction of AL amyloidosis, and death due to disease progression) is generally recorded as part of the efficacy evaluation and should not be reported as a specific AE or SAE term. When an AE resulting from disease progression meets the requirements to be considered serious, the SAE verbatim term should be reported as the diagnosis that best describes the event rather than as "disease progression." For instance, a subject with pleural effusion presents with shortness of breath. The cause of the shortness of breath is a pleural effusion resulting from disease progression. The event term may be reported as "pleural effusion" instead of disease progression.

Death should not be reported as an SAE term, but as a clinical outcome of a specific SAE. The cause of death, reported on a source document such as the Death Certificate or autopsy report, should be used as the event term for the SAE. For example, in a subject with acute heart failure that results in death, the SAE is reported as "acute heart failure" with an outcome of "death."

7.4.4 Serious Adverse Events—Reporting

It is the responsibility of the Investigator to report SAEs to the Sponsor or its designee within 24 hours of awareness of the event or safety information, whether initial or follow-up.

All SAEs must be reported immediately (within 24 hours of awareness) to the Sponsor or its designee (see Study Manual for details). Do **not** delay in the reporting of a suspected SAE in order to obtain additional information. Any additional information, if collected, can be reported to the Sponsor or its designee as a follow-up to the initial report. SAEs will be reported using the SAE forms provided as part of the Study Manual. Please remember to give details of the subject identification number or other appropriate terminology and ensure the narrative is comprehensive and includes a chronology and assessment of the event.

Reporting of SAEs to the IRB/IEC will be done in compliance with the standard operating procedures and policies of the IRB/IEC and with applicable regulatory requirements. Adequate information must be obtained by the Sponsor or its designee showing that the IRB/IEC was properly and promptly notified as required. Please refer to the Study Manual for details on reporting SAEs.

The Investigator is encouraged to discuss any AEs with the Sponsor Medical Monitor for which the issue of seriousness is unclear or questioned. Contact information for the Medical Monitor is listed on the Team Roster in the Study Manual.

The reporting period for SAEs is the period from signing of the ICF through 30 days after the last administration of study drug or last study visit, whichever is later. SAEs reported to the Investigator outside of this reporting period will be reported to the Sponsor or its designee only if, in the judgment of the Investigator, there is "a reasonable possibility" that the event may have been caused by the product.

All SAEs will continue to be followed until the end of the study or until such events have resolved or the Investigator, in conjunction with the Sponsor or its designee, deems them to be chronic or stable.

8 STATISTICAL METHODS AND CONSIDERATIONS

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

Endpoints are listed in Section 3.2.

8.1 Analysis Populations

The Intent-to-Treat (ITT) Population will include all randomized subjects who receive any amount of study drug (NEOD001 or placebo). The ITT Population will be the primary population used for efficacy analyses. Treatment assignment will be based on the randomized treatment.

The Safety Population will include all subjects who receive any amount of study drug (NEOD001 or placebo). The Safety Population will be the primary population used for safety analyses. Treatment assignment will be based on the randomized treatment.

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 one 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 due to AL amyloidosis etiologies answered as yes) and had a baseline Neuropathy Impairment Score–Lower Limbs (NIS-LL) total score of 2 or greater and at least one postbaseline NIS-LL total score.

The Hepatic Evaluable Population will include subjects who had hepatic involvement defined as >1.5 × ULN alkaline phosphatase at baseline and at least one postbaseline assessment of alkaline phosphatase.

8.2 Analysis of Study Population and Subject Characteristics

Enrollment, important protocol deviations, and discontinuations from the study will be summarized.

Demographic and baseline characteristics, such as age, sex, race, and weight at Screening will be summarized using means, standard deviations, medians, ranges for continuous variables, and proportions for categorical variables.

Study drug administration data will be listed and any dose modifications will be flagged. Study drug exposure will be summarized using total number of infusions received, percentage of expected infusions, total dose interruptions and reductions, and dose strength.

8.3 Analysis of Efficacy Endpoints

8.3.1 Primary Efficacy Analysis

The NT-proBNP best response rates in the two arms will be compared using the Cochran-Mantel-Haenszel (CMH) test at the alpha=0.05 (two-sided) level of significance. The analysis will be stratified by the randomization stratification factors.

8.3.2 Key Secondary Efficacy Analyses

NEOD001 and placebo will be compared on change from baseline in the SF-36v2 PCS score after 12 months of treatment using a REML-based 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 Kenward and Roger method will be used to calculate the denominator degrees of freedom for the test of fixed effects. All visits will be included in the model, with the primary comparison at the EOS Visit to evaluate 12 months of treatment.

The NEOD001 and placebo distributions of change from baseline in 6MWT distance (meters) after 12 months of treatment will be analyzed using a van Elteren test with stratification by randomization strata.

The analysis of NT-proBNP will be performed using a general linear mixed effects model to compare the rate of change (i.e., slope) of NT-proBNP over 12 months of treatment between treatment groups. The null hypothesis of no difference in slopes between the treatment groups will be determined by testing the significance of the treatment group by time interaction term.

For the primary and key secondary efficacy analyses, the overall 2-sided level of significance will be alpha=0.05. The hypothesis testing of key secondary endpoints will be conducted in a sequential closed testing gate-keeping procedure separately, provided the primary efficacy endpoint comparison is statistically significant at an alpha level 0.05. If this comparison is not statistically significant, then the comparison of key secondary efficacy endpoints will be considered nominal, descriptive, and exploratory. This procedure controls the study-wise type I error and is described below.

1. First placebo and NEOD001 will be compared with respect to the primary efficacy endpoint. If the comparison achieves statistical significance at the 2-sided 0.05 level in favor of NEOD001, then

2. Placebo and NEOD001 will be compared with respect to change from baseline to 12 months of treatment in the SF-36v2 PCS score. If the comparison achieves statistical significance at the 2-sided 0.05 level in favor of NEOD001, then

3. Placebo and NEOD001 will be compared with respect to change from baseline to 12 months of treatment in the 6MWT distance (meters). If the comparison achieves statistical significance at the 2-sided 0.05 level in favor of NEOD001, then

4. Placebo and NEOD001 NT-proBNP slopes over 12 months of treatment will be compared.

If at any step defined above, the comparison is not statistically significant at the 2-sided 0.05 level, then the remaining comparisons in the stated hierarchy will be considered nominal, descriptive, and exploratory. The study-wise type I error will be maintained with the above closed procedure.

8.3.3 Additional Secondary Efficacy Analyses

For the Renal Evaluable Population, renal best response will be analyzed in the same manner described for the primary efficacy endpoint.

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.

For the Hepatic Evaluable Population, hepatic best response will be analyzed in the same manner described for the primary efficacy endpoint.

8.3.4 Exploratory Efficacy Analyses

All exploratory quantitative endpoints, except the 6MWT, defined as the change and percent change from baseline will be analyzed in the same manner described for the SF-36v2. Exploratory 6MWT endpoints will be analyzed in the same manner described for the key 6MWT secondary endpoint.

Proportion endpoints will be analyzed in the same manner described for the primary efficacy endpoint.

Overall survival and other time-to-event endpoints will be analyzed in the same manner described for progression-free survival.

8.4 Analysis of Safety Endpoints

Safety will be assessed through summaries of AEs, changes in laboratory test results, and changes in vital signs. Additional safety assessments include 12-lead ECGs. Safety data will be summarized by treatment group using the Safety Population.

All collected AE data will be listed by study site, subject number, and visit. All AEs occurring on or after treatment on Day 1 will be summarized. TEAEs are defined as AEs or SAEs that occur from the initiation of the first study drug infusion through the 30-day period following the last dose of study drug. In addition, all SAEs, including deaths, will be listed and summarized separately.

Descriptive statistics of the quantitative laboratory results, vital signs, and ECG parameters will be presented by treatment group and study visit, as well as the change from baseline at each visit. The baseline value is defined as the last non-missing value before the initial administration of study drug.

8.5 Analysis of Other Endpoints

8.5.1 Pharmacokinetics

Serum NEOD001 concentrations from this study will be pooled with similar samples from other studies in a population PK analysis. Details will be provided in a separate document.

8.5.2 Immunogenicity

Serum anti-NEOD001 titers will be listed and correlated with clinical toxicity and serum NEOD001 concentrations (where available). 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.

8.6 Determination of Sample Size

For the primary endpoint, the assumed true rates for NEOD001 vs placebo are 50% and 22.5%, respectively. Based on a two-sample comparison of proportions at the alpha=0.05 level of significance, a total sample size of 100 subjects (50 in the NEOD001 arm, 50 in the placebo arm) will provide >80% power based on a two-sided CMH test. Based on the actual enrolled sample size (N~130), the final power is 91%.

8.7 Handling of Dropouts and Missing Data

Observed data will be included in listings and summary tables. Handling of missing data will be outlined in the Statistical Analysis Plan.

9 DATA RECORDING, RETENTION, AND MONITORING

9.1 Case Report Forms

The clinical site(s) participating in this study is (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 the system. 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 its designee (or via other data collection methods, e.g., electronic laboratory data transfer). The Investigator is responsible for reviewing all eCRFs, 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.

9.2 Availability and Retention of Records

The Investigator must make study data accessible to the study monitor, other authorized representatives of the Sponsor, and Regulatory Authority inspectors upon request. A file for each subject must be maintained at the clinical site that includes the signed 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 medications 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.

9.3 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 International Committee on Harmonisation (ICH) Good Clinical Practice (GCP) and the Sponsor's (or its 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.

9.4 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 date of birth or age, sex, and study-specific site and subject numbers. 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/IEC 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.

10 ETHICAL AND LEGAL ISSUES

10.1 Ethical Conduct of the Study

This study will be conducted in compliance with the current ICH E6 GCP, the ethical principles of the Declaration of Helsinki, current FDA GCP guidelines, and any additional national or IRB/IEC or competent authority-required procedures, whichever represents the greater protection for the individual.

10.2 Regulatory Approval

The Sponsor or its 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 until the required regulatory approvals have been obtained in the appropriate jurisdiction.

10.3 Ethics Committee Approval

The Investigator at the site is responsible for obtaining IRB/IEC approval for the final protocol, the Sponsor-approved ICF, and any materials used to recruit subjects. Written approval of these documents must be obtained from the IRB/IEC before any subject is enrolled at a site.

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

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

10.4 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/IEC for approval. An IRB/IEC-approved copy of the ICF and all amendments will be forwarded to the Sponsor.

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 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 given to the subject.

10.5 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.

10.6 Protocol Amendments and Study Termination

Protocol amendments and amendment to the Informed Consent must be made only with the prior approval of the Sponsor and/or its designee. The IRB/IEC must be informed of all amendments and give approval for any amendments likely to affect the safety of the subjects or the conduct of the trial. The Investigator must send a copy of the approval letter from the IRB/IEC to the Sponsor and/or designee.

Both the Sponsor and the Investigator reserve the right to terminate the study (Section 4.6), according to the study contract. The Investigator should notify the IRB/IEC in writing of the trial's completion or early termination and send a copy of the notification to the Sponsor and/or designee.

10.7 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 are delineated in the Clinical Study Agreement.

10.8 Publication Policy

All publication rights are delineated in the Clinical Study Agreement.

11 REFERENCES

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12 APPENDICES

Appendix 1 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)

Abbreviations: dFLC = difference between involved and uninvolved free light chains.
*Only applicable for subjects who had dFLC >50 mg/L (5 mg/dL) prior to treatment.
Source: Comenzo et al, 2012.

Appendix 2 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]
- Vasectomised partner[2,3]
- Sexual abstinence[4]

[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 women of childbearing potential (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, 2014.

Appendix 3 Revised International Myeloma Working Group (IMWG) 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, computerized tomography (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 positron emission tomography with computed tomography.

*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 et al, 2014.

Appendix 4 Organ Response and Progression Criteria

Organ	Response	Progression
Heart/Cardiac[a]	NT-proBNP response (>30% and >300 ng/L decrease in subjects with baseline NT-proBNP ≥650 ng/L) OR NYHA class response (≥2 class decrease in subjects with baseline NYHA class III or IV)	NT-proBNP progression (>30% and >300 ng/L increase)[b]
Kidney/Renal[c]	≥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[d]	NIS-LL increase from baseline of <2 points	NIS-LL increase from baseline of ≥2 points
Liver/Hepatic[a]	50% decrease in abnormal ALP value	≥50% increase in ALP above the lowest value

Abbreviations: ALP = alkaline phosphatase; eGFR = estimated glomerular filtration rate; NIS-LL = Neuropathy Impairment Score–Lower Limbs; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association.

a Modified from Table 2 in Comenzo et al, 2012. In addition to the progression criteria listed above, the 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.

b Subjects with progressively worsening renal function cannot be scored for NT-proBNP progression.

c Palladini et al, 2014.

d Coelho et al, 2012.

Appendix 5 Neuropathy Impairment Scale – Lower Limbs

Neuropathy Impairment Scale – Lower Limbs (NIS-LL)
NEOD001-201

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

Appendix 6 Visual Analog Scale – Pain Intensity (VASPI)

VISUAL ANALOG SCALE – PAIN INTENSITY

SAMPLE

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

No Pain	Worst Imaginable Pain

Appendix 7 Eastern Cooperative Oncology Group (ECOG) Performance Status

Grade	Description
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 et al, 1982.

Appendix 8 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.

Source: American Heart Association, 2015.

Appendix 9 Short Form-36v2 Health Survey

SF-36v2® Health Survey © 1992, 1996, 2000, 2010
Medical Outcomes Trust and
QualityMetric Incorporated.

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SF-36® is a registered trademark of
Medical Outcomes Trust.
(SF-36v2® Health Survey Standard,
United States (English))

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 10 Kansas City Cardiomyopathy Questionnaire (KCCQ)

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
☐	☐	☐	☐	☐	☐

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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
☐	☐	☐	☐	☐	☐	☐

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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
☐	☐	☐	☐	☐

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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	☐	☐	☐	☐	☐	☐

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Appendix 11 Laboratory Tests

Serum Chemistry:
- ALP (E)[a]
- ALT (E)
- AST (E)
- Bilirubin - total (E) and direct
- GGT
- BUN
- LDH
- Creatinine (E)
- Glucose
- Cholesterol
- Triglycerides
- Calcium
- Phosphate
- Protein - total
- Albumin
- Sodium
- Potassium
- Chloride
- Bicarbonate
- Magnesium
- Amylase
- Creatine kinase
- Uric acid
- Estimated glomerular filtration rate (E)[e]
- Estimated creatinine clearance
- Cystatin C

Hematology:
- Hemoglobin (E)
- Hematocrit
- RBC
- WBC
- Neutrophils (absolute [E], %)
- Lymphocytes (absolute, %)
- Monocytes (absolute, %)
- Eosinophils (absolute, %)
- Basophils (absolute, %)
- Platelet count (E)

Other[b]:
- Serum anti-NEOD001 antibodies[c]
- Serum NEOD001 concentration
- Serum FLCs[d]
- 24-hr urine protein excretion & total volume
- Serum & 24-hr urine PEP
- Serum & urine IFE

Inflammatory Biomarkers[b]:
- IL-6
- IL-8
- TNF-alpha
- INF-gamma
- Complements C3, C4, and CH50
- CRP
- SAA (A-SAA)
- Tryptase

Urinalysis - Dipstick:
- Color & clarity
- Specific gravity
- pH
- Protein
- Glucose
- Ketones
- Bilirubin
- Urobilinogen
- Blood
- Nitrite
- Leukocyte esterase
- Microscopic

Urinalysis - Quantitative Analysis/Renal Biomarkers[f]:
- Urine albumin/creatinine ratio
- Urine NGAL
- Urine RBP

Cardiac Biomarkers:
- Troponin T
- NT-proBNP

Coagulation:
- PT/INR
- PTT
- Additional indices - see Appendix 12

Women of childbearing potential only:
- Serum beta hCG pregnancy tests (E)

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; A-SAA = acute phase serum amyloid A; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CRP = C-reactive protein; (E) = may be used for eligibility; FLCs = free light chains; GGT = gamma-glutamyl transpeptidase; hCG = human chorionic gonadotropin; IFE = immunofixation electrophoresis; IL = interleukin; INF = interferon; LDH = lactate dehydrogenase; NGAL = neutrophil gelatinase-associated lipocalin; NT-proBNP = N-terminal pro-brain natriuretic peptide; PEP = protein electrophoresis; PT/INR = prothrombin time/international normalized ratio; PTT = partial thromboplastin time; RBC = red blood cell; RBP = retinol-binding protein; SAA = serum amyloid A; TNF = tumor necrosis factor; WBC = white blood cell.

a Including isozymes for subjects with ALP >5 × upper limit of normal.

b See details in Section 5.4.2 regarding collection of samples in cases of suspected systemic infusion-related/hypersensitivity reactions.

c Any sample found to be confirmed positive for anti-NEOD001 antibodies may be further evaluated by a neutralizing antibody assay.

d Including dFLC (difference between involved and uninvolved FLCs) and FLC ratio.

e GFR = $141 \times \min(\text{Scr}/\kappa, 1)^{\alpha} \times \max(\text{Scr}/\kappa, 1)^{-1.209} \times 0.993^{\text{Age}} \times 1.018$ [if female] × 1.159 [if black] where: Scr = serum creatinine in mg/dL; $\kappa = 0.7$ for females, 0.9 for males; $\alpha = -0.329$ for females, -0.411 for males; min = the minimum of Scr /κ or 1; max = the maximum of Scr /κ or 1.

f It is important that the sample be taken before exercising and at approximately the same time for each collection; therefore, the first morning void is recommended. Urine samples to be collected and frozen for potential future analysis.

Appendix 12 Coagulation Indices

At Screening, EOS/ETD, and as clinically indicated, citrated plasma samples will 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:

Test Name	
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 Schedule Of Events For Subjects Who Discontinue Study Drug Early but Agree to Return For Assessments After the ETD Visit

	Assessment or Procedure	Monthly Day 1 (±5 days)[1]	Every 3 Months after Last Visit
Clinical	Prior/Concomitant Medications/Therapy	X	
	Adverse Event Assessment	X	
	Physical Exam[2]	X	
	Vital Signs[3]	X	
	ECOG PS/NYHA Class[4]	X	
	NIS-LL & VASPI[5]	X	
	SF-36v2[6]	X	
	KCCQ[7]	X	
	6MWT[8,9]	X (Months 3, 6, 9, 12)	
	Echocardiogram[10]	X (Month 12)	
	ECG (12-lead triplicate)[11]	X (Months 3, 6, 9, 12)	
Laboratory[16]	Hematology & Chemistry (including amylase and creatine kinase)[12]	X	
	Coagulation[13]	X	
	Inflammatory Biomarkers[14]	X (Month 3)[15]	
	Troponin T	X	
	NT-proBNP[8]	X	
	Pregnancy (WOCBP)	X[17]	
	Serum Free Light Chain	X (Months 3, 6, 9, 12)	
	Serum IFE & PEP	X (Months 3, 6, 9, 12)	
	Urinalysis – Dipstick[18]	X (Months 3, 6, 9, 12)	
	Urinalysis - Quantitative/Renal Biomarkers[19]	X (Months 3, 6, 9, 12)	
	24-hour Urine Collection:		
	Urine IFE & PEP	X (Months 3, 6, 9, 12)	
	Urine Protein Excretion	X (Months 3, 6, 9, 12)	
Other	Anti-NEOD001 Serum Sample	X[20]	
	Vital Status Phone Call		X[21]

BP = blood pressure; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; ETD = Early Treatment Discontinuation; HR = heart rate; IFE = immunofixation electrophoresis; KCCQ = Kansas City Cardiomyopathy Questionnaire; NIS-LL = neuropathy impairment score – lower limbs; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; PEP = protein electrophoresis; RR = respiratory rate; 6MWT = 6-minute walk test; SF-36v2 = Short Form-36v2® Health Survey; VASPI = visual analog scale – pain intensity; WOCBP = women of childbearing potential.

1. Study visits will occur every 28 days based on scheduling from Month 1-Day 1. A ±5-day window is allowed for visits starting after Month 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 per Table 1 and Section 6.2 and then have assessments performed monthly, through Month 12, if willing. The most important visit is the Month 12-Day 1 Visit, so if a subject is unwilling to continue monthly visits, every effort should be made for the subject to return and complete the Month 12-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. An EOS Visit will not be conducted.
2. Conduct a directed physical examination, including weight, and the components of the exam as clinically indicated. Assess macroglossia, submandibular nodes/fullness, adenopathy, ecchymoses, liver/spleen size (palpable +/-), ascites (+/-), and edema (which should be quantified on a scale of 0-4).
3. Vital signs include HR, RR, BP, and body temperature; assess any time during visit after subject has been at rest ≥5 minutes.
4. See Appendix 7 (ECOG) and Appendix 8 (NYHA).
5. See Appendix 5 (NIS-LL; for all subjects with peripheral neuropathy at Screening) and Appendix 6 (VASPI; for subjects with painful peripheral neuropathy at Screening).
6. See Appendix 9; SF-36v2 should be administered before performing any other study assessments on the same calendar day it is administered.
7. See Appendix 10; administer KCCQ after the SF-36v2, but before conducting any other assessments on the same calendar day it is administered.
8. NT-proBNP should be drawn before conducting 6MWT if being performed on the same calendar day.
9. Collect BP and HR pre- and post-6MWT administration.
10. Perform echocardiogram locally within 10 days before Day 1.
11. Perform ECGs centrally any time during visit.
12. Hematology and chemistry per Appendix 11.
13. Collect PT/INR and PTT monthly. Collect citrated plasma samples as clinically indicated 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. Inflammatory biomarkers per Appendix 11.
15. Collect additional samples as clinically indicated, such as when significant toxicity occurs per Section 5.4.2.
16. All laboratory tests to be done centrally, unless otherwise noted. Please refer to Laboratory Manual for details.
17. Obtain local laboratory serum pregnancy test 90 (±5) days after the last study drug administration.
18. Per Appendix 11.
19. Per Appendix 11. It is important that the sample be taken before exercising and at approximately the same time for each collection; therefore, the first morning void is recommended. Urine samples will be collected and frozen for potential analysis at a later date.
20. Anti-NEOD001 serum samples: Collect if an earlier sample established the presence of anti-NEOD001 antibodies or if a subject discontinued treatment due to a suspected immunologic reaction.
21. For randomized subjects who received at least 1 dose of study drug, conduct vital status telephone call approximately 3 months after last visit and approximately every 3 months thereafter or until subject enrolls in a separate open-label study, death, or for up to 5 years.