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Statistical Analysis Plan for Protocol NEOD001-201 (PRONTO)

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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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Term
6MWT	6-minute walk test
^{99m}Tc	Radioisotope of Technetium
A-SAA	acute phase serum amyloid A
AE	adverse event
AIC	Akaike's information criterion
AL	amyloid light chain
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AR (1)	first-order autoregressive
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
BP	Bodily Pain (SF-36v2)
BUN	blood urea nitrogen
C	Celsius
CI	confidence interval
cm	Centimeter
CMH	Cochran-Mantel-Haenszel
CR	complete response
CRF	case report form
CRP	C-reactive protein
CS	compound symmetry
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DOB	date of birth
DOIC	date of informed consent
dFLC	difference between involved and uninvolved free light chains
eCRF	electronic case report form
ECG	Electrocardiogram

Abbreviation	Term
ECOG	Eastern Cooperative Oncology Group
EEOS	Efficacy End of Study
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
g/24 hours	grams per day (24 hours)
g	Gram
GH	General Health (SF-36v2)
GGT	gamma-glutamyl transferase
HCS	heterogeneous compound symmetry
HR	heart rate
ICF	informed consent form
ICH	International Council for Harmonisation
ID	Identification
IFE	immunofixation electrophoresis
in	Inches
IRT	item response theory
IV	intravenous
IVSd	intraventricular septal thickness at diastole
ITT	Intent-to-Treat
IXRS	interactive voice and web response system
KCCQ	Kansas City Cardiomyopathy Questionnaire
kg	kilogram
KM	Kaplan-Meier
L	Liter
lb	Pounds
LDH	lactate dehydrogenase
LLN	lower limit of normal
LN	lymph node

Abbreviation	Term
LS	least-square
LVEF	left ventricular ejection fraction
LPWd	left ventricular posterior wall in end-diastole
LSLV	last subject last visit
LVSd	intraventricular septal at diastole
m	Meter
m^2	meters squared
mBMI	modified Body Mass Index
MCS	Mental Component Summary (SF-36v2)
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mg/dL	milligrams per deciliter
MH	Mental Health (SF-36v2)
min	Minimum
mL	Milliliters
mmHg	millimeters of mercury
MMRM	mixed-effect repeated measures model
MOP	manual of procedures
msec	Milliseconds
NCS	not clinically significant
ng	Nanogram
ng/L	nanograms per liter
NGAL	neutrophil gelatinase-associated lipocalin
NIS-LL	Neuropathy Impairment Score-Lower Limbs
NR	no response
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
PCS	Physical Component Summary (SF-36v2)
PE	physical examination
PEP	protein electrophoresis
PF	Physical Functioning (SF-36v2)
PFS	progression free survival

Abbreviation	Term
PK	Pharmacokinetic
PN	peripheral neuropathy
PR	partial response
PS	performance status
PT	preferred term
PT/INR	prothrombin time/international normalized ratio
PTT	partial thromboplastin time
QT	measure of time between start of Q wave and end of T wave
QTcB	QT formula corrected by Bazett's formula
QTcF	QT interval corrected by Fridericia's formula
RBC	red blood cells
RBP	retinol-binding protein
RE	Role-Emotional Limitations (SF-36v2)
REML	restricted maximum likelihood
RP	Role-Physical Limitations (SF-36v2)
RR	respiratory rate or time between 2 consecutive R waves
SAE	serious adverse event
SAP	statistical analysis plan
SC	Subcutaneous
SD	standard deviation
SF	Social Functioning (SF-36v2)
SEM	standard error of the mean
SF-36v2	Short Form -36 version 2 ® Health Survey
sFLC	serum free light chains
SI	standard international unit
SMC	Safety Monitoring Committee
SMQ	standardized MedDRA query
SOC	system organ class
StdErr	least squares standard error
TEAE	treatment-emergent adverse event
temp	Temperature
TNF	Tumor Necrosis Factor

Abbreviation	Term
U/L	units per liter
ULN	upper limit of normal
VASPI	Visual Analogue Scale – Pain Intensity
VGPR	very good partial response
vs	Versus
VT	Vitality (SF-36v2)
WBC	white blood cells
WHO	World Health Organization
WOCBP	women of childbearing potential

1. INTRODUCTION

This document outlines the statistical methods to be implemented during the analyses of Study NEOD001-201 (PRONTO) data collected within the scope of the Prothena-sponsored protocol. The purpose of this plan is to provide specific guidelines from which the analyses will proceed. Any deviations from this statistical analysis plan will be documented in the clinical study report (CSR).

2. INFORMATION FROM THE STUDY PROTOCOL

2.1. Study 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.

Estimands for the primary and secondary endpoints are detailed in Section 8.7, Section 8.8, and Section 8.9.

2.2. Study Design

2.2.1. Overall Study Design

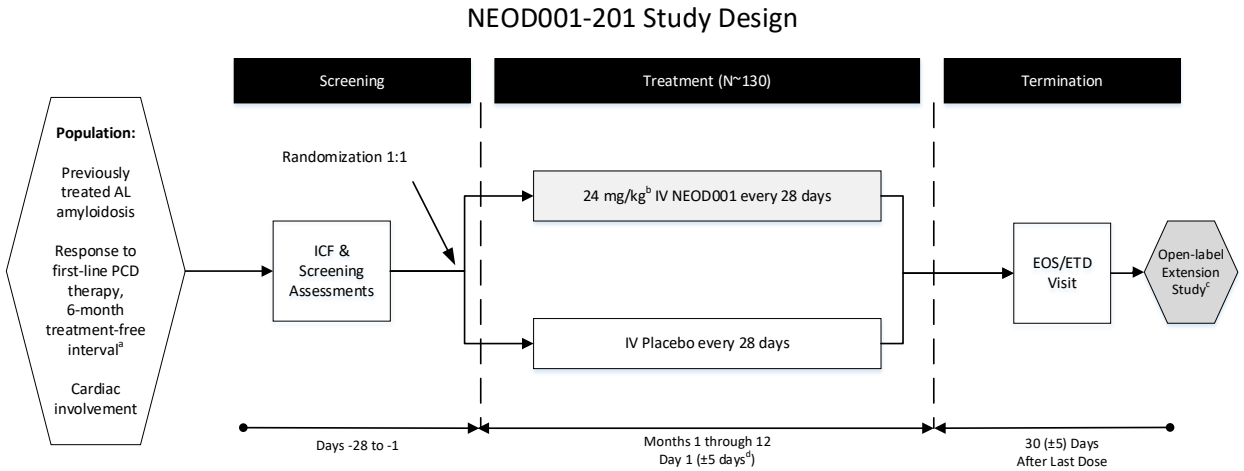
This is a global, multicenter, Phase 2b, randomized, double-blind, placebo-controlled, two-arm, parallel-group efficacy and safety study of NEOD001 as a single agent administered intravenously in adults with AL amyloidosis who had a hematologic response (Appendix 1) to previous treatment for their amyloidosis (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. If willing, subjects may continue in the study and have monthly assessments, through Month 12, per Appendix 12. 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.

2.2.2. Study Design Diagram

Figure 1: Study Design Schematic



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 Score; 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.

2.2.3. Study Population

The study population will include men and women with confirmed diagnosis of systemic AL amyloidosis, 18 years or older, who had a hematologic response to previous treatment for their amyloidosis (e.g., chemotherapy, ASCT) and have persistent cardiac dysfunction. Subjects must also provide written informed consent. Please refer to the protocol Sections 4.1 and 4.2 for a complete list of the subject selection criteria.

2.2.4. Study Drug

Study drug consists of NEOD001 or placebo. The NEOD001 dose is 24 mg/kg (not to exceed 2500 mg). Each vial of 500 mg of NEOD001 will be reconstituted with 9.6 mL sterile water for injection 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 from the IV bag 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 are assigned to the placebo group will be administered a 250 mL IV bag of 0.9% saline, which will look identical to the NEOD001 infusion bag. The volume contained in the administration tubing

should be completely flushed using approximately 30 mL of 0.9% Sodium Chloride Injection after administration of study drug.

Please refer to the protocol for complete product details.

2.2.5. Randomization Methodology

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 enrolled and randomized (1:1) to 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 ng/L vs ≥1800 ng/L

Upon successful randomization, the Unblinded Pharmacist or their designee will be provided with the treatment assignment. Numbers assigned to subjects who do not receive study drug will not be re-used.

2.2.6. Study Procedures

The schedule of assessments, as outlined in the study protocol, is presented in Table 1.

Table 1: Schedule of Study Procedures

		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 Assessments[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[32]

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 12. 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 5 (ECOG) and Appendix 6 (NYHA).
11. See Appendix 3 (NIS-LL; for all subjects with peripheral neuropathy at Screening) and Appendix 4 (VASPI; for subjects with painful peripheral neuropathy at Screening).
12. See Appendix 7; SF-36v2 should be administered before performing any other study assessments on the same calendar day it is administered.
13. See Appendix 8; 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 10.
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 11.
22. Inflammatory biomarkers per Appendix 10.
23. Collect additional samples as clinically indicated, such as when significant toxicity occurs per protocol 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 10.
28. Per Appendix 10. 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.

2.2.7. Definition of Baseline

The baseline for the 6MWT distance (meters) will be defined as the longest distance walked prior to the first study drug infusion. Baseline for all other efficacy and safety parameters will be defined as the last non-missing assessment prior to the first study drug infusion.

2.2.8. Definition of Efficacy End of Study Visit

The End of Study (EOS) visit occurs 30 (±5) days after last administration of study drug. In order to assess efficacy at or through 12 months of treatment, the Efficacy End of Study (EEOS) visit is defined as the visit occuring 30 (±5) days after the Month 12 infusion. This may include the EOS visit or other unscheduled visits. The visit window algorithm for the EEOS visit is specified in Section 4.6.

For subjects completing all assessments at the EOS visit after 12 months of treatment the EEOS visit is the EOS visit. For subjects who do not complete 12 months of treatment or who are missing an assessment in the EEOS visit window, EEOS visit efficacy assessments will be imputed as specified in Section 8.2.

2.3. Study Endpoints

2.3.1. Primary Efficacy Endpoint

The primary efficacy endpoint is cardiac response as defined by N-terminal pro-brain natriuretic peptide (NT-proBNP) best response from baseline through 12 months of treatment. All visits after the first infusion of study drug will be included up to and through the EEOS visit.

NT-proBNP response categories are defined as modified from Table 2 in Comenzo, 2012 (Appendix 2):

Response	Stable	Progression
Decrease in NT-proBNP from baseline of >30% and >300 ng/L	Assessment was neither Response nor Progression	Increase in NT-proBNP from baseline of >30% and from baseline >300 ng/L

Best response is defined as the most favorable category (response, stable, or progression) across all visits. Subjects will be classified as responders or non-responders. Non-response is defined as either stable or progression.

2.3.2. Key Secondary Efficacy Endpoints

The key secondary endpoints, in order of priority are:

2.3.2.1. Change from Baseline to 12 Months of Treatment in the Physical Component Score of the SF-36v2

The SF-36v2 is a 36-item self-report instrument that measures generic health-related quality of life in eight specific dimensions plus one additional question that asks respondents to rate the amount of change experienced in their health in general (Maruish 2011; Appendix 7). It allows for the scoring of two component summary indices: the Physical Component Summary (PCS) score and the Mental Component Summary (MCS) score. The SF-36v2 is scored as eight subscales representing separate domains of functional health and well-being:

- Physical Functioning (PF: 10 questions, # 3a to 3j)
- Role-Physical (RP; role limitations due to physical problems: 4 questions, # 4a to 4d)
- Bodily Pain (BP: 2 questions, # 7 to 8)
- General Health Perceptions (GH: 5 questions, # 1, 11a to 11d)
- Vitality (VT: 4 questions,# 9a, 9e, 9g, and 9i)
- Social Functioning (SF: 2 questions, # 6 and 10)
- Role-Emotional (RE; role limitations due to emotional problems: 3 questions, # 5a to 5c)
- Mental Health (MH: 5 questions, # 9b to 9d, 9f, 9h)

Responses to items allow for direct calculation of subscales for each of the eight dimensions, while PCS and MCS scores are computed from weighted subscale scores (Maruish 2011). The lower the score the more disability, the higher the score the less disability. A score of 50 is the mean in the US General Population. The standard deviation is 10 for all scales and both summary measures. The SF-36v2 will be scored using the algorithm provided by Optum with the instrument license (Health Outcomes™ Scoring Software 4.5). Algorithms that allow for the evaluation of summary component scores in the presence of missing data have been developed using Item Response Theory (IRT) and regression methods. Scores for respondents with incomplete answers can be derived using the maximum data recovery approach for the missing data estimation for all scales except the PF scale. For the PF scale, an estimated score based on an IRT model is utilized as long as at least one of its items has valid data, otherwise the scale score will be missing. Both the PCS score and the MCS score can be calculated if (1) at least seven scale scores are available, (2) the PF scale is not missing when evaluating the PCS score, and (3) the MH scale is not missing when calculating the MCS score. The scoring algorithm to apply to the calculation of the summary scores depends upon which particular scale score is missing from the eight scale profile.

The key secondary endpoint will include data from PCS score only, including all visits in the model (Section 8.8.1), with the primary comparison at the EEOS visit to evaluate 12 months of treatment.

2.3.2.2. Change from Baseline to 12 Months of Treatment in the 6-Minute Walk Test (6MWT) Distance (meters)

Per guidelines published by the American Thoracic Society (ATS 2002), the 6MWT is a practical simple test that requires a minimum walking length of 25 meters (m) but no exercise

equipment or advanced training for technicians. The walking track or area should be the same for all tests for a subject. This test measures the distance that a subject can quickly walk on a flat, hard surface in a period of 6 minutes. The primary comparison will be at the EEOS visit to evaluate 12 months of treatment.

2.3.2.3. NT-proBNP Slope over 12 Months of Treatment

The cardiac biomarker NT-proBNP provides important prognostic information in patients with AL amyloidosis and it has been demonstrated that decreasing NT-proBNP levels predict lower mortality rates (Palladini 2010). All visits after the first infusion of study drug will be included up to and through the EEOS visit to evaluate 12 months of treatment.

2.3.3. Additional Secondary Efficacy Endpoints

2.3.3.1. Renal Evaluable Subjects: Renal Best Response from Baseline through 12 Months of Treatment

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 post-baseline assessment of proteinuria. All visits after the first infusion of study drug up and through the EEOS visit will be included to evaluate 12 months of treatment.

For these subjects, renal response categories (modified from Palladini 2014; Appendix 2) are defined as:

Response	Stable	Progression
≥ 30% decrease from baseline or < 0.5g/24 hours post-baseline result of proteinuria (measured by 24-hour urine total protein excretion) in the absence of renal progression	Assessment was neither Response nor Progression	≥ 25% decrease in eGFR from baseline Note: if assessment qualifies as both Response and Progression, then assessments will be counted as progression

Best response is defined as the most favorable category (response, stable, or progression) across all visits. Subjects will be classified as responders or non-responders. Non-response is defined as either stable or progression.

2.3.3.2. Peripheral Neuropathy Evaluable Subjects: Change from Baseline to 12 Months of Treatment in Neuropathy Impairment Score–Lower Limbs (NIS-LL) Total Score

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 at screening answered as yes) and had a baseline NIS-LL score of 2 or greater and at least one post-baseline peripheral neuropathy assessment. All visits will be included in the model (Section 8.9.2), with the primary comparison at the EEOS visit to evaluate 12 months of treatment.

NIS-LL is a scoring system graduated from 0 points to a maximum of 88 points (the absence of all motor, sensory, and reflex activity in the lower extremities) (Dyck 1995; Appendix 3). 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. The component scores will be calculated by summing the values of the following assessments:

- Sensory Function (in the great toe) = Sum of (touch pressure, pinprick, vibration, joint position)
- Reflexes = Sum of (knee, ankle)
- Muscle Strength = Sum of (hip flexion, hip extension, knee flexion, knee extension, ankle dorsiflexion, ankle plantar flexion, toe extension, toe flexion)
- Total score = Sum of (sensory function, reflexes, muscle strength)

2.3.3.3. Hepatic Evaluable Subjects: Hepatic Best Response from Baseline through 12 Months of Treatment

The Hepatic Evaluable Population will include subjects who had hepatic involvement defined as >1.5 × ULN alkaline phosphatase (ALP) at baseline and at least one post-baseline assessment of ALP. All visits after the first infusion up to and through the EEOS visit will be included to evaluate 12 months of treatment.

For these subjects, hepatic response categories are modified from Table 2 in Comenzo, 2012 (Appendix 2), where response categories are defined as:

Response	Stable	Progression
≥ 50% decrease in alkaline phosphatase from baseline	Assessment was neither Response nor Progression	≥ 50% increase in alkaline phosphatase from baseline

Best response is defined as the most favorable category (response, stable, or progression) across all visits. Subjects will be classified as responders or non-responders. Non-response is defined as either stable or progression.

2.3.4. Exploratory Efficacy Endpoints

The following exploratory efficacy endpoints will evaluate NEOD001 compared to placebo:

2.3.4.1. Cardiac Endpoints

2.3.4.1.1. Cardiac Biomarkers (NT-proBNP and Troponin T)

- Cardiac response (Appendix 2), as assessed by NT-proBNP response criteria, at each visit
- Cardiac best response (Section 2.3.1), 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

2.3.4.1.2. Select Echocardiogram Cardiac Parameters

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

2.3.4.2. Functional Endpoint

2.3.4.2.1. 6MWT Distance

- Change and percent change from baseline to each visit in the 6MWT distance (meters) (except the key secondary endpoint)
- Categorical analysis of change from baseline to each visit in the 6MWT distance (meters)

2.3.4.3. Quality of Life Endpoints

2.3.4.3.1. SF-36v2

- Change and percent change from baseline to each visit in SF-36v2 PCS score (except the key secondary endpoint), MCS score, and the eight subscales

2.3.4.3.2. KCCQ

The KCCQ is a self-administered, 15-item questionnaire to assess physical limitation, symptom stability, symptom frequency, symptom burden, total symptom score, self-efficacy, quality of life, social limitation, overall summary score, and clinical summary score (Appendix 8). Scores are transformed to a range of 0-100, in which higher scores reflect better health status. The change and percent change from baseline to each visit in the KCCQ subscores and overall summary score will be evaluated.

2.3.4.4. Renal Endpoints

The following endpoints will be evaluated in the Renal Evaluable Population, unless otherwise specified.

2.3.4.4.1. Renal Response

- Renal response (Appendix 2) at each visit
- Renal best response through 3, 6, and 9 months of treatment

2.3.4.4.2. Renal Biomarkers

- 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]) in the Renal Evaluable Population and ITT Population

2.3.4.4.3. Creatinine, Proteinuria, and Estimated Glomerular Filtration Rate (eGFR)

- Change and percent change from baseline to each visit in creatinine, proteinuria, and eGFR in the Renal Evaluable Population and ITT Population
- Shifts from baseline in Chronic Kidney Stage in the Renal Evaluable Population and ITT Population

2.3.4.5. Peripheral Neuropathy Endpoints

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

2.3.4.5.1. NIS-LL Total Score

- Change and percent change from baseline to each visit in the NIS-LL total score (except the additional secondary endpoint)
- Peripheral neuropathy response (Appendix 2) at each visit

2.3.4.5.2. NIS-LL Component Scores

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

2.3.4.5.3. Visual Analog Scale – Pain Intensity (VASPI)

- The VASPI assesses a subject's level of pain related to peripheral neuropathy on a scale from 0 – 100 mm, where 0 is no pain and 100 is the worst imaginable pain (Appendix 4). For peripheral neuropathy evaluable subjects with painful neuropathy, defined as a baseline VASPI score > 0, change and percent change from baseline in the VASPI score to each visit

2.3.4.6. Hepatic Endpoints

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

- Hepatic response (Appendix 2) 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

2.3.4.7. Additional Time-to-Event Endpoints

- Time to All-Cause Mortality (Overall Survival): Any after the first infusion of study drug (i.e. study day 1) through the study's last subject last visit (LSLV). Time (months) to event will be calculated as: (date of death - the date of first study drug infusion + 1) / 30.4375. Subjects will be censored at their last assessment known to be alive prior to LSLV.
- Progression free survival: Time (days) to event will be calculated as the earliest of event dates (cardiac disease progression or death) minus the date of first infusion of study drug plus 1.

- Duration of Cardiac Response: Time (days) to event will be calculated as the earliest date of disease progression subsequent to the first response minus the date of first response plus 1. Subjects never achieving response are excluded.
- Time to derived organ progression for each organ (cardiac, renal) separately
- Time to cardiac or renal progression
- Time to first organ response for each organ (cardiac, renal) separately
- Time to cardiac or renal response

2.3.4.8. Other Efficacy Endpoints

2.3.4.8.1. Cardiac Hospitalizations

- Frequency of cardiac hospitalizations over the course of the study

2.3.4.8.2. ECOG Performance Status, NYHA Class, Renal Stage

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

2.3.4.8.3. Selected Hematological and Urine Analyte Endpoints

- 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

2.3.4.8.4. Disease-Related Symptoms

Disease-related symptoms include macroglossia, submandibular nodes/fullness, adenopathy, ecchymoses, edema, ascites, and liver/spleen size. Table 2 defines each symptom's scoring.

Table 2: Disease-Related Symptoms Scoring

Symptom	Score	Definition
Macroglossia	0	Absent
	1	Patient reports that tongue is enlarged and it appears mild to the observer. Patient is able to close mouth and swallow without difficulty.
	2	Patient reports difficulty in swallowing but is able to close mouth fully.
	3	Patient is unable to close mouth fully but able to swallow.
	4	Patient has significant difficulties in swallowing fluid or food.
Submandibular nodes/fullness	0	Absent
	1	Fullness but no discrete adenopathy identified by observer
	2	Discrete adenopathy, largest lymph node (LN) ≤ 2 cm

Symptom	Score	Definition
	3	Discrete adenopathy, largest LN >2 cm but ≤ 4 cm
	4	Discrete adenopathy, largest LN >4 cm
Adenopathy	0	Absent
	1	Discrete adenopathy in ≤ 2 LN stations identified by observer
	2	Discrete adenopathy in > 2 LN stations, largest LN ≤ 2 cm
	3	Discrete adenopathy in > 2 LN stations, largest LN >2 cm but ≤ 4 cm
	4	Discrete adenopathy in > 2 LN stations, largest LN >4 cm
Ecchymoses	0	Absent
	1	Discrete ecchymosis in ≤ 2 locations identified by observer
	2	Discrete ecchymosis in > 2 but < 10 locations, largest ecchymosis ≤ 5 cm
	3	Discrete ecchymosis in > 2 but < 10 locations, largest ecchymosis > 5 cm
	4	Discrete ecchymosis in > 10 locations
Edema	0	No edema
	1	Slight pitting, normal contour
	2	Moderate deeper pitting, contour preserved
	3	Deeper pitting, contour preserved
	4	Deep persistent pitting, contour not preserved, and appears puffy
Ascites	0	Positive
	1	Negative
Liver/spleen size palpable	0	Positive
	1	Negative

Disease-related symptoms at each visit will be evaluated including any changes from baseline.

2.3.4.8.5. Pharmacokinetics (PK)

Data on serum NEOD001 concentrations from this study will be pooled with data from similar samples from other studies in a population PK analysis. Population PK analyses will be reported separately from the NEOD001-201 CSR.

2.3.5. 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. 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 Cochran-Mantel-Haenszel (CMH) test. Based on the actual enrolled sample size (N~130), the final power is 91%.

4. GENERAL STATISTICAL METHODS

4.1. Reporting Conventions

Individual subject data obtained from electronic case report forms (eCRFs), central laboratories, external sources, and any derived data will be presented in data listings by subject. The primary data source will be used for all analyses. All data listings that contain an evaluation date will contain a relative study day. Pre-treatment and on-treatment study days are numbered relative to the day of the first dose of study drug which is designated as Day 1. The preceding day is Day -1, the day before that is Day -2, etc.

All output will be incorporated into Microsoft Word rich text format (.rtf) files, sorted and labeled according to the ICH recommendations, and formatted to the appropriate page size(s).

For categorical variables, summary tabulations of the number and percentage of subjects within each category (with a category for missing data) of the parameter will be presented. Percentage calculations will be based on non-missing data, unless otherwise specified. Percentages are rounded to 1 decimal place, unless otherwise specified.

For frequency counts of categorical variables, categories whose counts are zero will be displayed for the sake of completeness. For example, if none of the subjects discontinue due to "lost to follow-up," this reason will be included in the table with a count of 0. Percentages based on frequency counts will be presented to one decimal place, and values less than 1% will be presented as "<1%." Values less than 100% but greater than 99% will be presented as ">99%."

For continuous variables, the number of subjects, mean, standard deviation (SD), median, 25th (Q1) and 75th (Q3) quartiles, minimum, and maximum values will be presented. The precision of summary statistics, unless otherwise, specified will be as follows: mean and median to 1 more decimal place than the raw data, and SD to 2 decimal places more than the raw data. In general, the number of decimal places should not exceed 3 decimal places unless appropriate. Confidence intervals (CIs) will be provided and will be rounded to 1 decimal place, unless otherwise specified, in the table and listing shell.

For tables where rounding is required, rounding will be done to the nearest round-off unit. For example, when rounding to the nearest integer, values ≥XX.5 will be rounded up to XX+1 (e.g., 97.5 will round up to 98), while values <XX.5 will be rounded down to XX (e.g., 97.4 will round down to 97).

Time-to-event data will be summarized using Kaplan-Meier (KM) methodology using 25th, 50th (median), and 75th percentiles with associated 2-sided 95% CIs (where estimable), as well as percentage of censored observations.

All statistical tests comparing groups will be conducted at the 2-sided, 0.05 level of significance, unless otherwise specified. Summary statistics for each treatment group will be presented, as well as two-sided 95% CIs comparing groups will be provided.

4.2. Computing Environment

All descriptive statistical analyses will be performed using SAS software Version 9.4 or higher, unless otherwise noted. Medical history and AEs will be coded using Medical Dictionary for

Regulatory Activities (MedDRA) version 19.0. Concomitant medications will be coded using World Health Organization (WHO) Drug Dictionary, B2 Enhanced December 2015.

4.3. Partial Dates and Unknown Times

If only a partial date is available and is required for calculation, the following standards will be applied:

- Birth Date
    - For missing day only – Day will be imputed as the middle of the month (i.e., 15).
    - For missing day and month – Day and month will be imputed as the middle of the year (i.e., 15 June).
- Death Date
    - The last date that each subject was known to be alive will be identified as the greatest date associated with the subject's completed assessments, including telephone contacts at which the subject was confirmed to be alive.
    - For missing day only – Day will be imputed as the first day of the month (i.e., 1) with the following exception: if the partial date falls in the same month as the last known alive date, then the partial date will be imputed to equal the last known alive date.
    - For missing day and month – Day and month will be imputed as the first day of the year (i.e., 1 January) with the following exception: if the partial date falls in the same year as the last known alive date, then the partial date will be imputed to equal the last known alive date.
- Diagnosis Date
    - For missing day only – Day will be imputed as the first day of the month (i.e., 1).
    - For missing day and month – Day and month will be imputed as the first day of the year (i.e., 1 January).
- Start Dates (e.g., event date, adverse event [AE] onset date, or start date of medication)
    - For missing start day only – Day will be imputed as the first day of the month (i.e., 1) with the following exception: if the partial date falls in the same month and year as the date being used in the calculation (e.g., first infusion date, informed consent date), then the partial date will be imputed to equal the date being used for the calculation.
    - For missing start day and month – Day and month will be imputed as the first day of the year (i.e., 1 January) with the following exception: if the partial date falls in the same year as the date being used in the calculation (e.g., first infusion date, informed consent date), then the partial date will be imputed to equal the date being used for the calculation.
    - Imputed start dates must be prior to the stop date.
- Stop Dates (e.g., AE resolution date or stop date of medication)

- For missing stop day only – Day will be imputed as the last day of the month (i.e., 28, 29, 30, or 31).
- For missing stop day and month – Day and month will be imputed as the last day of the year (i.e., 31 December).
- Imputed stop dates must be on or after the start date.

If a time required for calculation related to exposure is missing, the following standards will be applied:

- If start time is missing for an infusion where the volume recorded on the eCRF is greater than 0 mL then start time will be imputed as the pre-dose time of vital signs at the same visit + 1 minute. This should only be done for the first dose time within a given visit should there be more than one record.
- If stop time is missing for an infusion where the volume is greater than 0 mL then stop time will be imputed as the 'immediately after infusion' time of the vital signs at the same visit - 1 minute. This will only be done for the last dose time within a given visit should there be more than one record.
- If vital sign assessment times are not available, infusion start date/time is missing, and infusion stop date/time is non-missing then the start date/time will be imputed as stop date/time - 2 hours at the Month 1 Day 1 visit or as the stop date/time - 1 hour for all other visits

If vital sign assessment times are not available, infusion stop date/time is missing, and infusion start date/time is non-missing then the stop date/time will be imputed as start date/time + 2 hours at the Month 1 Day 1 visit or as the start date/time + 1 hour for all other visits. All data recorded on the case report form will be included in data listings that will accompany the CSR.

4.4. Data Conventions

The precision of original measurements will be maintained in summaries, when possible.

Quantitative laboratory tests containing less than (<) and greater than (>) symbols are test results that are below and above quantifiable limits, respectively. In order to retain these values for analysis purpose, the numeric portion of the result will be imputed and stored within the analysis datasets.

Variables (e.g., urine albumin/creatinine ratio) with a non-normal distribution that impacts the interpretation or validity of the planned analysis may have a data transformation applied (e.g., ln, $\log_{10}$).

4.5. Standard Calculations

Variables requiring calculation will be derived using the following formulas:

- Days – A duration expressed in days between one date (*date1*) and another later date (*date2*) will be calculated using the following formulas:

  duration in days = date2 – date1 + 1, where date1 ≥first infusion date

  duration in days = date2 – date1, where date1 <first infusion date

- Months – A duration expressed in months is calculated as the number of days divided by 30.4375
- Years – A duration expressed in years between one date (*date1*) and another date (*date2*) is calculated using the following formulas:

  duration in years = (date2 – date1 + 1)/365.25, where date1 ≥first infusion date

  duration in years = (date2 – date1)/365.25, where date1<first infusion date
- Age – Age is calculated as the number of years from the date of birth (*DOB*) to the specified date, e.g., date of informed consent (*DOIC*):

  age (years) = (DOIC –DOB + 1) / 365.25.
- Height – Height entries made in inches (in) are converted to centimeters (cm) using the following formula:

  height (cm) = height (in) × 2.54
- Weight – Weight entries made in pounds (lb) are converted to kilograms (kg) using the following formula:

  weight (kg) = weight (lb) / 2.205
- Temperature – Temperature entries in degrees Fahrenheit are converted to degrees Celsius using the following formula:

  temp (degrees Celsius) = 5 / 9 × (temp [degrees Fahrenheit] – 32)
- Body Mass Index (BMI) – BMI is calculated using height (cm) and weight (kg) using the following formula:

  BMI (kg/m^2) = weight (kg) / ([height (cm)/100]^2)
- Change from baseline – Change from baseline will be calculated as:

  Change = post baseline value – baseline value
- Percent change from baseline – Change from baseline will be calculated as:

  Percent change from baseline = ([post baseline value – baseline value] / baseline value) × 100

4.6. Visit Windows

Each visit will be denoted by its "month" and "day" such that the first dose day is denoted as Month 1-Day 1; subsequent months will use sequential numbers (e.g., the second dose is administered on Month 2-Day 1). Each infusion is scheduled to be every 28 days (±5 days) based on the first infusion date. For reporting purposes, the nominal visits will be used for the by-visit analyses. Details of the protocol defined visits and visit windows are given in the protocol and Table 1. In the event of unscheduled visits, re-test assessments, or ETD assessments, these will be reassigned to a scheduled visit for analysis purposes according to Table 3 and Table 4 below. If multiple visits occur within a single visit window, after reassignment of unscheduled visits and ETD visits, then the visit closest to the target day of the visit window will be used in the analysis.

If there is a tie, the later visit will be used in the analysis. Unscheduled assessments that do not collect time will not be mapped to any scheduled visit/timepoint.

Table 3 defines the visit windows for assessments taken at 1-month intervals to be established with respect to relative day from the start of study drug.

Table 3: 1-Month Interval Visit Windows (Days)

Months	Target Study Day [a]	Analysis Window Study Day [a]	
		Low	High
Baseline[b]	1	Closest visit to Day 1, prior to first NEOD001 dose	
Month 2	28	14	42
Month 3	56	43	70
Month 4	84	71	98
Month 5	112	99	126
Month 6	140	127	154
Month 7	168	155	182
Month 8	196	183	210
Month 9	224	211	238
Month 10	252	239	266
Month 11	280	267	294
Month 12	308	295	319 [EEOS Low – 1]
EEOS[c]	338	320 [Month 12 Low + 30 – 5]	354 [Month 12 High + 30 + 5]

[a] Study day will be calculated from first dose date.

[b] Baseline is defined in Section 2.2.7.

[c] EEOS is defined in Section 2.2.8.

Table 4 defines the visit windows for assessments taken at 3-month intervals to be established with respect to relative day from the start of study drug.

Table 4: 3-Month Interval Visit Windows (Days)

Months	Target Study Day [a]	Analysis Window Study Day [a]	
		Low	High
Baseline[b]	1	Closest visit to Day 1, prior to first NEOD001 dose [b]	
Month 3	56	14	98
Month 6	140	99	182
Month 9	224	183	266
Month 12	308	267	319 [EEOS Low – 1]
EEOS[c]	338	320 [Same definition as table 3]	354 [Same definition as table 3]

[a] Study day will be calculated from first dose date.

[b] Baseline is defined in Section 2.2.7.

[c] EEOS is defined in Section 2.2.8.

In data listings, the relative study day from first infusion of all dates will be presented.

5. ANALYSIS POPULATIONS

The following subject populations will be evaluated and used for presentation and analysis of the data:

- 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 Efficacy Evaluable (EE) Population will include all subjects in the ITT Population who do not have any important protocol deviations (as defined prior to database lock and unblinding) and have at least one post baseline efficacy outcome measure of SF-36v2 PCS score or 6MWT distance.
- The Safety Population will include all subjects who received 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 treatment received.

6. EXAMINATION OF SUBGROUPS

Subgroups will be defined based on baseline values, unless otherwise specified, and only if there are a sufficient number of subjects in each category of the subgroup (e.g., >5 subjects per treatment group).

General baseline subgroups of interest are as follows:

- Age categories: <65 vs ≥65 years
- Sex: Male vs Female
- Race: White vs All Other Races (Black or African American, Asian, Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native)
- Geographic Region: North America vs Europe/Rest of World
- Derived Qualifying Screening NT-proBNP (from central lab): <1800 ng/L vs ≥1800 ng/L

Special baseline population subgroups of interest are as follows:

- Age categories: <75 vs ≥75 years
- Baseline Renal Function: eGFR < 30 mL/min.1.73m^2 vs ≥ 30 to < 60 mL/min.1.73m^2 vs ≥ 60 mL/min.1.73m^2

Efficacy baseline subgroups of interest are as follows:

- IWRS randomization stratification factor for NT-proBNP: <1800 ng/L vs ≥1800 ng/L
- IWRS randomization stratification factor for hematological response to first line therapy: CR/VGPR vs PR
- Derived hematological response to first line therapy as reported on the eCRF: CR/VGPR vs PR
- NYHA Class (Appendix 6): I vs II vs III/IV
- Number of prior regimens for amyloidosis: 1, 2, ≥3

The primary and key secondary efficacy endpoints will be analyzed for the general and efficacy baseline subject subgroups using the ITT population including the interaction between treatment group and the subgroup. In addition, select safety analyses will also be analyzed for the baseline special population subgroups using the Safety population as specified in Section 9. Subgroup characteristics will be summarized by treatment group. During the CSR preparation, additional subgroup analyses may be performed. Those analyses will be considered as ad-hoc analyses and will be presented and discussed in the CSR.

7. STUDY POPULATION

7.1. Subject Disposition

Subject disposition will be tabulated and will include the number of subjects screened, the number screened but not randomized with reasons for screen failure, the number randomized, the number randomized and not treated, the number in each subject population for analysis, the number who withdraw from study prior to completing the study and reason(s) for withdrawal, and the number who discontinued treatment early and reason(s) for discontinuation of treatment.

Time on study in months will be calculated as (last known date of contact minus date of randomization plus one)/30.4375. Time on study drug in months will be calculated as (last infusion date minus first infusion date plus one)/30.4375. KM estimates of the distribution of the time-to-study discontinuation and time-to-treatment discontinuation will be tabulated and graphed by treatment group. The tabulation will include the KM estimate of the medians, 25th and 75th percentiles, and corresponding 95% CIs, if estimable. The tabular and graphical summaries will include the at-risk counts for every visit. In addition, the number and percentage of subjects who complete scheduled visits will be presented. Scheduled visit names will be footnoted to clarify that nominal visits are spaced every 28 days based on study drug infusion occuring every 4 weeks.

The number and percentage of subjects randomized by geographical region and site will be presented by treatment group and overall for the ITT population. The same summary will be presented by calendar year and month.

A summary table will be produced of the IWRS stratification factors and the combined stratum groups:

- Hematologic response; CR/VGPR vs PR to first-line therapy
- Screening NT-proBNP <1800 ng/L vs ≥1800 ng/L
- Stratum Group 1: CR/VGPR, <1800 ng/L
- Stratum Group 2: CR/VGPR, ≥1800 ng/L
- Stratum Group 3: PR, <1800 ng/L
- Stratum Group 4: PR, ≥1800 ng/L

In addition, in case the site accidentally stratified a subject using the wrong stratification value, the derived stratification value reported in the eCRF or central lab data versus the one the site entered in the IWRS during randomization process will be presented separately.

By-subject data listings of all the above study disposition data including study completion and any reasons for premature treatment and/or study withdrawal will be presented. Also by-subject listings of informed consent and eligibility critieria details will be presented.

7.2. Demographics and Baseline Characteristics

Demographic variables will include the following:

- Age at informed consent including the subgroups defined in Section 6.

- Sex
- Race
- Ethnicity

Other baseline characteristics will include the following:

- Weight (kg)
- Height (cm)
- BMI (kg/m^2) including frequency of the following subgroups:
  - $<20, \geq 20 - <25, \geq 25 - <30, \geq 30$ kg/m^2

Both conventional BMI and modified BMI (mBMI [kg/m2 g/L], defined as subject's weight [kg] ÷ subjects squared height [meters] × serum albumin [g/L]) will be presented. Frequencies of categorizations for the above characteristics as defined in Section 6 will also be summarized.

Demographics and baseline characteristics will be presented by treatment group and overall for ITT and Safety populations.

No inferential statistical comparisons will be performed.

All demographic and baseline characteristics data will be presented in by-subject data listings.

7.3. Baseline AL Amyloidosis Disease Characteristics

Baseline disease characteristics will be presented by treatment group and all subjects for the ITT and Safety populations and the efficacy subsets as described in Section 8.5. No inferential statistical comparisons will be performed.

Baseline disease characteristics will be presented in by-subject data listings.

The following disease histories will be summarized:

- Age at AL amyloidosis diagnosis
- Duration (months) since AL amyloidosis diagnosis
- Increase in light chains identified prior to bone marrow biopsy (yes/no)
- Number of prior regimens for amyloidosis
- Duration (days) since last reported therapy for amyloidosis
- Response to last reported therapy for amyloidosis (CR, VGPR, PR, NR)
- Best response to previously reported therapy (CR, VGPR, PR, NR)
- Duration (days) since best response to previously reported therapy for amyloidosis
- Number of derived involved organs (1, 2, 3, or 4 organs: cardiac, renal, peripheral neuropathy, and hepatic) as defined in Section 8.5
- Number of physician assessed involved organs: The Investigator also assessed other organ involvement including gastrointestinal, autonomic nervous system, lung, soft tissue/lymphatic, or other. (1, 2, 3, 4, or 5 organs)

- Total number of involved organs (derived plus physician assessed)
- Screening and Baseline NT-proBNP (ng/L)
- Renal Stage (Appendix 9): I, II, III; I/II, III; I, II/III
- Chronic Kidney Stage: 1, 2, 3, 4, 5
- NYHA Class (Appendix 6): I, II, III, IV; I/II vs III/IV
- Baseline FLC Ratio: Low (<0.26), Normal (0.26 – 1.65), High (>1.65)

Historical NT-proBNP or BNP (if NT-proBNP is not available) will be listed including the date of assessment, number of days from first dose of study drug since the historical result, result, and result unit will be included in a by-subject data listing. Data collected for tissue typing will be presented in a listing.

7.4. Disease History Specific AL Symptoms

Disease history specific AL symptoms verbatim terms as recorded on the Disease History eCRF will be mapped to preferred terms (PT) and system organ classes (SOC) using MedDRA version 19.0. AL symptoms will be summarized by SOC, PT, and treatment group using the Safety Population. Summaries will be ordered by descending order of total incidence of SOC and PT within each SOC.

Disease history specific AL symptoms will be presented in a by-subject data listing.

7.5. General Medical History

Verbatim terms on eCRFs will be mapped to preferred terms and system organ classes using MedDRA version 19.0.

Medical history will be summarized by SOC, PT, and treatment group using the Safety Population. Summaries will be ordered by descending order of total incidence of SOC and PT within each SOC.

General medical history will be presented in a by-subject data listing.

7.6. Protocol Deviations

The Investigator is not permitted to deviate from the protocol in any significant way without prior notification to the Sponsor (or designee) as described in the protocol.

All protocol deviations will be collected by the clinical research associates.

Important protocol deviations that could potentially affect the efficacy or safety conclusions of the study will be identified prior to database lock and unblinding of individual subject treatment information. Important protocol deviations will be summarized by deviation category and treatment group using the ITT Population.

All protocol deviations and separately only important protocol deviations will be summarized by deviation category and presented in a by-subject data listing.

7.7. Pretreatment, Prior, and New Concomitant Medications

Verbatim terms on the Concomitant Medicaion eCRF will be mapped to Anatomical Therapeutic Chemical (ATC) class and Preferred Name using the WHO Drug Dictionary, B2 Enhanced December 2015.

Pretreatment medications are those medications with start and stop prior to the first infusion of study drug. Prior concomitant medications are those medications started prior and continued after the first infusion of study drug. New concomitant medications are those medications that were started on or after the first infusion of study drug. If it cannot be determined whether the medication was a new concomitant medication due to a partial start or stop date or if the medication is taken on the same date as the first infusion of study drug, then it will be counted as a new concomitant medication.

Due to the limited number of infusion-related reactions (IRRs) reported to date, premedication was not required, unless the Investigator observed an IRR with a prior infusion of study drug in an individual subject or if premedication is required by the Investigator's institution for the administration of monoclonal antibodies. By definition, premedications administered prior to each infusion are new concomitant medications. Summaries of premedications are detailed in Section 9.1.1.

Pretreatment medications will only be listed. Prior and new concomitant medications will be summarized for each treatment group by WHO ATC level 3, WHO ATC level 4, and preferred name using the Safety Population. Prior and new concomitant medications will also be summarized separately. These summaries will present the number and percentage of subjects using each medication. Subjects may have more than one medication per ATC level and preferred name. At each level of subject summarization, a subject is counted once if he/she reported one or more medications at that level. Each summary will be ordered by descending order of NEOD001 incidence of ATC level and preferred name within each ATC level.

8. EFFICACY ANALYSES

All efficacy analyses will use the ITT Population, except where noted for the Efficacy Subset Populations (Section 8.5). If the total ITT and EE Population differ by more than 10 subjects, efficacy analyses will be repeated for the EE Population for relevant primary, key secondary, other secondary efficacy endpoint analyses, and select exploratory efficacy endpoints. All efficacy endpoints, recorded and derived, will be presented in by-subject data listings. The analyses of primary and key secondary endpoints will be repeated for the general and efficacy baseline subject subgroups as specified in Section 6.

8.1. Adjustments for Covariates

For comparison of treatment groups with respect to change and percent change from baseline, restricted maximum likelihood (REML) based mixed-effect model for repeated measures (MMRM) and analysis of covariance (ANCOVA) models will be used. The corresponding baseline value will be used as a covariate in the model.

8.2. Handling of Dropouts or Missing Data

At any point in the study, if a subject is unwilling to continue monthly visits, every effort will be made for the subject to return to the clinic and complete the Month 12-Day 1 Visit on schedule. 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 12 . For randomized subjects who received any amount of study drug, vital status telephone calls will be conducted 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.

For the SF-36v2, missing data conventions for partially completed questionnaires are specified in Section 2.3.4.3.1.

The following methods will be implemented to address missing data for relevant primary, key secondary, other secondary efficacy endpoint analyses, and select exploratory efficacy endpoints.

8.2.1. Time to Event Endpoints

Censoring rules are defined in the applicable study endpoint section (Section 8.10.7). Subjects with no data after randomization will be censored on Day 1 (first day of study drug dosing). As a sensitivity analysis, subjects with no data after randomization will be considered to have an event on Day 1 (first day of study drug dosing). These sensitivity analyses will only be performed for analyses where death or progression are events and only in cases where at least one subject is missing the relevant post-randomization data. Methods for handling missing data for time to event endpoints are included in the applicable study endpoint section because the censoring and event dates are specific to the events being analyzed.

8.2.2. Responder Endpoints

The primary analysis for best response analyses will consider a subject as a non-responder until a response is achieved.

For other categorical efficacy endpoints in which subjects are classified as either a responder or a non-responder (binary outcome) based on dichotomizing a continuous variable at each visit, analyses will use "observed cases," where subjects who do not provide an assessment at the specified time point for the defining of response will not be included. That is, for the percentage of responders, the subject will not be included in the numerator or the denominator. To assess the effect of missing data as a sensitivity analyses, any subject who does not provide an assessment at the specified time point for the response definition will be considered as a non-responder, regardless of treatment group. For analyses using a 3-category response (response, stable, progression), any subject who does not provide an assessment at the specified time point for the defining of response will be considered to have progressed, regardless of treatment group.

8.2.3. Parametric Analyses

8.2.3.1. Missing Not at Random (MNAR): Imputation for Deaths

For the primary analysis of the SF-36v2 PCS score and NIS-LL total score, subjects who missed the EEOS visit due to death will be imputed as the worst EEOS value in the total population. Sensitivity analyses will be conducted imputing subjects who missed the EEOS visit due to death as: Zero, i.e. no quality of life (SF-36); or 88 for NIS-LL, i.e. no neurological function.

Exploratory analyses at other visits (i.e. not the EEOS visit) will use the same imputation methodology for time points at which no value is observed.

8.2.3.2. Missing at Random (MAR): Multiple Imputation

For the primary analysis of the SF-36v2 PCS score and NIS-LL total score, subjects who missed the EEOS visit for reasons other than death will be imputed using multiple imputation (MI) methodology using the total study sample. MI will be performed under the assumption of MAR. Intermittent missing value(s) will also be replaced using MI. MI will impute 10 integer values using Markov Chain Monte Carlo (MCMC) methods assuming nonmonotone missing, a seed of 100201, 500 burn-in iterations, 100 iterations between imputations, and a non-informative prior. The imputation models based on all subjects (regardless of treatment group) will include randomization stratification factors, and baseline value of the endpoint and all previous values of the endpoint at each time point. Other baseline characteristics that may be explored will be documented in the CSR. Change from baseline to each post-baseline visit will be calculated based on observed and imputed data. Data will be analyzed using the primary REML based MMRM model. Results from the analysis of each of the 10 imputed datasets will be combined using Rubin's imputation rules (Rubin 1987) to produce a pooled least squares mean (LSM) estimate of treatment difference.

8.2.3.3. MNAR: Multiple Imputation Placebo-Based

A placebo-based multiple imputation will be performed using a pattern mixture model under the assumption of MNAR for the following sensitivity analyses of the SF-36v2 PCS score and NIS-LL total score:

1) As a sensitivity analysis for those subjects who missed the EEOS visit for reasons other than death.
2) As a sensitivity analyses for all subjects who missed the EEOS visit, regardless of reason.

For these analyses, the imputation model will be estimated using placebo subjects only. The imputation models will include randomization stratification factors, and baseline value of the endpoint and all previous values of the endpoint at each time point. See Ratitch and O'Kelly (2011) for additional details regarding the methodology used to obtain the placebo-based imputation datasets. Similar methods as described for the previous multiple imputation method will be used to produce a pooled LSM estimate of treatment difference.

Additional pattern-mixture models may be explored should an unexpected pattern of reason for study or treatment discontinuation based on KM distributions or a high percentage (>20%) of missing data be observed for reasons other than reaching a primary endpoint.

Exploratory analyses at other visits (i.e. not EEOS) will use the same imputation methodology for time points at which no value is observed.

8.2.4. Non-Parametric Analyses

8.2.4.1. Ranking

For the primary analysis of 6MWT, subjects will be ranked as follows ordered from worst to best:

1. Subjects who died prior to EEOS where time to death is used to rank earlier deaths worse than later deaths,
2. Subjects who are missing EEOS and vital status is unknown at EEOS will be ranked according to time on study drug from worst (shortest time) to best (longest time)
3. Subjects who are missing EEOS because the subject physically cannot perform the test, due to physical incapacity or other reason will be ranked according to time on study drug from worst (shortest time) to best (longest time)
4. Subjects who are missing EEOS and are known to be alive will be ranked according to time on study drug from worst (shortest time) to best (longest time)
5. Completed subject's values will be ranked from worst (lowest distance) to best (highest distance) performance

Sensitivity analyses of the ranking will be performed by

a) Only including ranks 1 and 5 above, and for missing reasons besides death, duration on study will be used to rank with shorter duration worse than longer duration

b) Only including ranks 1, 3, and 5 above, and duration on study will be used to rank subjects who did not die and who are physically able to perform the test with shorter duration worse than longer duration

c) Imputing subjects who died and who are physically not able to perform the test as zero distance in meters first, then imputing ranks for missing data using ranks 2, 4, and 5 above

d) Imputing subjects who died or who are physically not able to perform the test (due to physical incapacity, hospitalization, or other reason) as zero distance in meters first, then imputing other missing values as the median of the observed placebo subjects at

the specified visit, then ranking all values from worst (lowest distance) to best (highest distance) performance.

The ranking paradigm with 5 levels and the ranking paradigms a and c above will also be used as sensitivity analyses for the SF-36v2 PCS score key secondary endpoint analyses.

8.2.5. Last Observation Carried Forward (LOCF)

As sensitivity analyses for changes from baseline in SF-36v2 PCS score, SF-36v2 MCS score, SF-36v2 subscales, and NIS-LL total and component scores, subjects who missed a scheduled visit will also have their missing visit values imputed using LOCF. For LOCF, each subject's last non-missing observation will be carried forward to the missing visit observation.

8.2.6. Complete Case Analysis

As sensitivity analyses for changes from baseline in SF-36v2 PCS score, SF-36v2 MCS score, SF-36v2 subscales, and NIS-LL total and component scores will be analyzed for subjects with a non-missing baseline and specified visit assessment (i.e., complete case analysis).

8.3. Interim Analyses and Data Monitoring

8.3.1. Interim Analysis

No interim analyses are planned for this study.

8.3.2. 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.

There are 4 planned data review meetings and they are as follows:

- After the 20th subject reaches Month 3-Day 1
- After the 60th subject reaches the Month 3-Day 1 visit
- After the last enrolled subject reaches Month 3-Day 1
- After the last enrolled subject reaches Month 9-Day 1

A non-scheduled meeting may be called at the discretion of the Chairperson or the request of the Sponsor. The purpose of these independent data review is to assess the totality of the safety data and provide recommendations to the Sponsor for continuation of dosing or protocol study modifications. Details are provided in the SMC Charter.

8.4. Multicenter Studies

The randomization is not stratified by site. Likewise, analyses of efficacy data will not be stratified by study site. The number and percentage of subjects randomized by geographical region and study site will be summarized by treatment group and for all subjects.

8.5. Use of an "Efficacy Subset" of Patients

The Renal Evaluable Population will include subjects who had renal involvement, i.e., proteinuria >0.5g/24 hours (measured by 24-hour urine total protein excretion), at baseline and at least one post-baseline 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 at screening answered as yes) and had a baseline Neuropathy Impairment Score–Lower Limbs (NIS-LL) total score of 2 or greater and at least one post-baseline 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 post-baseline assessment of alkaline phosphatase.

8.6. Multiple Comparisons/Multiplicity

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 using a gatekeeping procedure based on a closed fixed-sequence test, 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.

8.7. Primary Efficacy Analysis

The estimand for NT-proBNP (cardiac) best response is the difference in cardiac best response rate between treatment groups through 12 months of treatment in all randomized subjects with AL amyloidosis who received any amount of drug.

The primary efficacy analysis will test the following hypothesis:

- H_0: The percentage of NT-proBNP best responders through 12 months of treatment is equal between placebo and NEOD001.
- H_1: The percentage of NT-proBNP best responders through 12 months of treatment is different between placebo and NEOD001.

The primary efficacy analyses will compare placebo and NEOD001 on the distribution of NT-proBNP (cardiac) best response through 12 months of treatment, at alpha level of 0.05, using a CMH test stratified by the randomization stratification factors. All visits after the first infusion of study drug will be included up to and through the EEOS visit to evaluate 12 months of treatment. The number and percentage, with associated two-sided exact (Clopper-Pearson) 95% CIs, of subjects in each category of best response (response, nonresponse) will be presented by treatment group.

8.7.1. Additional Analyses of the Primary Endpoint

A logistic regression (proportional odds model) will be performed with best response as the dependent variable and factors for treatment group and randomization strata. Estimates of the odds ratio comparing NEOD001 to placebo and the 95% CI of the odds ratio will be presented. An odds ratio greater than 1 favors the NEOD001 treatment group.

Cardiac response as 3 categories (response, stable, and progression) will be analyzed in the same manner described above, except ordinal logistic regression will be used for the analysis of 3 category response.

Cardiac response will also be analyzed according to Comenzo 2012 (Appendix 2), where a decrease ≥ 2 NYHA class from baseline (must have baseline class of 3 or 4) is also considered a response. The same statistical methods described above will be used to evaluate treatment differences.

Cardiac progression will also be analyzed according to Comenzo 2012 (Appendix 2), where subject visits that meet renal progression (defined as an eGFR of < 30 mL/min/1.73 m^2) will be excluded. The same statistical methods described above will be used to evaluate treatment differences.

8.8. Key Secondary Efficacy Analyses

Key secondary efficacy endpoints are described in Section 2.3.2, multiplicity adjustments in Section 8.6, and missing data conventions in Section 8.2.

8.8.1. SF-36v2 PCS Score to 12 Months of Treatment

The estimand for the SF-36v2 PCS score is the mean difference in SF-36v2 PCS score change from baseline between treatment groups at EEOS in all randomized subjects with AL amyloidosis who received any amount of study drug.

The key secondary efficacy analysis will test the following hypotheses:

- H_0: The mean change from baseline in the SF-36v2 PCS score after 12 months of treatment is equal between placebo and NEOD001.

- H_1: The mean change from baseline in the SF-36v2 PCS score after 12 months of treatment is different between placebo and NEOD001.

For the primary analysis of the SF-36v2 PCS score, subjects who are missing EEOS due to death, will be imputed as the worst EEOS value in the total population. Subjects who are missing EEOS for reasons other than death, will be imputed using MI methodology using the total study sample. Sensitivity analyses to assess the effect of missing data are detailed in Section 8.2.

NEOD001 and placebo will be compared on change from baseline 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. If the computational algorithm fails to converge, the following structures will be executed: heterogeneous Toeplitz, Toeplitz, heterogeneous First-Order Autoregressive [AR(1)], AR(1), heterogeneous compound symmetry (HCS), and compound symmetry (CS). The covariance structure converging to the best fit, as determined by Akaike's information criterion (AIC), 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 EEOS visit to evaluate 12 months of treatment.

The assumption for a REML based MMRM model without missing data is that the data are normally distributed. In the presence of missing data, the REML based MMRM assumes the missing data are missing at random. The use of an unstructured covariance model assumes independence over the repeated measurements, where variances and covariances are estimated individually from the data.

A plot of the EEOS change from baseline values will be presented. If visual inspection of the data finds the normality assumption is violated, a non-parametric rank analysis of covariance model (ANCOVA) including fixed effects for randomization strata and treatment group, with the ranked baseline value included as a covariate will be used and the Hodges-Lehman estimate of the median treatment difference with associated 95% CI will be presented. A plot of the EEOS change from baseline ranks will be presented. If visual inspection of the ranks finds the normality assumption is violated, the change from baseline at EEOS in SF-36v2 PCS score will be analyzed using a van Elteren test with stratification by randomization strata.

Estimates of least-square (LS) means, standard errors (StdErr), and 95% CIs will be presented by treatment group. In addition, the LS mean difference comparisons between each NEOD001 and placebo, the StdErr of the difference, and 95% CI of the difference will be presented.

Descriptive statistics for SF-36v2 PCS scores, change from baseline, and percent change from baseline will be presented by visit for each treatment group. Mean SF-36v2 PCS scores with associated standard deviation error bars will be plotted by treatment group over time. LS mean change and percent change from baseline in SF-36v2 PCS score with associated StdErr bars will be plotted by treatment group over time. In addition, the cumulative distribution of change from baseline at the EEOS visit will be plotted.

8.8.2. 6MWT Distance to 12 Months of Treatment

The estimand for the 6MWT is the median difference in 6MWT distance change from baseline between treatment groups after 12 months of treatment in all randomized subjects with AL amyloidosis who received any amount of study drug.

The key secondary efficacy analysis will test the following hypotheses:

- H_0: The distribution of change from baseline in 6MWT distance (meters) after 12 months of treatment is equal between placebo and NEOD001.
- H_1: The distribution of change from baseline in 6MWT distance (meters) after 12 months of treatment is different between placebo and NEOD001.

For the primary analysis of 6MWT, subjects will be ranked as follows ordered from worst to best:

1. Subjects who died prior to EEOS where time to death is used to rank earlier deaths worse than later deaths
2. Subjects who are missing EEOS and vital status is unknown at EEOS where duration on study is used to rank shorter duration worse than longer duration will be ranked according to time on study drug from worst (shortest time) to best (longest time)
3. Subjects who are missing EEOS because the subject physically cannot perform the test, due to physical incapacity or other reason where duration on study is used to rank shorter duration worse than longer duration will be ranked according to time on study drug from worst (shortest time) to best (longest time)
4. Subjects who are missing EEOS and are known to be alive where duration on study is used to rank shorter duration worse than longer duration will be ranked according to time on study drug from worst (shortest time) to best (longest time)
5. Completed subject's values will be ranked from worst (lowest distance) to best (highest distance) performance

Sensitivity analyses to assess the effect of missing data are specified in Section 8.2.

Descriptive statistics for 6MWT distance, change from baseline, and percent change from baseline will be presented by visit for each treatment group. The change from baseline at EEOS in 6MWT distance (meters) will be analyzed using a rank ANCOVA model including fixed effects for randomization strata and treatment group, with the ranked baseline value included as a covariate. The Hodges-Lehman estimate of the median treatment difference with associated 95% CI will be presented.

The rank ANCOVA assumes the ranked data are normally distributed and homogenous variance. A plot of the EEOS change from baseline ranks and the baseline ranks will be presented. If visual inspection of the ranks finds the normality assumption is violated, the change from baseline at EEOS in 6MWT distance (meters) will be analyzed using a van Elteren test with stratification by randomization strata.

Only valid assessments 6MWT distance will be included in analysis. Reasons for results being invalid will be presented in a listing and will be finalized prior to database lock. Reasons for results being invalid may include:

- Incorrect course length
- Use of unapproved course
- Unapproved administrator of test
- A site staff member has stopped the stopwatch either inadvertently or incorrectly before the 6 minutes are complete and the subject is still able to walk

In addition, the cumulative distribution of change from baseline at EEOS will be plotted for each treatment group.

The percent change from baseline will be analyzed in the same manner.

In addition to the planned sensitivity analyses for handling of missing data (Section 8.2), subjects who have invalid tests recorded will be used (as if the test was completely correctly) instead of being considered as missing.

8.8.3. NT-proBNP Slope Through 12 Months of Treatment

The estimand for the NT-proBNP is the difference in slopes between treatment groups over 12 months of treatment in all randomized subjects with AL amyloidosis who received any amount of study drug.

The key secondary efficacy analysis will test the following hypotheses:

- H_0: The rate of change (i.e., slope) of NT-proBNP over 12 months of treatment is equal between placebo and NEOD001.
- H_1: The rate of change (i.e., slope) of NT-proBNP over 12 months of treatment is different between placebo and NEOD001.

The primary 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 model will fit a random intercept and slope for each subject and will include fixed effects for treatment group, time, randomization strata, and treatment group × time interaction. Time will be expressed in months as a continuous variable and will include all scheduled time points including baseline. An unstructured covariance structure will be used to model the within-subject errors. If the computational algorithm fails to converge, the following structures will be executed: heterogeneous Toeplitz, Toeplitz, heterogeneous First-Order Autoregressive [AR (1)], AR(1), heterogeneous compound symmetry (HCS), and compound symmetry (CS). The covariance structure converging to the best fit, as determined by Akaike's information criterion (AIC), will be used. The Kenward and Roger method will be used to calculate the denominator degrees of freedom for the test of fixed effects. 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.

Estimates of the slope will be presented by treatment group along with corresponding 95% CIs. The estimate of the difference between slopes (NEOD001-Placebo) and the 95% CI of the difference between slopes will also be presented. Appropriate contrasts for pairwise differences in coefficients at time points of interest between NEOD001 and placebo with corresponding 95% CIs will be estimated from the model and tested for significance.

8.9. Additional Secondary Efficacy Analysis

8.9.1. Renal Evaluable Subjects: Renal Best Response

The estimand for renal best response is the difference in renal best response rate between treatment groups through 12 months of treatment in all randomized subjects with AL amyloidosis and renal involvement (Section 8.5) who received any amount of drug.

The secondary efficacy analysis will test the following hypotheses:

- H_0: The percentage of renal best response through 12 months of treatment is equal between placebo and NEOD001.
- H_1: The percentage of renal best response through 12 months of treatment is different between placebo and NEOD001.

All visits after the first infusion of study drug up to and through the EEOS visit will be used to evaluate 12 months of treatment. Best renal response will be analyzed in the same manner described in Section 8.7 for the primary efficacy endpoint.

If an assessment qualifies as both response and progression (see Section 2.3.3.1), then assessments will be counted as progression for the primary analysis. A sensitivity analysis will be conducted counting an assessment that qualifies both as response and progression as a response.

8.9.2. Peripheral Neuropathy Evaluable Subjects: NIS-LL Total Score

The estimand for peripheral neurological function is the mean difference in NIS-LL total score change from baseline between treatment groups after 12 months of treatment in all randomized subjects with AL amyloidosis and peripheral neuropathy involvement (Section 8.5) who received any amount of study drug.

The secondary efficacy analysis will test the following hypotheses:

- H_0: The mean change from baseline in NIS-LL total score after 12 months of treatment is equal between placebo and NEOD001.
- H_1: The mean change from baseline in NIS-LL total score after 12 months of treatment is different between placebo and NEOD001.

The change from baseline in NIS-LL total score will be analyzed in the same manner described for SF-36v2 PCS score in Section 8.8.1. The EEOS visit will be used to evaluate 12 months of treatment.

If the assumptions of the planned parametric analyses are violated and inhibit the interpretation of the results, appropriate data transformations or non-parametric analyses will be performed in addition to the other planned sensitivity analyses to support the interpretation of the treatment effect.

8.9.3. Hepatic Evaluable Subjects: Hepatic Best Response

The estimand for hepatic best response is the difference in hepatic best response rate between treatment groups through 12 months of treatment in all randomized subjects with AL amyloidosis and hepatic involvement (Section 8.5) who received any amount of drug.

The secondary efficacy analysis will test the following hypotheses:

- H_0: The percentage of hepatic best response through 12 months of treatment is equal between placebo and NEOD001.
- H_1: The percentage of hepatic best response through 12 months of treatment is different between placebo and NEOD001.

All visits after the first infusion of study drug up to and through the EEOS visit will be used to evaluate 12 months of treatment. Best hepatic response will be analyzed in the same manner described in Section 8.7 for the primary efficacy endpoint.

8.10. Exploratory Efficacy Analyses

For applicable exploratory efficacy analyses, if the assumptions of the planned parametric analyses are violated and inhibit the interpretation of the results, appropriate data transformations or parametric analyses will be performed in addition to the other planned sensitivity analyses to support the interpretation of the treatment effect.

8.10.1. Cardiac Endpoint Analyses

8.10.1.1. Cardiac Biomarkers: NT-proBNP and Troponin T

NT-proBNP and troponin T results, change from baseline, and percentage change from baseline will be analyzed in the same manner described in Section 8.8.1. In addition, the cumulative distribution of NT-proBNP change from baseline at EEOS will be plotted.

Mean NT-proBNP values with associated standard deviation error bars will be plotted by treatment group over time, including a reference line at 1800 ng/L. LS mean change and percentage change from baseline in NT-proBNP with associated StdErr bars will be presented by treatment group over time.

NT-proBNP best response will be determined for different time intervals, such as through 3, 6, and 9 months of treatment. Best response at each of these and response at each visit will be analyzed in the same manner described in Section 8.7 and Section 8.7.1.

If sufficient mortality data are available, NT-proBNP best response will be evaluated as a potential predictor for the primary endpoint using a Cox regression model with time to the primary endpoint as the outcome, fixed effects for treatment group and NT-proBNP best response over different time intervals, and the treatment group × NT-proBNP best response interaction. In addition, NT-proBNP change from baseline as a continuous variable may also be evaluated as potential predictors of the primary endpoint. Similar analyses may be conducted for additional time to event endpoints.

8.10.1.2. Select Echocardiogram Cardiac Parameters

Descriptive statistics for Echocardiogram cardiac parameter (see Section 2.3.4.1.2) results, change from baseline, and percent change from baseline will be presented by visit for each treatment group. Change from baseline and percentage change from baseline will be analyzed using an ANCOVA model including fixed effects for randomization strata and treatment group, with the baseline value included as a covariate.

LVEF is captured in the eCRF as text to allow entry of ranges that may be recorded on the source document report. If the eCRF LVEF value contains only numbers, "%", or ">" the numeric portion of the value will be used for LVEF summary. If the eCRF value contains a range, the midpoint of the range will be used as the value for LVEF summary.

The number and percentage of subjects with LVEF (%) change from baseline categorized as follows will be summarized: >20% Reduction, 10-20% Reduction, <10% Increase - <10% Reduction, 10-20% Increase, and >20% Increase. The number and percentage of subjects with LPWd (mm) change from baseline categorized as follows will be summarized: ≥ 2 mm Increase and < 2 mm Increase.

8.10.2. Functional Endpoint Analyses

8.10.2.1. 6MWT Distance

In addition to the key secondary endpoint, 6MWT distance, change from baseline, and percent change from baseline to all visits will be analyzed in the same manner described in Section 8.8.2.

The 6MWT change from baseline will also be categorized as follows:

- ≥ 30-meter decline (Worsening)
- < 30-meter decline to < 30-meter improvement (No Change)
- ≥ 30 -meter improvement (Improvement).

The categorical change from baseline will be summarized by visit for each scheduled post-baseline visit. For each post-baseline visit ordinal logistic regression will be performed with 6MWT categorical change from baseline (Worsening, No Change, Improvement) as the dependent variable and factors for treatment group and randomization strata. Estimates of the proportional odds ratio comparing NEOD001 to placebo and the 95% CI of the odds ratio will be presented. An odds ratio greater than 1 favors the NEOD001 treatment group.

8.10.3. Quality of Life Endpoint Analyses

8.10.3.1. SF-36v2

In addition to the key secondary endpoint, the SF-36v2 PCS and MCS scores and the eight subscales to all visits will be analyzed in the same manner described in Section 8.8.1. The cumulative distribution of change from baseline at the Month 9 visit will also be plotted.

The rate of change (i.e. slopes) in the SF-36v2 PCS and MCS scores and the eight subscales will be analyzed in the same manner described in Section 8.8.3.

Table 5 below presents the responder definitions recommended by Optum for SF-36v2 domains and component summary scores.

Table 5: Responder Criteria for SF-36v2 Domains and Summary Measures

SF-36v2 Domain	Responder Threshold (≥)
Physical Functioning (PF)	4.3
Role-Physical (RP)	3.4
Bodily Pain (BP)	6.2
General Health Perceptions (GH)	7.2
Vitality (VT)	6.2
Social Functioning (SF)	6.9
Role-Emotional (RE)	4.5
Mental Health (MH)	6.2
Physical Component Summary (PCS)	3.4
Mental Component Summary (MCS)	4.6

Response will be defined as greater than or equal to the specified threshold and non-response will be less than the specified threshold. Response will be derived for each subject at each visit for each subscale, MCS score, and PCS score. NEOD001 and placebo will be compared on each response distribution at each visit using a CMH test stratified by the randomization stratification factors. The number and percentage, with associated two-sided 95% CIs, of subjects in each category of response (response, nonresponse) at each visit will be presented by treatment group.

8.10.3.2. KCCQ

All KCCQ subscores and overall summary score, changes and percent changes from baseline to all visits will be analyzed in the same manner described in Section 8.8.1.

The rate of change (i.e. slopes) in the KCCQ subscores and overall summary score will be analyzed in the same manner described in Section 8.8.3.

8.10.4. Renal Endpoint Analyses

The following endpoints will be evaluated in the Renal Evaluable Population, unless otherwise specified.

8.10.4.1. Renal Response

In addition to the secondary endpoint for the Renal Evaluable Population, renal best response will be determined for different time intervals, such as through 3, 6, and 9 months of treatment. Best response at each of these time intervals and response at each visit will be analyzed in the same manner described in Section 8.9.1.

8.10.4.2. Renal Biomarkers

Renal biomarkers (urine albumin/creatinine ratio, urinary neutrophil gelatinase-associated lipocalin [NGAL] and urinary retinol-binding protein [RBP]) results, change from baseline, and

percent change from baseline to all visits will be analyzed in the same manner described in Section 8.8.1. Renal biomarkers will be evaluated in the Renal Evaluable Population and repeated for the ITT Population.

8.10.4.3. Creatinine, Proteinuria, and eGFR

Creatinine, proteinuria (measured by 24-hour urine total protein excretion), and estimated glomerular filtration rate (eGFR) to all visits will be analyzed in the same manner described in Section 8.8.1. Creatinine, Proteinuria, and eGFR will be evaluated in the Renal Evaluable Population and repeated for the ITT Population.

Shifts in Chronic Kidney Stage from baseline to worst post-baseline value, last post-baseline value, best post-baseline value, and at each post-baseline visit will be provided by treatment group. Shifts in Chronic Kidney Stage will be evaluated in the Renal Evaluable Population and repeated for the ITT Population.

8.10.5. Peripheral Neuropathy Endpoint Analyses

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

8.10.5.1. NIS-LL Total and Component Scores

In addition to the secondary endpoint for the Peripheral Neuropathy Evaluable Population, the NIS-LL total scores at other visits and the 3 deficit component scores (sensory function, reflexes, muscle strength) to all visits will be analyzed in the same manner described in Section 8.9.2.

Peripheral neuropathy response and progression as defined in Coelho 2012 (Appendix 2), are those with an increase from baseline in NIS-LL total score of <2 points and those with an increase from baseline in NIS-LL of ≥2 points, respectively. Response at each visit will be analyzed in the same manner described in Section 8.7 for the primary efficacy endpoint. Peripheral neuropathy response at each visit will be analyzed in the same manner described in Section 8.7.

The rate of change (i.e. slopes) in the NIS-LL component scores and total score will be analyzed in the same manner described in Section 8.8.3.

8.10.5.2. VASPI

For the Peripheral Neuropathy Evaluable Population with painful neuropathy, defined as a baseline VASPI score > 0, the change and percent change from baseline at in VASPI scores will be analyzed in the same manner described in Section 8.8.1.

8.10.6. Hepatic Endpoint Analyses

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

8.10.6.1. Hepatic Response

In addition to the secondary endpoint, for subjects in the Hepatic Evaluable Population, hepatic best response will be determined for different time intervals, such as through 3, 6, and 9 months of treatment. Hepatic best response at each of these time intervals and response at each visit will be analyzed in the same manner described in Section 8.9.3.

Alkaline phosphatase values, change from baseline, and percent change from baseline to all visits will be analyzed in the same manner described in Section 8.8.1.

8.10.7. Additional Time-to-Event Endpoints

8.10.7.1. Time to All-Cause Mortality (Overall Survival)

Overall survival, time to all-cause mortality, will be calculated in days as the date of death minus the date of first study drug infusion plus 1. Subjects will be censored at their last assessment known to be alive prior to LSLV.

NEOD001 will be compared to placebo using the log rank test stratified by the randomization stratification factors. Kaplan-Meier (KM) estimates of the distribution of the time-to-event will be tabulated and graphed by treatment group. The tabulation will include the KM estimate of the medians, 25th and 75th quartiles, and corresponding 95% CIs, if estimable. The tabular and graphical summaries will include the at-risk counts for every visit. The number and percent of subjects censored and with events will be presented. The hazard ratio and 95% CI will be determined based on a Cox regression model stratified by randomization strata to estimate the magnitude of the effect.

In addition, the frequency of deaths in NEOD001 and placebo will be analyzed in the same manner described in Section 8.7 for the primary efficacy endpoint.

8.10.7.2. Cardiac Progression-Free Survival

Cardiac progression is defined as NT-proBNP progression of >30% increase and >300 ng/L increase or death. Cardiac progression will not be evaluated in the presence of renal progression, defined as an eGFR of < 30 mL/min/1.73 m^2, according to Comenzo 2012 (Appendix 2).

Progression-free survival is defined as the time from first infusion of study drug to the earliest of:

- first documented date of disease progression (as defined by NT-proBNP [Section 2.3.4.1.1]) or
- withdrawal from treatment or study due to organ (cardiac) progression or
- death on the study or
- death following withdrawal from treatment due to any cause.

Progression-free survival will be calculated in days as the earliest of the above dates (disease progression or death) minus the date of first infusion of study drug plus 1.

Subjects who are alive with no documented progression prior to the end of the study will be censored at the earliest of their date of the first assessment that meets renal progression (defined as an eGFR of < 30 mL/min/1.73 m^2), date of the last NT-proBNP measurement, or date they withdraw consent or are lost to follow-up.

NEOD001 will be compared to placebo using the log rank test stratified by the randomization stratification factors. KM estimates of the distribution of the time-to-event will be tabulated and graphed by treatment group. The tabulation will include the KM estimate of the medians, 25th and 75th percentiles, and corresponding 95% CIs, if estimable. The tabular and graphical summaries will include the at-risk counts for every visit. The number and percent of subjects

censored and with events will be presented overall and for each visit, using last day of the visit window. The hazard ratio and 95% CI will be determined based on a Cox regression model stratified by randomization strata to estimate the magnitude of the effect.

In addition, a sensitivity analysis will be performed counting death or progression without subsequent response as an event.

8.10.7.3. Duration of Cardiac Response

Cardiac response is defined as >30% decrease and >300 ng/L decrease in NT-proBNP from baseline.

Duration of cardiac response is defined for subjects experiencing response as the time from the earliest cardiac response to the first documented date of disease progression, as defined by NT-proBNP progression of >30% increase and >300 ng/L increase. Subjects without response will be excluded from this analysis.

Duration of Cardiac Response will be calculated in days as the date of disease progression minus the date of first response plus 1.

Subjects will be censored at their date of the last NT-proBNP measurement if they complete the study or discontinue with no documented progression.

NEOD001 will be compared to placebo using the log rank test stratified by the randomization stratification factors. KM estimates of the distribution of the time-to-event will be tabulated and graphed by treatment group. The tabulation will include the summary statistics as described for continuous variables in Section 4.1, KM estimate of the medians, 25th and 75th percentiles, and corresponding 95% CIs, if estimable. The tabular and graphical summaries will include the at-risk counts for every visit. The number and percent of subjects censored and with events will be presented overall and for each visit, using last day of the visit window. The hazard ratio and 95% CI will be determined based on a Cox regression model stratified by randomization strata to estimate the magnitude of the effect.

In addition, a sensitivity analysis will be performed for subjects experiencing response as the time from the earliest cardiac response to the first documented date of disease progression without subsequent response.

8.10.7.4. Time to Derived Organ Progression

The following time-to progression endpoints will be analyzed in the same manner described in Section 8.10.7.1. For all of the endpoints below, subjects who die prior to having documented disease progression will be assumed to have progressed at their date of death and subjects who discontinue due to disease progression, as reported on the ETD or EOS eCRF, will be assumed to have progressed at the date of their last contact.

- Time (months) to cardiac progression calculated as: (date first assessed with progression (Section 8.7) - the date of first study drug infusion + 1) / 30.4375. Subjects who do not experience progression will be censored at the date of last NT-proBNP assessment.
- For renal evaluable subjects, time (months) to renal progression calculated as: (date first assessed with progression (Section 8.9.1) - the date of first study drug infusion + 1) /

30.4375. Subjects who do not progress will be censored at the date of last eGFR assessment.

- Time (months) to cardiac or renal progression calculated as: (earliest date assessed as a NT-proBNP or renal progressor - the date of first study drug infusion + 1) / 30.4375. Subjects who do not progress will be censored at the minimum of the last NT-proBNP assessment date or last eGFR assessment date.

8.10.7.5. Time to First Organ Response

The following time-to response endpoints will be analyzed in the same manner described in Section 8.10.7.1.

- Time (months) to first cardiac response calculated as: (date first assessed with response (Section 8.7) - the date of first study drug infusion + 1) / 30.4375. Subjects who do not respond will be censored at the date of last NT-proBNP assessment.
- For renal evaluable subjects, time (months) to first renal response calculated as: (date first assessed with response (Section 8.9.1) - the date of first study drug infusion + 1) / 30.4375. Subjects who do not respond will be censored at the date of last proteinuria (urine total protein) assessment.
- Time (months) to cardiac or renal response calculated as: (earliest date assessed as a cardiac or renal responder - the date of first study drug infusion + 1) / 30.4375. Subjects who do not respond will be censored at the minimum of the last NT-proBNP assessment date, last proteinuria (urine total protein) assessment date, or last eGFR assessment date.

8.10.8. Other Efficacy Analyses

8.10.8.1. Cardiac Hospitalizations

Hospitalization reason will be coded using MedDRA version 19.0. Any adverse event with a preferred term in the broad standardized MedDRA query (SMQ) definition of Cardiac Failure or in the SMQ definition of Cardiac Arrhythmias that results in hospitalization will be counted as a Cardiac Hospitalization.

Time to first cardiac hospitalization admission will be calculated in days as the date of first cardiac hospitalization admission minus the date of first study drug infusion plus 1. Subjects who do not experience an event will be censored at the date of last contact. NEOD001 will be compared to placebo using the same methods described in Section 8.10.7.1. In addition, the time to recurrent cardiac hospitalization, i.e., time to next cardiac hospitalization after the first, will be analyzed in the same manner.

The number of cardiac hospitalizations per subject over the course of the study will be summarized both as a continuous and categorical variable by treatment group. A Poisson regression model will be fit using the continuous number of cardiac hospitalizations as the dependent variable, the total time in study as the offset variable, and treatment group as a factor. The number of cardiac hospitalizations per subject will be categorized as 0, 1, and ≥2. The categorical variable will be analyzed using a CMH test stratified by the randomization stratification factors. The number and percentage, with associated two-sided 95% CIs, of subjects in each category will be presented by treatment group. An ordinal logistic regression

will be performed with categorical number of hospitalizations (0, 1, and ≥2) as the dependent variable and factors for treatment group and randomization strata.

8.10.8.2. ECOG Performance Status, NYHA Class, Renal Stage

The number and percentage of subjects in each ECOG Performance Status (Appendix 5), NYHA class (Appendix 6), and Renal Stage (Appendix 9; separately) at each visit will be presented by treatment group. Shift tables in a contingency table from baseline to worst post-baseline value, last post-baseline value, best post-baseline, and at each post-baseline visit will be provided for by treatment group.

8.10.8.3. Selected Hematological and Urine Analyte Analyses

Serum FLCs, serum PEP, and serum and urine IFE results will be summarized by treatment group using descriptive statistics at baseline, each post-baseline visit, minimum value, and maximum value. The change and percentage change from baseline will also be summarized and analyzed in the same manner described in Section 8.8.1.

8.10.8.4. Disease-Related Symptoms

The number and percentage of subjects in each category of response and best response through 12 months of treatment will be presented by treatment group.

In addition, shift tables in a contingency table from baseline to worst post-baseline value, last post-baseline value, best post-baseline value, and at each post-baseline visit will be provided by treatment group.

8.10.8.5. Pharmacokinetic Analyses

Serum NEOD001 concentrations and elapsed time from the preceding NEOD001 dose will be listed. Serum NEOD001 concentrations from this study will be pooled with data from similar samples from other NEOD001 studies in a population PK analysis. Details will be described in a separate analysis plan and reported separately from the NEOD001-201 CSR.

8.10.8.6. PK/PD Analyses

PK/PD analyses will be described in a separate analysis plan and reported separately from the CSR.

9. SAFETY ANALYSES

Safety analyses will be conducted using the Safety Population.

No inferential comparison of safety endpoints will be performed, unless otherwise specified.

9.1. Extent of Exposure

The total patient exposure years (PEY) for each subject is defined as the time interval between the first dose and the last dose, inclusive, of study drug based on the subject's study drug administration information. One PEY is the equivalent of 1 subject exposed to study drug for 1 year. Two subjects who are exposed to study drug for half a year together contribute one PEY. The total PEY of a treatment group is the sum of the person exposure years of each subject in that treatment group. Duration of exposure is defined in days as the date of the last infusion of study drug – the date of the first infusion of study drug + 1.

Study drug exposure will be summarized by treatment group and will include:

- The number of subjects exposed to NEOD001, the total PEY, and duration of exposure will be summarized using descriptive statistics. This summary will be repeated for all general and special baseline subgroups defined in Section 6.
- Total Number of Infusions received will be determined for each subject by number of times the start time of drug infused is reported. If multiple infusion start times are reported on a single day, then only 1 infusion will be counted for that day. If the start time of drug infused is missing but total volume infused is greater than 0 mL, 1 infusion will be counted for that day.
- Percentage of Expected Infusions will be determined for each subject as the total number of infusions received divided by the total number of expected infusions multiplied by 100. Total number of expected infusions will be defined as the maximum of (the total number of infusions received, and the floor of ((EOS/ETD date - first infusion date + 1)/28), i.e. integer part of the function).
- Total Number of Dose Interruptions will be determined for each subject by the number of times the IV was not completed.
- Dose Strength (mg/kg) will be calculated for each subject for each visit. Total dose (mg) per infusion is not captured on the eCRF. Total dose (mg) is captured in the materials kit schedule maintained by IWRS. After unblinding, the total dose in mg will be calculated as the number of NEOD001 vials infused at each visit per IWRS, multiplied by 500 mg per vial. Total dose (mg) will be divided by the weight used to calculate total dose. If the total dose (mg) is missing but the total duration of infusion is 120 +/- 10 minutes for Month 1-Day 1 or the total duration of infusion is 60 +/10 minutes for visits after Month 1-Day1 and IV completed is marked "Yes" then total dose will be imputed to be equal to the planned dose strength (described below). Dose strength will only be calculated where both the total dose and weight used are available. Once visit/individual specific Dose Strengths are determined, subjects will be assigned a single average Dose Strength value across all visits to be used for summary statistics in the table.

- Percent of Planned Dose Strength will be determined by dividing the actual dose strength by the planned dose strength. Calculation of actual dose strength is described above. Planned dose strength will be determined in a similar manner except the planned dose will be calculated by multiplying the reported NEOD001 dose concentration by the weight used.
- Total Number of Dose Reductions will be determined for each subject by the number of times the percent of planned dose was less than 100.

9.1.1. Use of Premedication

The use of premedications will be summarized for any infusion and by each planned infusion by treatment group and will include the following:

- Total Number of Subjects Infused
- Total Number of Infusions Administered: number of times the start time of drug infused is reported. If multiple infusion start times are reported on a single day, then only 1 infusion will be counted for that day. If the start time of drug infused is missing but total volume infused is greater than 0 mL, 1 infusion will be counted for that day.
- Number of Subjects Receiving Premedication
- For subjects receiving premedication, number of infusions requiring premedication per subject: note that because this value is by definition 1 for by-infusion summaries, this should only be presented for the any-infusion summary.
- For subjects requiring premedication, number of premedications per subject per infusion.

All recorded and derived exposure data will be presented in a by-subject data listing and any dose modifications will be flagged.

9.2. Adverse Events

Verbatim terms on eCRFs will be mapped to PTs and SOCs using MedDRA version 19.0. AEs will be reported and severity will be categorized using the Common Terminology Criteria for Adverse Events (CTCAE, Version 4.03).

Pretreatment AEs are those AEs with a start date prior to the first infusion of study drug. All AE summaries will be restricted to TEAEs, which are defined as any AE that newly appears, increases in frequency, or worsens in severity following initiation of study drug and through the last study visit or up to 30 days after date of last dose, whichever is later. If it cannot be determined whether the AE is treatment emergent due to a partial onset date, then it will be counted as such.

Each AE summary will be displayed by treatment group. Summaries that are displayed by SOC and PT will be ordered by descending order of NEOD001 incidence of SOC and PT within each SOC. Summaries of the following types will be presented:

- Overall summary of AEs including the number and percent of subjects with at least one of the following:
  - Any TEAE

  - TEAE by maximum CTCAE Grade
  - CTCAE Grade ≥3 TEAE
  - Serious TEAE
  - TEAE leading to death (outcome="Fatal" or severity=CTCAE grade 5)
  - Treatment-related TEAE
  - Treatment-related serious TEAE
  - Treatment-related TEAE of CTCAE ≥ Grade 3
  - Treatment-related TEAE leading to death
  - TEAE leading to infusion interruption
  - TEAE leading to dose reduction of study treatment
  - TEAE leading to dose being held
  - TEAE leading to prolongation of infusion time (>2.5 hours)
  - Infusion associated TEAE overall
    - Infusion associated TEAE with premedication concomitant medication for infusion related reaction
    - Infusion associated TEAE without premedication concomitant medication for infusion related reaction
  - TEAE leading to study drug withdrawal
- Subject incidence of TEAEs by MedDRA SOC and PT. This summary will be repeated for all general and special baseline population subgroups defined in Section 6.
- Subject incidence of TEAEs by MedDRA SOC and PT occurring in ≥5% of NEOD001 subjects with greater frequency than placebo.
- Subject incidence of TEAEs by MedDRA SOC and PT occurring in ≥10% of NEOD001 subjects with greater frequency than placebo.
- Subject incidence of TEAEs by MedDRA SOC and PT occurring with greater frequency than placebo.
- Subject incidence of TEAEs by MedDRA SOC and PT occurring in NEOD001 subjects at frequencies of Very common (≥10%); Common (≥1 to <10%); Uncommon (≥0.01 to <1%); Rare (≥0.001 to <0.01%); Very rare (< 0.001%).
- Subject incidence of TEAEs by MedDRA SOC, PT, and highest severity (CTCAE grade). At each level of subject summarization, a subject is classified according to the highest severity if the subject reported 1 or more events. AEs with missing severity (CTCAE grade) will be considered grade 3 (severe) for this summary.
- Subject incidence of CTCAE grade 3 or higher TEAEs by MedDRA SOC and PT. At each level of subject summarization, a subject is classified according to the highest severity if the subject reported 1 or more events. AEs with missing severity (CTCAE

grade) will be considered grade 3 (severe) for this summary. This summary will be repeated for the general and special baseline population subgroups defined in Section 6.

- Subject incidence of TEAEs by MedDRA SOC, PT, and closest relationship to study drug (Related/Not Related). At each level of subject summarization, a subject is classified according to the closest relationship to study drug if the subject reported 1 or more events. AEs with a missing relationship will be considered related for this summary.
- Subject incidence of related TEAEs by MedDRA SOC and PT. At each level of subject summarization, a subject is classified according to the closest relationship to study drug if the subject reported 1 or more events. AEs with a missing relationship will be considered related for this summary.
- Subject incidence of related CTCAE grade 3 or higher TEAEs by MedDRA SOC and PT. At each level of subject summarization, a subject is classified according to the highest severity if the subject reported 1 or more events. AEs with missing severity (CTCAE grade) will be considered grade 3 (severe) for this summary. AEs with a missing relationship will be considered related for this summary.
- Subject incidence of serious TEAEs by MedDRA SOC and PT. This summary will be repeated for all general and special baseline population subgroups defined in Section 6.
- Subject incidence of serious related TEAEs by MedDRA SOC and PT. At each level of subject summarization, a subject is classified according to the closest relationship to study drug if the subject reported 1 or more events. AEs with a missing relationship will be considered related for this summary.
- Subject incidence of TEAEs leading to study drug withdrawal by MedDRA SOC and PT. This is a subset of the AEs where Action Taken with Study Treatment is checked as "Drug Permanently Withdrawn" is checked.
- Subject incidence of TEAEs leading to infusion interruption by MedDRA SOC and PT. This is a subset of the AEs where Action Taken with Study Treatment is checked as "Dose Interrupted" is checked.
- Subject incidence of TEAEs leading to dose reduction by MedDRA SOC and PT. This is a subset of the AEs where Action Taken with Study Treatment is checked as "Dose Reduced" is checked.
- Subject incidence of TEAEs leading to dose held by MedDRA SOC and PT. This is a subset of the AEs where Action Taken with Study Treatment is checked as "Dose Held" is checked.
- Subject incidence of TEAEs leading to prolongation of infusion time (>2.5 hours) by MedDRA SOC and PT.

All of the above tables will be repeated only for MedDRA PT, excluding MedDRA SOC.

The following listings will be presented by treatment group and subject:

- All AEs
- SAEs (this is a subset of the AEs where serious is marked as "Yes")

- CTCAE Grade 3 or higher AEs (this is a subset of AEs where severity is marked as CTCAE grade 3, 4, or 5)
- Related AEs (this is a subset of the AEs where relationship marked as "Related")
- AEs leading to Study Drug Withdrawal (this is a subset of the AEs where Action Taken with Study Treatment is checked as "Drug Permanently Withdrawn")
- AEs leading to death (This is a subset of the AEs where outcome is indicated as "Fatal" or the CTCAE grade is 5)
- AEs resulting in any dose change (i.e. interruption, reduction, held, or prolongation)
- All adverse events for subjects who received the wrong study drug

9.2.1. Other Adverse Events: Infusion Reactions

The incidence of infusion associated TEAEs by MedDRA SOC and PT will be summarized by treatment group and presented in a listing. This is a subset of the AEs where the question "Was the event an infusion-associated adverse event?" is checked "Yes". Summaries will be repeated for all general baseline subgroups indicated in Section 6.

A separate summary will also be presented by planned infusion number. A TEAE will be counted based on AE and infusion start dates. For example, if an AE starts after infusion #2 but before infusion #3, the AE will be counted under infusion #2.

If applicable, the incidence of anaphylactic reaction, defined as the broad algorithmic SMQ of "Anaphylactic reaction" given in Appendix 13 will be summarized by treatment group.

In order to explore the temporal relationship of TEAEs that may be associated with the infusion, the incidence of all TEAEs occurring within 24 hours (1 day) of an infusion will be summarized by treatment group and presented in a listing. In addition, for this subset of TEAEs, the following will be summarized by treatment group for any infusion and at each infusion overall and by PT:

- the number and percent of subjects infused
- the number and percent subjects experiencing an event within 24 hours
- the number of the events
- descriptive statitstics for the number of events per subject
- descriptive statistics for the duration (days) of the events

TEAEs will be counted as occurring within 24 hours (1 day) of an infusion if:

- the start date/time of the TEAE is not missing and the infusion start date/time ≤ the start date/time of the TEAE ≤ the infusion start date/time + 24 hours or
- the start time of the TEAE is missing and the TEAE start date = the infusion start date or the TEAE start date = the infusion start date + 1 day.

9.3. Clinical Laboratory Evaluations

All laboratory assessments are given in Appendix 10. Laboratory parameters will be summarized in standard international (SI) system of units.

The following normal ranges will be used where not provided in the central laboratory data:

- INR Upper Limit of Normal (ULN) = 1.1
- Creatinine Clearance Lower Limit of Normal (LLN) = 90 mL/sec = 1.5 mL/min
- eGFR LLN = 90 mL/min/1.73m^2

All clinical laboratory data will be presented in by-subject data listings. In addition, separate listings will be presented for any subject with a post-baseline CTCAE grade 3 or 4 laboratory value. Normal ranges provided by the central laboratory will be presented in a listing.

9.3.1. Serum Chemistry, Hematology, and Coagulation

Quantitative serum chemistry, hematology, and coagulation results by treatment group using descriptive statistics at baseline and at each post-baseline visit. The change and percentage change from baseline will also be summarized.

9.3.2. Inflammatory Biomarkers

Inflammatory biomarker (Appendix 10) results, change from baseline, and percentage change from baseline will be summarized in the same manner described in Section 9.3.1.

9.3.3. Shifts in CTCAE Grade

Quantitative laboratory tests will be assigned grades based on CTCAE Version 4.03, where applicable. Shifts in CTCAE grade of laboratory tests will be presented from baseline to worst post-baseline value, last post-baseline value, best post-baseline value, and at each post-baseline visit. Summaries will present the number and percentage of subjects with shifts in laboratory grade by treatment group. Denominators for percentages will be the number of subjects with non-missing data at the specific assessment and baseline.

These summaries of shifts in CTCAE grade will be repeated for general baseline subgroups as described in Section 6.

In addition, for each laboratory test the number and percent of subjects with a lab value with CTCAE grade ≥3 and the number and percent of subjects with a CTCAE shift of ≥2 grades will be presented.

Where applicable, if the quantitative criteria for grading are equivalent for two grades, only differentiated by clinical interventions, the clinical intervention will be ignored and the highest CTCAE grade will be used.

For urine protein, values of TRACE or NEGATIVE will be considered normal.

9.3.4. Shifts in Normal Range

In addition, for laboratory tests that cannot be graded via CTCAE, shift tables (i.e., low-normal-high at baseline versus low-normal-high at post-baseline visit in a 3-by-3 contingency table) from baseline to worst post-baseline value, last post-baseline value, best post-baseline value, and at each post-baseline visit will be presented for by treatment group. Denominators for percentages will be the number of subjects with non-missing data at the specific assessment and baseline.

9.3.5. Pregnancy Testing and Urinalysis Dipstick

All pregnancy test results and urinalysis dipstick results will not be summarized but will be provided in a by-subject data listing.

9.4. Weight and BMI

Weight (kg), BMI (kg/m^2), and mBMI (kg/m^2 g/L), defined as a subject's weight (kg) × subjects squared height (meters) ÷ serum albumin (g/L), will be summarized by treatment group using descriptive statistics at baseline and at each post-baseline visit. In addition, change and percent change from baseline will be presented.

9.5. Vital Signs

Vital sign parameters including temperature (C), systolic and diastolic pressure (mmHg), pulse (beats/min) and respiratory rate (breaths/min) will be presented in a data listing. Method of collection will be provided in the listing, however summaries will be generated without regard to the method of collection. Pulse pressure, the difference between diastolic and systolic blood pressure, will be calculated. Mean arterial pressure will be calculated as the pulse pressure, divided by 3, plus the diastolic blood pressure.

Summaries of vital sign parameter results, change from baseline, and percentage change from baseline will be summarized by treatment group using descriptive statistics at baseline and at each post-baseline visit. In addition, change and percent change from baseline will be presented from pre-dose to post-dose at each infusion visit.

9.6. Electrocardiograms

ECGs measurements will be made in triplicate, 5 to 10 minutes apart and assessed by a central reader. For summary purposes the mean of the three measurements will be used. ECG parameters including time between 2 consecutive R waves [RR], PR interval, QRS duration, QT (uncorrected) interval, QT interval corrected by the Bazett's formula [QTcB], and QT interval corrected by the Fridericia's formula [QTcF] will be summarized by treatment group. Descriptive statistics will be presented for observed values and changes from baseline at each post-baseline time point.

A categorical summary of the following abnormal maximum mean triplicate QTcF values will be presented by treatment group: >450 msec, >480 msec, and >500 msec. Change from baseline summaries will also be presented for measurements that represent a change from baseline of >30 msec and >60 msec. Three separate listings for those subjects with any QTcF >450 msec or a QTcF change from baseline >30 msec, any QTcF >480 msec or a QTcF change from baseline >30 msec, and any QTcF >500 msec or a QTcF change from baseline >60 msec will be presented. The observation(s) meeting criteria for inclusion will be flagged in the listing.

QTcF will be assigned grades based on CTCAE Version 4.03, without regard to the clinical assessment necessary for Grade 4. Shifts in QTcF CTCAE grade will be presented from baseline to worst post-baseline value, last post-baseline value, and at each post-baseline visit. Summaries will present the number and percentage of subjects with shifts in grade by treatment group. Denominators for percentages will be the number of subjects with non-missing data at the specific assessment and baseline.

Overall interpretation results for ECGs and the investigator interpretation results are collected as normal, abnormal not clinically significant, and abnormal clinically significant. Subjects whose interpretation shifts from normal to abnormal clinically significant or not clinically significant will be listed separately including description of the abnormality and any associated comments.

All ECG results will be presented in by-subject data listings.

9.7. Physical Examination

Analysis of disease-related symptoms collected on the Physical Examination eCRF are detailed in Section 8.10.8.4.

Other physical examination findings based on body systems entered on the eCRF will be included in a data listing only.

9.8. Immunogenicity Analyses

Immunogenicity of NEOD001 will be assessed by anti-NEOD001 antibody levels. Any sample found to be confirmed positive for anti-NEOD001 antibodies will be further evaluated by a neutralizing antibody assay. Serum anti-NEOD001 antibody levels will be listed and, if sufficient data exist, summarized by treatment group. Serum anti-NEOD001 antibody levels may be correlated with serum NEOD001 concentrations and select safety endpoints, if sufficient data exist.

10. CHANGES TO PROTOCOL PLANNED ANALYSES

Per Protocol A3, Section 8.3.4: "All exploratory quantitative endpoints, except the 6MWT…. will be analyzed in the same manner described for the SF-36v2…". The exploratory analyses of LVEF are performed per Section 8.10.1.2 of this SAP.

Appendix 4 of the protocol, footnotes a and b, state "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." and "Subjects with progressively worsening renal function cannot be scored for NT-proBNP progression." Repeat assessments were only done using local laboratories and therefore not included in the central laboratory data for inclusion in analyses. In addition, per the SAP renal progression is not considered for the primary endpoint analyses and is only included as a sensitivity analysis.

Renal endpoints other than renal response will be repeated for the ITT population.

The Safety Population was updated to use treatment received for all subjects instead of randomized treatment.

The following endpoints were removed:

- Time to eGFR ≤15 mL/min/1.73 m^2 (Chronic Kidney Stage 5)
- Time to doubling of creatinine
- Time to peripheral neuropathy organ progression
- Time to peripheral neuropathy organ response
- Time to hepatic organ progression
- Time to hepatic organ response
- Hematologic response at each visit
- Hematologic best response through 3, 6, 9, and 12 months of treatment
- Mayo Clinic Stage including any subgroup analyses
- Peripheral neuropathy best response through 3, 6, 9, and 12 months of treatment

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 2012.

APPENDIX 2. ORGAN RESPONSE AND PROGRESSION CRITERIA

Organ	Response	Progression
Heart/Cardiac[a,b]	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)[b]	NT-proBNP progression (>30% and >300 ng/L increase)[c]
Renal[d]	≥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[f]	NIS-LL increase from baseline of <2 points	NIS-LL increase from baseline of ≥2 points
Liver/Hepatic[a,e]	50% decrease in ALP value from baseline OR ≥2 cm reduction in liver size radiographically[e]	≥50% increase in ALP from baseline

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 2012.
b NYHA class not considered for primary efficacy endpoint analyses.
c Subjects with progressively worsening renal function cannot be scored for NT-proBNP progression.
d Palladini 2014.
e Liver size was not collected and is therefore not considered for evaluation of hepatic response.
f Coelho 2012.

APPENDIX 3. NEUROPATHY IMPAIRMENT SCALE – LOWER LIMBS

prothena

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.

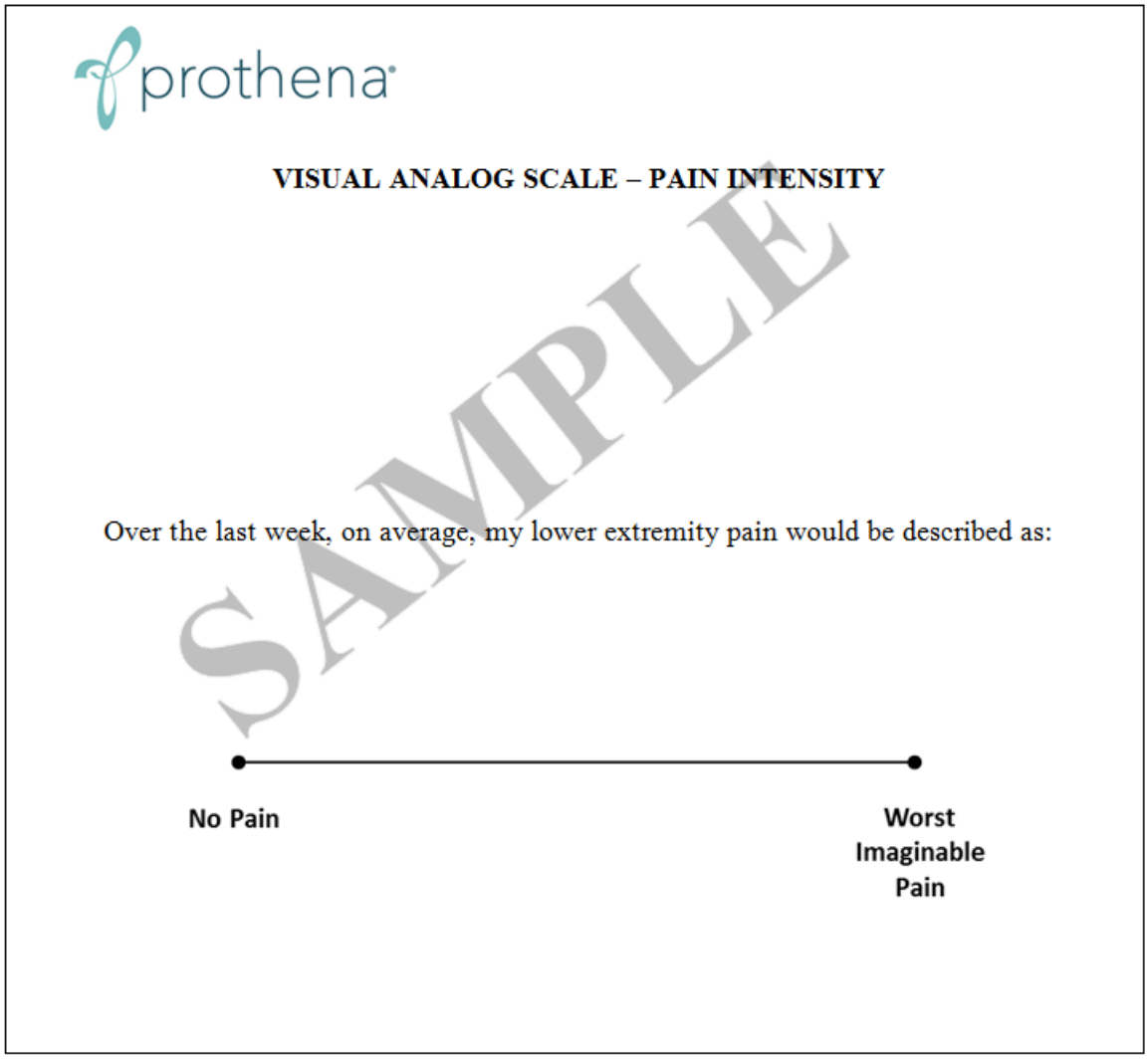
Assessment	*Right*	*Left*	*Sum*
Muscle Weakness - Score each assessment as: 0 - normal, 1 - 25% weakened, 2 - 50% weakened, 3 - 75% weakened, 4 - paralysis			
Hip Flexion (iliopsoas)			
Hip Extension (gluteus max.)			
Knee Flexion (biceps femoris)			
Knee Extension (quadriceps)			
Ankle Dorsiflexors (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 4. VISUAL ANALOG SCALE – PAIN INTENSITY (VASPI)



APPENDIX 5. 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 1982.

APPENDIX 6. 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 7. SF-36V2 HEALTH SURVEY

Your Health and Well-Being

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

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

In general, would you say your health is:

Excellent
Very good
Good
Fair
Poor

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

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

The following question is about activities you might do during a typical day.

Does your health now limit you in vigorous activities, such as running, lifting heavy objects, participating in strenuous sports? If so, how much?

Yes, limited a lot
Yes, limited a little
No, not limited at all

The following question is about activities you might do during a typical day.

Does your health now limit you in moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf? If so, how much?

Yes, limited a lot
Yes, limited a little
No, not limited at all

The following question is about activities you might do during a typical day.

Does your health now limit you in lifting or carrying groceries? If so, how much?

Yes, limited a lot
Yes, limited a little
No, not limited at all

The following question is about activities you might do during a typical day.

Does your health now limit you in climbing several flights of stairs? If so, how much?

Yes, limited a lot
Yes, limited a little
No, not limited at all

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

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

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

During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities? Accomplished less than you would like as a result of any emotional problems (such as feeling depressed or anxious) All of the time Most of the time Some of the time A little of the time None of the time
During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities? Did work or other activities less carefully than usual as a result of any emotional problems (such as feeling depressed or anxious) All of the time Most of the time Some of the time A little of the time None of the time
During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups? Not at all Slightly Moderately Quite a bit Extremely
How much bodily pain have you had during the past 4 weeks? None Very mild Mild Moderate Severe Very Severe

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

Not at all
A little bit
Moderately
Quite a bit
Extremely

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)? All of the time Most of the time Some of the time A little of the time None of the time
How TRUE or FALSE is the following statement for you? I seem to get sick a little easier than other people. Definitely true Mostly true Don't know Mostly false Definitely false
How TRUE or FALSE is the following statement for you? I am as healthy as anybody I know. Definitely true Mostly true Don't know Mostly false Definitely false
How TRUE or FALSE is the following statement for you? I expect my health to get worse. Definitely true Mostly true Don't know Mostly false Definitely false

How TRUE or FALSE is the following statement for you?

My health is excellent.

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

APPENDIX 8. KANSAS CITY CARDIOMYOPATHY QUESTIONNAIRE (KCCQ)

The KC Cardiomyopathy Questionnaire

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

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

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

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

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

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

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

Original US English

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

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

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

It has been ...

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

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

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

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

It has been ...

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

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

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

Original US English

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

It has been ...

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

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

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

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

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

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

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

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

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

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

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

Original US English

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

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

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

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

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

Original US English

APPENDIX 9. RENAL STAGE

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

eGFR = estimated glomerular filtration rate.

RCSource: Palladini 2014.

APPENDIX 10. LABORATORY TESTS

<table>
<tr>
<td colspan="2">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</td>
<td>Hematology:
Hemoglobin (E)
Hematocrit
RBC
WBC
Neutrophils (absolute [E], %)
Lymphocytes (absolute, %)
Monocytes (absolute, %)
Eosinophils (absolute, %)
Basophils (absolute, %)
Platelet count (E)</td>
</tr>
<tr>
<td colspan="2" rowspan="2"></td>
<td>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</td>
</tr>
<tr>
<td>Inflammatory Biomarkers[b]:
IL-6
IL-8
TNF-alpha
INF-gamma
Complements C3, C4, and CH50
CRP
SAA (A-SAA)
Tryptase</td>
</tr>
<tr>
<td>Urinalysis - Dipstick:
Color & clarity
Specific gravity
pH
Protein
Glucose
Ketones
Bilirubin
Urobilinogen
Blood
Nitrite
Leukocyte esterase
Microscopic</td>
<td>Urinalysis - Quantitative Analysis/Renal Biomarkers[f]:
Urine albumin/creatinine ratio
Urine NGAL
Urine RBP</td>
<td>Cardiac Biomarkers:
Troponin T
NT-proBNP

Coagulation:
PT/INR
PTT
Additional indices - see Appendix 11

Women of childbearing potential only:
Serum beta hCG pregnancy tests (E)</td>
</tr>
</table>

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 protocol 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 = $141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [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 11. COAGULATION INDICES

For each coagulation time point in Table 1, citrated plasma samples will be 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 12. 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 rior 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 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 5 (ECOG) and Appendix 6 (NYHA).
5. See Appendix 3 (NIS-LL; for all subjects with peripheral neuropathy at Screening) and Appendix 4 (VASPI; for subjects with painful peripheral neuropathy at Screening).
6. See Appendix 7; SF-36v2 should be administered before performing any other study assessments on the same calendar day it is administered.
7. See Appendix 8; 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 10.
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 11 .
14. Inflammatory biomarkers per Appendix 10
15. Collect additional samples as clinically indicated, such as when significant toxicity occurs per protocol 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 10 .
19. Per Appendix 10. t 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.

APPENDIX 13. ANAPHYLACTIC REACTION SMQ

An Adverse Event or group of Adverse Events starting on the same day should be flagged as Anaphylactic Reaction per SMQ if the AE(s) meets one or more of the following criteria:

- Any term from Group A
- Any two terms, with one from Group B and one from Group C
- Any two terms, with one from Group D and one from either Group B or Group C

Group A Terms	
Preferred Term	**Preferred Term Code**
Anaphylactic reaction	10002198
Anaphylactic shock	10002199
Anaphylactic transfusion reaction	10067113
Anaphylactoid reaction	10002216
Anaphylactoid shock	10063119
Circulatory collapse	10009192
Dialysis membrane reaction	10076665
Kounis syndrome	10069167
Shock	10040560
Shock symptom	10040581
Type I hypersensitivity	10045240

Group B Terms	
Preferred Term	**Preferred Term Code**
Acute respiratory failure	10001053
Asthma	10003553
Bronchial oedema	10056695
Bronchospasm	10006482
Cardio-respiratory distress	10049874
Chest discomfort	10008469
Choking	10008589
Choking sensation	10008590
Circumoral oedema	10052250

Group B Terms	
Cough	10011224
Cyanosis	10011703
Dyspnoea	10013968
Hyperventilation	10020910
Irregular breathing	10076213
Laryngeal dyspnoea	10052390
Laryngeal oedema	10023845
Laryngospasm	10023891
Laryngotracheal oedema	10023893
Mouth swelling	10075203
Nasal obstruction	10028748
Oedema mouth	10030110
Oropharyngeal oedema	10078783
Oropharyngeal spasm	10031111
Oropharyngeal swelling	10031118
Pharyngeal oedema	10034829
Respiratory arrest	10038669
Respiratory distress	10038687
Respiratory failure	10038695
Reversible airways obstruction	10062109
Sensation of foreign body	10061549
Sneezing	10041232
Stridor	10042241
Swollen tongue	10042727
Tachypnoea	10043089
Throat tightness	10043528
Tongue oedema	10043967
Tracheal obstruction	10044291
Tracheal oedema	10044296
Upper airway obstruction	10067775
Wheezing	10047924

Group C Terms	
Preferred Term	**Preferred Term Code**
Allergic oedema	10060934
Angioedema	10002424
Erythema	10015150
Eye oedema	10052139
Eye pruritus	10052140
Eye swelling	10015967
Eyelid oedema	10015993
Face oedema	10016029
Flushing	10016825
Generalised erythema	10051576
Injection site urticaria	10022107
Lip oedema	10024558
Lip swelling	10024570
Nodular rash	10075807
Ocular hyperaemia	10030041
Oedema	10030095
Periorbital oedema	10034545
Pruritus	10037087
Pruritus allergic	10063438
Pruritus generalised	10052576
Rash	10037844
Rash erythematous	10037855
Rash generalised	10037858
Rash pruritic	10037884
Skin swelling	10053262
Swelling	10042674
Swelling face	10042682
Urticaria	10046735
Urticaria papular	10046750

Group D Terms	
Preferred Term	**Preferred Term Code**
Blood pressure decreased	10005734
Blood pressure diastolic decreased	10005737
Blood pressure systolic decreased	10005758
Cardiac arrest	10007515
Cardio-respiratory arrest	10007617
Cardiovascular insufficiency	10065929
Diastolic hypotension	10066077
Hypotension	10021097