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Statistical Analysis Plan for Protocol NEOD001-CL002 (VITAL)

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

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Term
6MWT	6-minute walk test
^{99m} Tc	Radioisotope of Technetium
ADL	activities of daily living
AE	adverse event
AIC	Akaike's information criterion
AL	amyloid light chain
ALP	alkaline phosphatase
ANCOVA	analysis of covariance
AR(1)	first-order autoregressive
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
BP	blood pressure
C	Celsius
CAC	Cardiovascular Adjudication Committee
CEC	Clinical Events Committee
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
DMC	Data Monitoring Committee
DOB	date of birth
DOIC	date of informed consent

Abbreviation	Term
dFLC	difference between involved and uninvolved free light chains
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eGFR	estimated glomerular filtration rate
EOI	end of infusion
EOS	end of study
ETD	early treatment discontinuation
FACT-GOG NTX	Functional Assessment of Cancer Treatment Gynecologic Oncology Group - Neurotoxicity
FDA	Food and Drug Administration
FLC	free light chain
g/24 hours	grams per day (24 hours)
g	gram
GH	General Health (SF-36v2)
HCS	heterogeneous compound symmetry
HR	heart rate
ICH	International Council for Harmonisation
ID	identification
IFE	immunofixation electrophoresis
in	inches
IQR	interquartile range
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

Abbreviation	Term
kg	kilogram
KM	Kaplan-Meier
L	liter
lb	pounds
LN	lymph node
LPWd	left ventricular posterior wall in end-diastole
LS	least-square
LVEF	left ventricular ejection fraction
LVSd	intraventricular septal at diastole
m	meter
m ²	meters squared
MCS	Mental Component Score (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

Abbreviation	Term
NYHA	New York Heart Association
PCS	Physical Component Score (SF-36v2)
PE	physical examination
PEP	protein electrophoresis
PF	Physical Functioning (SF-36v2)
PK	pharmacokinetic
pg/mL	picogram per milliliter
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
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

Abbreviation	Term
SI	standard international unit
SOC	system organ class
StdErr	least squares standard error
TEAE	treatment-emergent adverse event
temp	temperature
ULN	upper limit of normal
VASPI	Visual Analogue Scale – Pain Intensity
VGPR	very good partial response
vs	versus
VT	Vitality (SF-36v2)
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-CL002 (VITAL) 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 these guidelines will be documented in the clinical study report (CSR).

2. INFORMATION FROM THE STUDY PROTOCOL

2.1. Study Objective

2.1.1. Primary Objective

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

The primary estimand is the difference in survival distributions of the time-to all-cause mortality or cardiac hospitalization in all randomized subjects with AL amyloidosis who received any amount of study drug.

2.1.2. Key Secondary Objectives

The secondary efficacy objectives include the evaluation of NEOD001 plus standard of care compared to placebo plus standard of care on the following:

2.1.2.1. Change in Health-Related Quality of Life

Objective: Change from baseline in health-related quality of life using the Short Form 36 questionnaire (SF-36v2)

Estimand: The mean difference in SF-36v2 physical functioning score (PCS) change from baseline between treatment groups at Month 9 in all randomized subjects with AL amyloidosis who received any amount of study drug.

2.1.2.2. Change in Cardiac Functional Response

Objective: Change from baseline in cardiac functional response using the 6-Minute Walk Test (6MWT)

Estimand: The median difference in 6MWT distance change from baseline between treatment groups at Month 9 in all randomized subjects with AL amyloidosis who received any amount of study drug.

2.1.2.3. Cardiac Response Rate

Objective: Cardiac best response rate as assessed by N-terminal pro-brain natriuretic peptide (NT-proBNP) ([Appendix 1](#))

Estimand: The difference in cardiac best response rate between treatment groups through Month 9 in all randomized subjects with AL amyloidosis who received any amount of drug.

2.1.3. Additional Secondary Objectives

Additional secondary efficacy objectives include the evaluation of NEOD001 plus standard of care compared to placebo plus standard of care in the organ-specific populations below. In addition, the safety and tolerability of NEOD001 plus standard of care will be evaluated.

2.1.3.1. Renal Response Rate

Objective: Renal best response rate using established criteria ([Appendix 1](#)) in subjects with renal amyloid involvement at baseline

Estimand: The difference in renal best response rate between treatment groups through Month 9 in all randomized subjects with AL amyloidosis and renal amyloid involvement at baseline who received any amount of drug.

2.1.3.2. Change in Peripheral Neurological Function

Objective: Change from baseline in peripheral neurological function using the Neuropathy Impairment Score – Lower Limbs (NIS-LL; [Appendix 8](#)) in subjects with peripheral neuropathy due to amyloidosis at baseline.

Estimand: The mean difference in NIS-LL total score change from baseline between treatment groups at Month 9 in all randomized subjects with AL amyloidosis and peripheral nerve involvement at baseline who received any amount of study drug.

2.1.4. Exploratory Objectives

The exploratory efficacy objectives include the evaluation of NEOD001 plus standard of care compared to placebo plus standard of care on other cardiac, renal, peripheral neuropathy, and disease-related clinical outcome measures.

2.2. Study Design

2.2.1. Overall Study Design

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

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

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

Subjects will remain on study until study completion, which will occur when approximately 156 primary endpoint events (all-cause mortality or cardiac hospitalizations as adjudicated by the clinical endpoint committee [CEC]) have been observed. As the number of adjudicated primary endpoints events get closer to 156, a data base cutoff date will be determined. Therefore, the final number of adjudicated primary endpoint events for analysis will be the number of adjudicated events as of that data cutoff date.

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

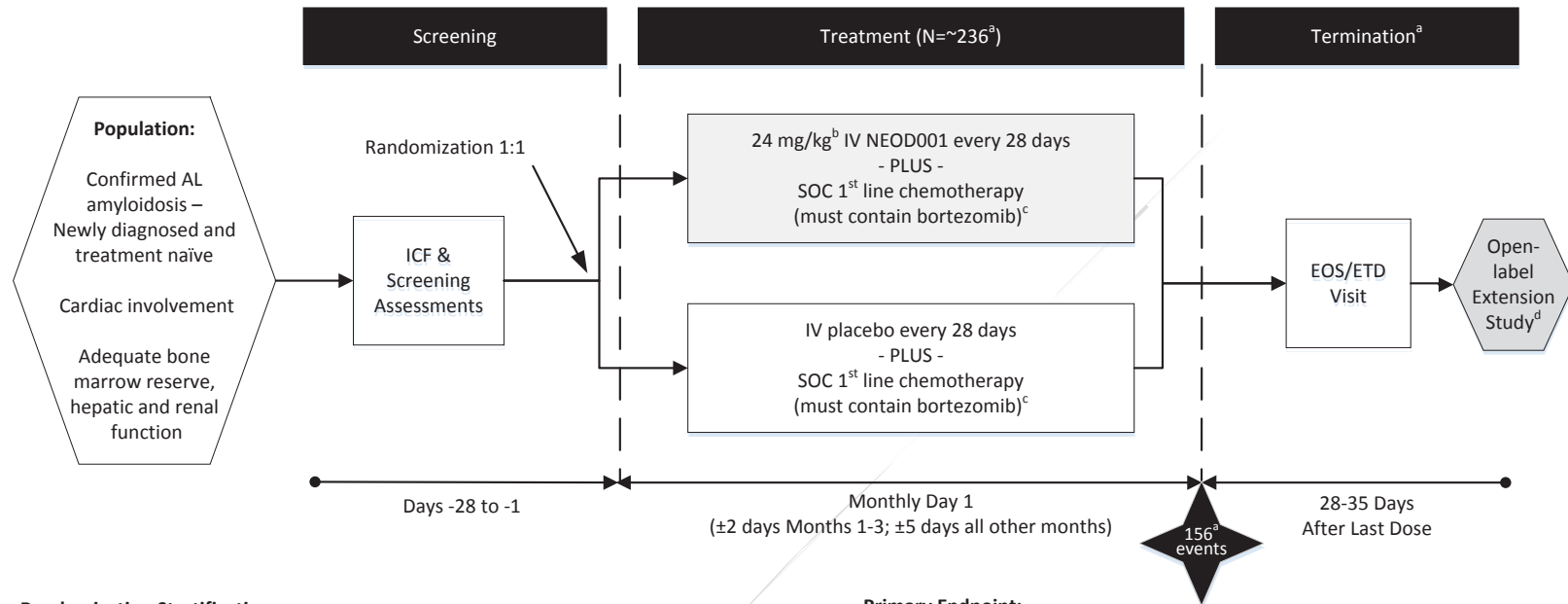
If the subject discontinues study drug prior to the end of the study, but is willing to continue to participate in study visits, the subject should have an Early Treatment Discontinuation (ETD) Visit within 28-35 days after the last study drug administration (per Table 1 and protocol section 7.1.6) and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

Follow-up phone calls should be made to randomized subjects (or their caregivers) who received a dose of study drug and are no longer receiving study drug every 3 months, beginning approximately 3 months from the subject’s last treatment visit (protocol section 7.1.7). The subject’s health status, as well as details of any hospitalizations will be collected accordingly in the study database to ensure adequate capture of primary endpoint events.

At the time of study completion (i.e., once approximately 156 events have been observed), subjects still receiving study drug (i.e., NEOD001 or placebo) may be considered for entry into a separate open-label extension study of NEOD001.

2.2.2. Study Design Diagram

Figure 1: Study Design Schematic



Randomization Stratification:

- Mayo Clinic Stage: Stages I and II vs. Stages III and IV
 - NT-proBNP: <1800 pg/mL = 0; ≥1800 pg/mL = 1
 - Troponin-T: ≤0.03 ng/mL = 0; >0.03 ng/mL = 1
 - dFLC: <18 mg/dL = 0; ≥18 mg/dL = 1
 - Total Score: 0 = Mayo Stage I; 1 = Mayo Stage II; 2 = Mayo Stage III; 3 = Mayo Stage IV
- Renal Stage: Stage I vs. Stages II and III
 - Proteinuria: ≤5 g/24 hours = 0; >5g/24 hours = 1
 - eGFR: ≥50 mL/min/1.73 m² = 0; <50 mL/min/1.73 m² = 1
 - Total Score: 0 = Renal Stage I; 1 = Renal Stage II; 2 = Renal Stage III
- 6MWT distance: <300 meters vs. ≥300 meters

Primary Endpoint:

- Time to all-cause mortality or cardiac hospitalization

Key Secondary Endpoints:

- SF-36 PCS change from baseline to Month 9
- 6MWT distance change from baseline to Month 9
- NT-proBNP best response from baseline through Month 9

Secondary Endpoints in Efficacy Subset Populations^e:

- Renal best response from baseline through Month 9
- NIS-LL Total Score change from baseline to Month 9
- Hepatic best response from baseline through Month 9

CEC = Clinical Events Committee; dFLC=difference between involved and uninvolved free light chains; eGFR = estimated glomerular filtration rate; EOS/ETD = End of Study/Early Treatment Discontinuation; ICF = informed consent form; IV = intravenous; NIS-LL =Neuropathy Impairment Scale – Lower Limbs; NT-proBNP=N-terminal pro B-type natriuretic peptide; PCS = Physical Component Score; SF-36 = Short Form-36; 6MWT = 6-minute walk test; SOC=standard of care.

^a An estimated sample size of approximately 236 subjects will be required to attain 156 events; after approximately 156 primary endpoint events have occurred, the study will conclude and all subjects will have an EOS Visit.

^b Maximum dose not to exceed 2500 mg.

^c Number of cycles per Investigator's discretion.

^d Subjects may be considered for entry into a separate open-label extension study.

^e Renal-evaluable subjects, peripheral neuropathy-evaluable subjects, and hepatic-evaluable subjects, respectively.

2.2.3. 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 intravenous (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.

Please refer to the protocol for complete product details.

2.2.4. Randomization Methodology

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

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

Upon successful randomization, the subject will be assigned a 6-digit Subject ID consisting of the 3-digit site number plus the 3-digit subject number, and the Unblinded Pharmacist or their designee (henceforth collectively referred to as the Unblinded Pharmacy Staff) will be provided access to the treatment assignment. Subject IDs that are assigned to subjects who are randomized but do not receive study drug will not be re-utilized. Each arm of this 2-arm study will consist of approximately 118 subjects for an estimated total of 236 subjects.

2.2.5. Study Procedures

The schedule of assessments, as outlined in the study protocol, is presented in [Table 1](#).

Table 1: Schedule of Study Procedures

Assessments	Screening ¹		Month 1		Month 2		Month 3		Months 6, 9, 12, etc. (Every 3 rd Month)	All Other Months	EOS/ ETD ³
	Day-28 to Day -1	Day -2 or Day -1	Day 1	Days 8, 15 22 (±2)	Day 1 (±2)	Days 8 ² , 15 ² , 22 ² (±2)	Day 1 (±2)	Days 8 ² , 15 ² , 22 ² (±2)	Day 1 (±5)	Day 1 (±5)	
Written Informed Consent	X										
Eligibility Review	X										
Medical History ⁴	X										
Confirmation of AL Amyloidosis ⁵	X										
SF-36v2 ⁶		X			X		X		X		X
KCCQ ⁶		X			X		X		X		X
FACT-GOG NTX ^{6,7}	X	X	X	X	X	X	X	X	Per Protocol Section 7.4		X
Echocardiogram	X ⁸								Every 6 th mo ⁸		X ⁸
Liver Imaging (CT)	X ⁹								Every 6 th mo ¹⁰	X ¹⁰	X ¹⁰
12-lead Triplicate ECG ¹¹	X		X		X		X		X	X	X
Complete PE ¹²	X										X
Symptom-Directed PE ¹³			X		X		X		X	X	
ECOG PS & NYHA Class	X		X		X		X		X	X	X
NIS-LL ¹⁴	X		X		X		X		Per Protocol Section 7.4		X
VASPI ¹⁵	X		X		X		X		Per Protocol Section 7.4		X
Local Laboratory											
Hematology & Chemistry ¹⁶				X	X	X ¹⁷	X	X ¹⁷	X	X	
Serum Pregnancy (WOCBP)			X ¹⁸		X		X		X	X	X ¹⁹
Central Laboratory²⁰											
Hematology & Chemistry	X	X		X	X	X	X	X	X	X	X
Amylase	X	X			X		X		X	X	X
Coagulation – PT/INR, PTT, & Indices ²¹		X			X		X		X	X	X
Complements C ₃ , C ₄		X					X		X		X
Troponin T	X	X			X		X		X	X	X
NT-proBNP	X	X			X		X		X	X	X

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

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

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

22. Perform serum IFE/PEP monthly. If a subject's first on-study hematologic complete response was assessed at the previous visit, perform serum IFE/PEP (and 24-hour urine IFE/PEP) at least 28 days after the initial assessment of response to confirm response.
23. Urine sample will be collected per protocol Section 7.3 and frozen for potential analysis of quantitative/renal biomarkers (i.e., urine albumin/creatinine ratio, urine NGAL, and urine RBP) at a later date. Collect the final sample within 1 week prior to EOS/ETD Visit.
24. The 24-hour urine protein excretion and 24-hour urine IFE/PEP tests will be performed using the same 24-hour urine collection sample when required at the same visit.
25. If a subject's first on-study hematologic complete response was assessed at the previous visit, perform 24-hour urine IFE/PEP (and serum IFE/PEP) at least 28 days after the initial assessment of response to confirm response. Repeat every odd-numbered month (to correspond with 24-hour urine protein excretion collection) to assess for continuing response or progression. If the initial response confirmation needs to occur on an even-numbered month, perform an additional 24-hour urine collection.
26. Subject should plan to be able to return to the same clinical site for each 6MWT from first Screening through Month 9. The 6MWT must not be administered on the same day as study drug administration at any visit; therefore, it should be performed within 2 days prior to the Day 1 visit. Collect BP and HR pre- and post-6MWT administration.
27. The first Screening 6MWT must be performed between Days -28 and -5, at least 4 days prior to the second Screening 6MWT, which should be performed within 2 days prior to the Month 1-Day 1 visit (i.e., on Day -2 or Day -1).
28. Collect PK samples **pre-dose** on study drug or chemotherapy dosing days, anytime during **EOS/ETD** Visit, and at these additional time points: **Month 1-Day 1**: EOI (+5 min), 0.5 hour (± 5 min) post-EOI, and 1 hour (± 10 min) post-EOI; **Month 2-Day 1**: EOI (+5 min), and 1 hour (± 10 min) post-EOI; **Month 6-Day 1 and Month 12-Day 1**: EOI (+5 min), 0.5 hour (± 5 min) post-EOI, and 1 hour (± 10 min) post-EOI. Additional samples may be collected as clinically indicated, such as when significant toxicity occurs.
29. Archive serum samples will only be collected from those subjects who have consented to the collection and archiving of their samples for future correlative testing.
30. All subjects are to receive 25 mg diphenhydramine (or an equivalent dose of a H1 antihistamine) and 650 mg acetaminophen (or an equivalent paracetamol dose) within 30-90 minutes prior to the start of infusion.
31. Vital signs include BP, HR, RR, and temperature; assess in same position for all time points after the subject has been at rest for ≥ 5 minutes. Pre-dose assessments should be performed **after** administration of premedication. **Screening and non-infusion days**: any time; **Month 1-Day 1**: Within 30 minutes before dosing, halfway through infusion (i.e., approximately 60 minutes after the start of the infusion), immediately at EOI (+10 min), 0.5 hour (± 10 min) post-EOI, and 1 hour (± 10 min) post-EOI. **All Other Months-Day 1**: Within 30 minutes before dosing, EOI (+10 min), and 1 hour (± 10 min) post-EOI.
32. Administer per protocol Section 6.5.1. Subjects should be closely monitored for 90 (± 10) minutes following completion of the study drug infusion. The Investigator may increase this standard monitoring time if deemed appropriate or per local standards. In the event of any clinical concerns or suspicious signs or symptoms after the infusion, the subject will remain under observation for as long as the Investigator deems it appropriate.
33. First-line chemotherapy must be a bortezomib-containing regimen, with bortezomib administered weekly, SC, according to the approved prescribing information and local institutional practices. Antiviral prophylaxis is required. When chemotherapy is administered on same day as study drug, the chemotherapy must be administered **AFTER** the post-study drug infusion observation period. Number of first-line chemotherapy cycles and subsequent chemotherapy regimens will be administered per standard of care at the Investigator's discretion.
34. Bortezomib must be administered at the study site for Cycle 1-Days 1, 8, 15, and 22; Cycle 2-Days 1 and 15; and on Day 1 of subsequent cycles, after review of local labs, study drug administration, and the post-study drug infusion observation period.
35. Cycle 2-Days 8 and 22, and Cycle 3-Days 8, 15, and 22 chemotherapy may be administered by local physician with a Homecare visit by a Prothena-sponsored healthcare professional to the subject within 1 day prior to or pre-dose on the day of each bortezomib administration to administer FACT-GOG NTX, and to obtain vital signs, blood samples for central laboratory testing, and bioanalytical samples (if applicable). If bortezomib is administered on a Monday, the Homecare visit may occur on the previous Friday. If significant toxicity occurs during Cycle 1, subject should return to the study site for Cycle 2 and Cycle 3 visits until Investigator deems it appropriate for local administration.
36. For all subjects who are randomized and received a dose of study drug: Conduct vital status phone call per protocol Section 7.1.8 approximately 3 months after the subject's last visit and approximately every 3 months thereafter.

Table 2: Peripheral Neuropathy Assessments

Assessment	Screening	Months 1-3	Months 4-12	Months 13+	EOS/ETD
FACT-GOG NTX (Appendix 7)	All Subjects: Once between Days -28 and -1 and again on Day -2 or Day -1	All Subjects: Weekly (Day 1, 8 ^a , 15 ^a , and 22 ^a Visits)	<ul style="list-style-type: none"> • Subjects who had positive scores at Screening and/or Month 3: Months 6, 9, and 12 (Day 1 Visit) • Subjects who are receiving identified concomitant medication^b: Monthly (Day 1 Visit) • Subjects who had negative scores at Screening and Month 3 and new PN signs and symptoms develop: Monthly (Day 1 Visit) 	<ul style="list-style-type: none"> • Subjects who had positive scores at Screening and/or Month 3: Every <u>sixth</u> month (e.g., Months 18, 24 [Day 1 Visit]) • Subjects who are receiving identified concomitant medication^b: Monthly (Day 1 Visit) • Subjects who had negative scores at Screening and Month 3 and new PN signs and symptoms develop: Monthly (Day 1 Visit) 	All Subjects
NIS-LL and VASPI (Appendix 8) and (Appendix 9)	All Subjects: Once between Days -28 and -1	All Subjects: Monthly (Day 1 Visit)	<ul style="list-style-type: none"> • Subjects who had positive scores at Screening and/or Month 3: Months 6, 9, and 12 (Day 1 Visit) • Subjects who are receiving identified concomitant medication^b: Monthly^a (Day 1 Visit) until completion of concomitant medication & then at Months 6, 9, and 12 (Day 1 Visit) or whatever remains of these months • Subjects who had negative scores at Screening and Month 3 and new PN signs and symptoms develop: At the next scheduled visit and then at Months 6, 9, and 12 (Day 1 Visit) or whatever remains of these months 	<ul style="list-style-type: none"> • Subjects who had positive scores at Screening and/or Month 3: Every sixth month (e.g., Months 18, 24 [Day 1 Visit]) • Subjects who are receiving identified concomitant medication^b: Monthly (Day 1 Visit) until completion of concomitant medication & then every <u>sixth</u> month (e.g., Months 18, 24 [Day 1 Visit]) • Subjects who had negative scores at Screening and Month 3 and new PN signs and symptoms develop: At the next scheduled visit and then every <u>third</u> month (e.g., Months 15, 18 [Day 1 Visit]) 	All Subjects

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

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

^bBortezomib, another proteasome inhibitor, or other drug with the propensity to cause peripheral neuropathy.

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

2.3. Study Endpoints

2.3.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the time to all-cause mortality or cardiac hospitalization as adjudicated by the CEC.

For all-cause mortality, all deaths occurring after the first infusion of study drug (i.e. study day 1) through the study's last subject last visit (LSLV; see [Section 2.2.1](#)) will be included. Cardiac hospitalizations occurring ≥ 91 days after a subject's first infusion of study drug through LSLV will be included. All primary endpoint events will be adjudicated. Each subject will be counted only once in the primary analysis, based on their first adjudicated occurrence of an endpoint event.

The following censoring rules will apply:

- Subjects who complete the study and experience a confirmed CEC cardiac hospitalization on or after study day 1 but prior to study day 91, have no other confirmed CEC cardiac hospitalizations on or after study day 91, and are not known to have died, will be censored at their last assessment (visit or phone call) known to be alive.
- Subjects who complete the study and do not experience any confirmed CEC cardiac hospitalization and are not known to have died will be censored at their last assessment (visit or phone call) known to be alive.
- Subjects who withdraw from the study or are lost to follow-up prior to experiencing a confirmed CEC cardiac hospitalization on or after study day 91 or death will be censored at their last assessment (visit or phone call) where both vital status and hospitalization information was available.

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

2.3.2. Key Secondary Efficacy Endpoints

The following secondary efficacy endpoints are considered key in evaluating subjects' response to treatment in terms of how s/he feels, how s/he functions, and survival time. The key secondary endpoints, in order of priority are as follow.

2.3.2.1. Change from Baseline to Month 9 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 5](#); <https://campaign.optum.com/optum-outcomes.html>). It allows for the scoring of two component summary indices: the Physical Component Score (PCS) and the Mental Component Score (MCS). 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 4b)

- 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, and (3) the MH scale is not missing when calculating the MCS. 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 Month 9 visit.

2.3.2.2. Change from Baseline to Month 9 in the 6-Minute Walk Test (6MWT) Distance (meters)

The 6MWT is a test that requires a minimum walking length of 25 meters but no exercise equipment or advanced training for technicians. The walking track or area should be the same for all tests for a subject. Walking is an activity performed daily by all but the most severely impaired subjects. 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 Month 9 visit.

2.3.2.3. NT-proBNP (Cardiac) Best Response from Baseline Through Month 9

Cardiac response as defined by NT-proBNP best response from baseline through Month 9. All visits after the first infusion of study drug up to and through the Month 9 visit will be included.

NT-proBNP response categories (modified from Table 2 in [Comenzo 2012](#); [Appendix 1](#)) are defined as:

Response	Stable Disease	Progression
Decrease in NT-proBNP from baseline >30% and from baseline >300 ng/L (pg/mL)	Assessment was neither Response nor Progression	Increase in NT-proBNP from baseline >30% and from baseline >300 ng/L (pg/mL)

Best response is defined as the most favorable category (response, stable disease, or progression) up to and through the Month 9 visit. Subjects will be classified as responders or non-responders. Non-response is defined as either stable disease or progression.

2.3.3. Additional Secondary Efficacy Endpoints

2.3.3.1. Renal Evaluable Subjects: Renal Best Response from Baseline through Month 9

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. All visits after the first infusion of study drug up to and through the Month 9 visit will be included.

For these subjects, renal response categories (modified from [Palladini 2014](#); [Appendix 1](#)) are defined as:

Response	Stable Disease	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 disease, or progression) up to and through the Month 9 visit. Subjects will be classified as responders or non-responders. Non-response is defined as either stable disease or progression.

2.3.3.2. Peripheral Neuropathy Evaluable Subjects: Change from Baseline to Month 9 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 at screening due to AL amyloidosis etiologies 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 Month 9 visit.

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 8](#)). The scale is an 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)

2.3.4. Exploratory Efficacy Endpoints

The following exploratory efficacy endpoints will evaluate NEOD001 plus standard of care compared to placebo plus standard of care.

2.3.4.1. Cardiac Endpoints

2.3.4.1.1. Cardiac Biomarkers (NT-proBNP)

- Cardiac response ([Appendix 1](#)), as assessed by NT-proBNP response criteria, at each visit
- Cardiac best response ([Section 2.3.2.3](#)), as assessed by NT-proBNP response criteria, through Month 3 visit, Month 6 visit, and Month 12 visit, and over course of study
- Change and percent change from baseline in NT-proBNP at each visit

2.3.4.2. Functional Endpoint - 6MWT Distance

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

2.3.4.3. Quality of Life Endpoints - SF-36v2

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

2.3.4.4. Renal Endpoints

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

2.3.4.4.1. Renal Response

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

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

- Change and percent change from baseline to each visit in creatinine, proteinuria, and eGFR

2.3.4.5. Peripheral Neuropathy Endpoints

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

- Change and percent change from baseline in the NIS-LL total score and the 3 deficit component scores to each visit (except Month 9 [the additional secondary endpoint])

2.3.4.6. Additional Time-to-Event Endpoints

Details regarding events, time derivations, and censoring methods are included in the corresponding endpoint analysis [Section 8.10.6](#).

- Time to cardiac mortality at any time or cardiac hospitalization (occurring ≥ 91 days after a subject's first infusion of study drug) as adjudicated by the CEC
- Time to cardiac mortality as adjudicated by the CEC
- Time to derived organ progression ([Appendix 1](#))
- Time to first derived organ response ([Appendix 1](#))

2.3.4.7. Other Efficacy Endpoints

Below are the other efficacy data collected in NEOD001-CL002 study:

- Echocardiogram Cardiac Parameters: Left ventricular ejection fraction (LVEF), Intraventricular septal at end diastole (LVSD), Left posterior wall at end diastole (LPWd)
- Cardiac Biomarker: Troponin T ($\mu\text{g/L}$)
- Kansas City Cardiomyopathy Questionnaire (KCCQ)
- Visual Analog Scale – Pain Intensity (VASPI)
- Liver size
- Eastern Cooperative Oncology Group (ECOG) performance, New York Heart Association (NYHA) Class, Mayo Clinic Stage, and Renal Stage
- Free light chains (sFLCs), serum and 24-hour urine protein electrophoresis (PEP), and serum and urine immunofixation electrophoresis (IFE)
- Disease-related symptoms
- Pharmacokinetics (PK)

2.3.5. Safety Endpoints

Safety evaluations performed during the study include:

- Vital signs
- 12-lead ECGs
- Routine laboratory assessments
- AEs
- Immunogenicity

3. SAMPLE SIZE JUSTIFICATION

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

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 International Council for Harmonisation (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 discontinued 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 quartile (Q1), 75th quartile (Q3), 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 and SEM 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 $\geq XX.5$ 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 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 95% CIs comparing groups will be provided.

4.2. Computing Environment

All descriptive statistical analyses will be performed using SAS statistical 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 September 2015.

4.3. Definition of Baseline

To minimize the impact of variability in the 6MWT distance, the baseline for the 6MWT distance (meters) will be defined as the longest distance walked prior to first study drug infusion. If only one valid assessment is available prior to first study drug infusion, it will be used as the baseline value. Baseline for all other efficacy and safety parameters will be defined as the last non-missing assessment prior to the first study drug infusion.

4.4. Partial Dates

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.

- Diagnostic 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, start date of medication, or hospitalization admission date)
 - 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.
 - When applicable, 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.

4.5. 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, log₁₀). Only transformations that lead to clinically meaningful interpretations will be used.

4.6. 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:

$$\text{duration in days} = \text{date2} - \text{date1} + 1, \text{ where } \text{date1} \geq \text{first infusion date}$$

$$\text{duration in days} = \text{date2} - \text{date1}, \text{ where } \text{date1} < \text{first infusion date}$$

- 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:

$$\text{duration in years} = (\text{date2} - \text{date1} + 1)/365.25, \text{ where } \text{date1} \geq \text{first infusion date}$$

$$\text{duration in years} = (\text{date2} - \text{date1})/365.25, \text{ where } \text{date1} < \text{first infusion date}$$

- 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*).

$$\text{age (years)} = (\text{DOIC} - \text{DOB} + 1) / 365.25.$$

- Height – Height entries made in inches (in) are converted to centimeters (cm) using the following formula:

$$\text{height (cm)} = \text{height (in)} \times 2.54$$

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

$$\text{weight (kg)} = \text{weight (lb)} / 2.205$$

- Temperature – Temperature entries in degrees Fahrenheit are converted to degrees Celsius using the following formula:

$$\text{temp (degrees Celsius)} = 5 / 9 \times (\text{temp [degrees Fahrenheit]} - 32)$$

- Body Mass Index (BMI) – BMI is calculated using height (cm) and weight (kg) using the following formula:

$$\text{BMI (kg/m}^2\text{)} = \text{weight (kg)} / ([\text{height (cm)} / 100]^2)$$

- Change from baseline – Change from baseline will be calculated as:

$$\text{Change} = \text{post baseline value} - \text{baseline value}$$

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

$$\text{Percent change from baseline} = ([\text{post baseline value} - \text{baseline value}] / \text{baseline value}) \times 100$$

4.7. 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 28 days from the previous infusion (± 2 days for Months 2 and 3; ± 5 days for Months 4 and beyond). All visits, including scheduled visits, unscheduled visits, re-test, and ETD assessments, will be remapped to a scheduled visit for analysis purposes according to visit window as described in [Table 3](#) and [Table 4](#) below, the nominal visits will not be used for any by-visit analyses.

If multiple visits occur within a single visit window, unique assessment will be selected step by step as follows:

1. Choose the assessments with shortest distance from the target day.
2. If multiple assessments are the same distance from the target day for a particular analysis window, the later assessments are chosen.
3. If there are 2 or more assessments taken on the same date or same date and time, the rules for choosing the assessment are:
 - a. First take the assessment from the scheduled visit, then take the assessment from the re-test visit (applicable to laboratory tests), then take the assessment from the discontinuation visit, then take the assessment from the unscheduled visit.
 - b. Take the assessment with the most abnormal value. Most abnormal value is determined by taking the value that is the further from the lower limit of normal (LLN) or ULN.

[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)

	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	2	42 [= 28 + 28/2]
Month 3	56	43 [= (28 + 28/2 + 1)]	70 [= 56 + 28/2]
Month x	28*(x-1)	(x-2)*28 + 28/2 + 1	(x-1)*28 + 28/2

^a Study day will be calculated from first dose date.

^b Baseline is defined [Section 4.3](#).

[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	2	98
Month 6	140	99	182
Month x	28*(x-1)	(x-4)*28 + 84/2 + 1	(x-1)*28 + 84/2

^a Study day will be calculated from first dose date.

^b Baseline is defined in [Section 4.3](#).

“Cycle” is reserved to denote administration of chemotherapy. It is expected that all visits should occur according to the protocol schedule.

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 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 the randomized treatment.

6. EXAMINATION OF SUBGROUPS

No subgroup analyses will be done for this study.

7. STUDY POPULATION

7.1. Subject Disposition

Subject disposition will be tabulated for all screened subjects and will include the number of subjects screened, the number screened but not randomized with reasons for screen failure, 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 treatment in months will be calculated as (last infusion date minus first infusion date plus one)/30.4375.

The number and percentage of subjects randomized by geographical region and site will also be presented by treatment group and for ITT subjects.

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

- Mayo Clinic Stage ([Kumar 2012](#)): Stage I/II vs Stage III/IV
- Renal Stage ([Palladini 2014](#)): Stage I vs Stages II and III
- 6MWT distance: <300 meters vs \geq 300 meters
- Stratum Group 1: Mayo Clinic Stage I/II, Renal Stage I, 6MWT <300 meters
- Stratum Group 2: Mayo Clinic Stage I/II, Renal Stage I, 6MWT \geq 300 meters
- Stratum Group 3: Mayo Clinic Stage I/II, Renal Stage II/III, 6MWT <300 meters
- Stratum Group 4: Mayo Clinic Stage I/II, Renal Stage II/III, 6MWT \geq 300 meters
- Stratum Group 5: Mayo Clinic Stage III/IV, Renal Stage I, 6MWT <300 meters
- Stratum Group 6: Mayo Clinic Stage III/IV, Renal Stage I, 6MWT \geq 300 meters
- Stratum Group 7: Mayo Clinic Stage III/IV, Renal Stage II/III, 6MWT <300 meters
- Stratum Group 8: Mayo Clinic Stage III/IV, Renal Stage II/III, 6MWT \geq 300 meters.

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.

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.

7.2. Demographics and Baseline Characteristics

Demographic variables will include the following:

- Age at informed consent
- Sex
- Race
- Ethnicity

Other baseline characteristics will include the following:

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

Both conventional BMI and modified BMI (mBMI [$\text{kg}/\text{m}^2 \text{ g}/\text{L}$], defined as subject's weight (kg) x subjects squared height (meters) x serum albumin (g/L)) will be presented.

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)
- Concurrent Monoclonal Gammopathy (yes/no)
- History of Familial Amyloidosis (yes/no/unknown)
- Number of involved organs (1, 2, 3, or 4 organs: cardiac, renal, peripheral neuropathy) as defined in [Section 8.5](#)
- Screening NT-proBNP: $<1800 \text{ pg}/\text{mL}, \geq 1800 \text{ pg}/\text{mL}$
- Mayo Clinic Stage: I, II, III, IV; I/II, III/IV; I/II/III, IV
- Renal Stage: I, II, III; I/II, III; I, II/III
- NYHA Class: I, II, III, IV; I/II vs III/IV
- 6MWT distance: $< 300 \text{ meters vs. } \geq 300 \text{ meters}$

- Baseline FLC:
 - Ratio: Low (<0.26), Normal (0.26 – 1.65), High (>1.65)
 - dFLC: <18 mg/dL, ≥18 mg/dL

Historical NT-proBNP results will be listed including the date of assessment, number of days from first dose of study since the historical result, result, and result unit will be included in a by-subject data listing.

7.4. Disease Specific AL Symptoms

Disease specific AL symptoms verbatim terms as recorded on the Disease-Specific Medical History eCRF will be mapped to preferred terms (PT) and system organ classes (SOC) using MedDRA version 19.0.

Disease 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 PTs and SOCs using MedDRA version 19.0.

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 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 will be presented in a by-subject data listing.

7.7. Pre-Treatment, Prior, and New Concomitant Medications

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

Pretreatment medications, recorded on the Concomitant Medications eCRF, are those medications with start and stop dates 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.

Pretreatment medications, prior and new concomitant medications will be listed.

7.8. Chemotherapy

Chemotherapy regimens will be prescribed as per standard of care at the Investigator's discretion. All chemotherapy recorded on the Prescribed Chemotherapy Regimens and Concomitant Chemotherapy Treatment Medications eCRFs will be listed.

8. EFFICACY ANALYSES

All efficacy analyses will use the ITT Population, except where noted for the Efficacy Subset Populations ([Section 8.5](#)). All efficacy endpoints, recorded and derived, will be presented in by-subject data listings. For applicable efficacy analyses, 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 to support the interpretation of the treatment effect.

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 who was randomized and received any amount study drug is unwilling to return to the study site for further visits but is willing to provide his/her health status (AEs if during treatment emergent period, mortality, and hospitalizations) by phone, follow-up phone calls should be made to the subject or their caregiver, per protocol [Section 7.1.7](#) and [Appendix 3](#). If a subject discontinues study drug prior to the end of the study, but is willing to continue to participate in study visits, the subject should have an ETD Visit within 28-35 days after the last study drug administration and then have assessments performed every third month. Vital status will be collected within legal and ethical boundaries for all randomized subjects receiving any amount of study drug and will be searched in public sources. During the study close-out period, survival status will be collected within legal and ethical boundaries for all randomized subjects who withdrew participation from the study. If vital status is determined, the subject will not be considered lost to follow-up and the vital status will be included in relevant analyses.

For the SF-36v2, missing data conventions for partially completed questionnaires are specified in [Section 2.3.2.1](#).

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 8.10.6](#)). Subjects with no data after randomization will be censored on Day 1 (first day of study drug dosing). 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. Parametric Analyses

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

For the primary analysis of the SF-36v2 PCS and NIS-LL total score, subjects who are missing Month 9 due to death, will be imputed as the worst Month 9 value in the total population.

8.2.2.2. Missing at Random (MAR): Multiple Imputation

For the primary analysis of the SF-36v2 PCS and NIS-LL total score, subjects who are missing Month 9 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 nonmontone 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. 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. Non-Parametric Analyses

8.2.3.1. Ranking

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

1. Subjects who died prior to Month 9 where time to death is used to rank earlier deaths worse than later deaths,
2. Subjects who are missing Month 9 and vital status is unknown at Month 9
3. Subjects who are missing Month 9 because they are hospitalized for cardiac reasons (as adjudicated by the CEC) where duration of hospitalization is used to rank longer length of stay (LOS) worse than shorter LOS
4. Subjects who are missing Month 9 because the subject physically cannot perform the test, due to physical incapacity, non-cardiac hospitalization, or other reason
5. Subjects who are missing Month 9, known to be alive, but it is unknown if they are missing due to a cardiac hospitalization
6. Subjects who are missing Month 9, known to be alive, and are known not to be in the hospital
7. Completed subject's values will be ranked from worst (lowest distance) to best (highest distance) performance

Exploratory analyses at other visits (i.e. not Month 9) will use the same ranking methodology.

8.2.4. 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.

8.2.5. Observed Cases

In order to estimate the effect in those who survive, analyses of continuous efficacy endpoints will be presented where no imputations are made for missing values.

8.3. Interim Analyses and Data Monitoring

8.3.1. Data Monitoring Committee (DMC)

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

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

8.3.2. Interim Analysis

No interim analyses were planned for this study. Based on the results from a separate Phase 2b PRONTO study (NEOD001-201) in the same indication, which did not meet its primary or secondary endpoints, the DMC was requested to review an unplanned interim efficacy and futility analysis of the ongoing VITAL study (NEOD001-CL002). The unplanned interim efficacy and futility analysis was conducted using a Lan-DeMets spending function with non-binding futility and Pocock monitoring (stopping) boundaries based on 103 adjudicated events. The analysis needed to yield a HR of less than 0.664 for efficacy and greater than 0.739 for futility. The interim analysis HR was 0.84, leading the DMC to recommend the discontinuation

of the VITAL study for futility. It was therefore decided to discontinue all development of NEOD001, including the VITAL study as well as the open label extension studies.

8.3.3. Adjudication Committee

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

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

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 $>0.5\text{g}/24$ 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 answered as yes) and had a baseline NIS-LL score of 2 or greater and at least one post-baseline NIS-LL total score.

8.6. Multiple Comparisons/Multiplicity

For the primary and the 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 Month 9 in the SF-36v2 PCS. 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 Month 9 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 will be compared with respect to NT-proBNP (cardiac) best response from baseline through Month 9.

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 primary efficacy endpoint (defined in [Section 2.3.1](#)) is the time to all-cause mortality or cardiac hospitalization as determined by the CEC.

The primary estimand is the difference in survival distributions of the time-to all-cause mortality or cardiac hospitalization in all randomized subjects with AL amyloidosis who received any amount of study drug.

Time (months) to event for each subject will be calculated as the (earliest date of first cardiac hospitalization admission occurring ≥ 91 days after first study drug infusion or death - the date of first study drug infusion + 1) / 30.4375. The censoring rules are defined in [Section 2.3.1](#).

NEOD001 will be compared to placebo using the log rank test stratified by the randomization stratification factors. Kaplan-Meier (KM) estimates of the survival distributions 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 they can be estimated. The tabular and graphical summaries will include the at-risk counts for every visit. The number and percent of subjects censored, reason for censoring, and with events will be presented overall and for each visit, using last day of the visit window by treatment group.

The log rank test uses a weight of 1, where all time intervals are weighted equally.

The log rank test and KM methods have the following assumptions.

1. Independence of censoring and the event, i.e. the reason why cases are censored does not relate to the event: A scatter plot of the censored and event values against survival time will be presented together and separately to evaluate if any patterns arise and if the patterns are similar across treatment groups.
2. Censoring is random, with a similar amount and pattern of censorship per group: In addition to the above scatter plot, the percentage of censoring between treatment groups will be compared.

The hazard ratio and 95% CI will be determined based on the semi-parametric Cox regression model stratified by randomization strata to estimate the magnitude of the effect.

8.7.1. Sensitivity Analyses of the Primary Endpoint

8.7.1.1. Time to Event Methods

In order to assess the effect of weight assignment used by the log rank test, the analyses will be repeated using the Peto-Peto test (weight=KM survival function), Modified Peto-Peto test (weight=survival function multiplied by the ratio of the number at risk over the number at risk plus one), Wilcoxon test (weight=number at risk, where gives more weight to differences that occur earlier in the follow-up time), and the likelihood ratio test which assumes exponentially distributed survival times.

As the independence assumption is not easily verified, the cumulative incidence curve will be presented estimating the marginal probability of an event to assess treatment utility regardless of independence assumption.

In order to assess constant survival probabilities and the effects of including cardiac hospitalizations on or after study day 91, the following sensitivity analyses may be conducted in the same manner as specified for the primary endpoint (Section 8.7):

1. Removing any time constraints on cardiac hospitalizations, i.e., including all confirmed CEC cardiac hospitalizations regardless of when they occur from study day 1 until end of study. Subjects will be censored at their last contact date with who do not have a confirmed CEC cardiac hospitalization prior to the end of the study, withdraw consent, or are lost to follow-up.
2. Including only cardiac hospitalizations within the first 90 days after first study drug dosing, i.e. on or after study day 1 before study day 91. If a subject has a cardiac hospitalization after study day 91, then the subject will be censored at study day 91 or if they withdraw from the study or are lost to follow-up prior to documented cardiac hospitalization.

In addition to the semi-parametric Cox model, different parametric regression models (lognormal, Weibull, and exponential) will be assessed. If the graph of the hazard functions is U shaped, first increasing and then decreasing, the lognormal distribution will be chosen. If the graph of the log of the survival function, against time appears as a straight line passing through the origin, the exponential distribution will be chosen. If a graph of the log of the log of the survival function against the log of time appears as a straight line, the Weibull distribution will be chosen.

In order to test assess the effects of the stratification factors, the unadjusted/not stratified hazard ratio with associated 95% CI will be presented. KM plots will also be presented for each stratification factor by treatment group.

The frequency and percentage of subjects who died with their reported primary cause of death from the Death eCRF and the adjudicated cause of death will be summarized by treatment group and for all subjects. Similarly, the frequency and percentage of subjects who were hospitalized with their reported cause of hospitalization from the Hospitalization eCRF and the adjudicated cause of hospitalization will be summarized by treatment group and for all subjects for hospitalizations occurring <91 days and \geq 91 days and overall.

A by-subject listing will present all events which were adjudicated.

8.7.1.2. Finkelstein–Schoenfeld Method

Finkelstein–Schoenfeld method is a modified Wilcoxon rank sum test, may be used to analyze the impact of treatment on all-cause mortality and frequency of cardiac hospitalization during the course of study.

The analysis will test the following hypotheses:

- H_0 : Neither all-cause mortality nor frequency of cardiac hospitalizations is different between placebo and NEOD001.
- H_1 : At least one and possibly both mortality and frequency of cardiac hospitalizations are different between placebo and NEOD001.

Table 5: Finkelstein–Schoenfeld Scoring Algorithm

Scenario	Mortality	Survival Time ^a	Cardiac Hospitalization Frequency	Score
1	Dead	-1
	Alive	+1
2	Dead	Low	...	-1
	Dead	High	...	+1
3	Dead	Tied	High	-1
	Dead	Tied	Low	+1
4	Dead	Tied	Tied	0
	Dead	Tied	Tied	0
5	Alive		High	-1
	Alive		Low	+1
6	Alive		Tied	0
	Alive		Tied	0

^a Survival time will be derived as date of death - the date of first study drug infusion + 1.

In each scenario as presented in Table 5, a pairwise comparison of patients is made by first taking mortality into account. If there is a clear difference (scenario 1), then a score is assigned. If both subjects died (scenario 2), then survival time is considered, and a score is assigned if there is a difference between the patients. If there is no difference between the 2 patients in survival time, then the frequency of cardiac hospitalization (scenario 3) is considered, and a score is assigned. If there is no difference in cardiac hospitalization frequency between the 2 patients (scenario 4), then a score of 0 is assigned. If both subjects are alive, then the frequency of cardiovascular related hospitalization (scenario 5) is considered, and a score is assigned. If there is no difference in cardiovascular related hospitalization (scenario 6), then a score of 0 is assigned.

The Finkelstein–Schoenfeld method increases the sensitivity and power of the analysis while also preserving the importance of the all-cause mortality end point. The test is based on the principle that each patient in the clinical study is compared with every other patient within each stratum in a pairwise manner. The method recognizes the higher importance of all-cause mortality. The pairwise comparison proceeds in a hierarchical fashion using all-cause mortality first, assigning a +1 to the better patients and a –1 to the worse patients. The test statistic is based on the sum of these scores within each stratum and then summed across the all strata.

Number and percentage of subjects who died will be presented. Percentage will be based on ITT population. Descriptive statistics for frequency of cardiac hospitalization will be summarized for patients who are alive. A p-value (Dianne 1999) will be presented to compare NEOD001 and Placebo on all-cause mortality and frequency of cardiac hospitalization.

8.7.2. Analyses of Each Component of the Primary Endpoint

In order to assess the contribution of each component of the primary endpoint, the primary analyses will be repeated for each component of the primary endpoint.

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

Time (months) to all-cause mortality will be calculated as: $(\text{date of death} - \text{the date of first study drug infusion} + 1) / 30.4375$. All adjudicated deaths will be included in analyses. Subjects who do not die will be censored at the date last known to be alive.

8.7.2.2. Time to Cardiac Hospitalization

Time (months) to cardiac hospitalization, as adjudicated by the CEC, will be calculated as: $(\text{date of first cardiac hospitalization admission} - \text{the date of first study drug infusion} + 1) / 30.4375$. Only adjudicated cardiac hospitalizations occurring ≥ 91 days after a subject's first infusion of study drug will be included. Sensitivity analyses are specified in [Section 8.10.6.3](#).

The following censoring rules will apply:

1. If a subject withdraws from the study and is no longer being followed for hospitalization information, the subject will be censored at their last known date of contact at which both vital status and hospitalization information is available.
2. If a subject dies while on study and does not have a prior cardiac hospitalization, the subject will be censored at date of death (regardless of cause).
3. If a subject completes the study and never has a confirmed CEC cardiac hospitalization that occurred on or after study day 91, then the subject will be censored at the last assessment (visit or phone call).
4. If a subject completes the study and experiences a confirmed CEC cardiac hospitalization on or after study day 1 but prior to study day 91, has no other confirmed CEC cardiac hospitalizations on or after study day 91, then the subject will be censored at their last assessment (visit or phone call).

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

The estimand for the SF-36v2 PCS is the mean difference in SF-36v2 PCS change from baseline between treatment groups at Month 9 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 at Month 9 in SF-36v2 PCS score is equal between placebo and NEOD001.
- H_1 : The mean change from baseline at Month 9 in SF-36v2 PCS score is different between placebo and NEOD001.

For the primary analysis of the SF-36v2 PCS, subjects who are missing Month 9 due to death, will be imputed as the worst Month 9 value in the total population. Subjects who are missing Month 9 for reasons other than death, will be imputed using MI methodology using the total study sample.

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 \times 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 Month 9 visit.

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.

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 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.

8.8.2. 6MWT Distance

The estimand for the 6MWT is the median difference in 6MWT distance change from baseline between treatment groups at Month 9 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 at Month 9 in 6MWT distance (meters) is equal between placebo and NEOD001.
- H_1 : The distribution of change from baseline at Month 9 in 6MWT distance (meters) 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 Month 9 where time to death is used to rank earlier deaths worse than later deaths,
2. Subjects who are missing Month 9 6MWT and vital status is unknown at Month 9 will be ranked according to time on study drug from worst (shortest time) to best (longest time)
3. Subjects who are missing Month 9 6MWT because they are hospitalized for cardiac reasons (as adjudicated by the CEC) where duration of hospitalization is used to rank longer length of stay (LOS) worse than shorter LOS
4. Subjects who are missing Month 9 6MWT because the subject physically cannot perform the test, due to physical incapacity, non-cardiac hospitalization, or other reason, will be ranked according to time on study drug from worst (shortest time) to best (longest time)
5. Subjects who are missing Month 9 6MWT, known to be alive, but it is unknown if they are missing due to a cardiac hospitalization, will be ranked according to time on study drug from worst (shortest time) to best (longest time)
6. Subjects who are missing Month 9 6MWT, known to be alive, and are known not to be in the hospital, will be ranked according to time on study drug from worst (shortest time) to best (longest time)
7. Completed subject's values will be ranked from worst (lowest distance) to best (highest distance) performance

Descriptive statistics for 6MWT distance, change from baseline, and percent change from baseline will be presented by visit for each treatment group. The change and percent change from baseline at Month 9 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.

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 NEOD001 and placebo, the StdErr of the difference, and 95% CI of the difference will be presented. 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. If above assumptions are violated and inhibit the interpretation of the results, appropriate data transformations or non-parametric analyses will be performed.

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

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

8.8.3. NT-proBNP (Cardiac) Best Response

The key secondary estimand for NT-proBNP (cardiac) best response is the difference in cardiac best response rate between treatment groups through Month 9 in all randomized subjects with AL amyloidosis who received any amount of drug.

The key secondary efficacy endpoint of cardiac best response is assessed by cardiac best response from baseline through Month 9. All visits after the first infusion of study drug up to and through the Month 9 visit will be included. The key secondary efficacy analysis will test the following hypothesis:

- H_0 : The percentage of cardiac best responders from baseline through Month 9 is equal between placebo and NEOD001.
- H_1 : The percentage of cardiac best responders from baseline through Month 9 is different between placebo and NEOD001.

The primary analysis of cardiac best response will consider subjects with missing values through Month 9 as a non-responder.

The key secondary efficacy analyses will compare placebo and NEOD001 on the percentage of cardiac best responders from baseline through Month 9, using a CMH test stratified by the randomization stratification factors. The number and percentage, with associated two-sided 95% confidence intervals (CI), of subjects in each category of best response (response, nonresponse) will be presented by treatment group. The proportional treatment difference with associated two-sided 95% CI will be presented.

The CMH test assumes the effect of the treatment is homogeneous in all strata. The Breslow-Day test will be used to test this assumption.

In addition, an analysis using a logistic regression 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 two-sided 95% CI of the odds ratio will be presented. An odds ratio greater than 1 favors the NEOD001 treatment group.

8.9. Additional Secondary Efficacy Analyses

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 Month 9 in 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 from baseline through Month 9 is equal between placebo and NEOD001.
- H_1 : The percentage of renal best response from baseline through Month 9 is different between placebo and NEOD001.

All visits after the first dose of study drug up to and through the Month 9 visit will be included. The primary analysis of best response will consider subjects with missing values through Month 9 as a non-responder. Best renal response will be analyzed in the same manner described in [Section 8.8.3](#).

If an assessment qualifies as both response and progression ([Section 2.3.3.1](#)), then assessments will be counted as progression for the primary analysis.

8.9.2. Peripheral Neuropathy Evaluable Subjects: NIS-LL Score

The estimand for peripheral neurological function is the mean difference in NIS-LL total score change from baseline between treatment groups at Month 9 in 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 at Month 9 in NIS-LL total score is equal between placebo and NEOD001.
- H_1 : The mean change from baseline at Month 9 in NIS-LL total score is different between placebo and NEOD001.

For the primary analysis of the NIS-LL total score, subjects who are missing Month 9 NIS-LL score will have their score imputed as the worst Month 9 value in peripheral neuropathy evaluable subjects. Subjects who are missing Month 9 for reasons other than death, will be imputed using MI methodology using peripheral neuropathy evaluable subjects.

The change from baseline in NIS-LL total score will be analyzed in the same manner described above in [Section 8.8.1](#).

8.10. Exploratory Efficacy Analyses

8.10.1. Cardiac Endpoint Analyses

Cardiac (NT-proBNP) best response (response, nonresponse) will be determined for different time intervals, such as through Month 3 visit, Month 6 visit, and Month 12 visit, and over course of study. Best response at each of these time points (in addition to Month 9 as described above

for the key secondary endpoint) and response (response, nonresponse) at each visit may be analyzed using the CMH test and logistic regression analysis methods described in [Section 8.8.3](#).

Cardiac best response and response as 3 categories (response, stable disease, and progression) may be analyzed in the same manner described above, except ordinal logistic regression will be used to analyze the 3 category response.

Observed NT-proBNP results, change from baseline, and percentage change from baseline may be analyzed in the same manner described in [Section 8.8.1](#).

An analysis of the rate of decrease (ie, slope) of NT-proBNP may be performed for different time intervals, such as through Month 9 visit, and Month 12 visit, and over course of study, using a general linear mixed effects model to compare 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 \times 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.

8.10.2. 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](#).

Descriptive statistics will be presented for observed values, changes from baseline and percent change from baseline at each post-baseline time point.

The change from baseline to Month 9 will 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 may be analyzed in the same manner described in [Section 8.8.3](#).

8.10.3. Quality of Life Endpoint Analyses

8.10.3.1. SF-36v2 PCS Score

In addition to the key secondary endpoint, the SF-36v2 PCS, MCS scores and the eight subscales to all visits will be analyzed in the same manner described in [Section 8.8.1](#) using observed value.

The rate of increase (i.e. slopes) may be analyzed in the same manner described in [Section 8.10.1](#).

8.10.4. Renal Endpoint Analyses

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

8.10.4.1. Renal Response

In addition to the secondary endpoint, for the Renal Evaluable Population, the renal best response may be determined for different time intervals, including through Month 3 visit, Month 6 visit, and Month 12 visit, and over course of study. Best response at each of these time points (in addition to Month 9 as described above for the secondary endpoint) may be analyzed in the same manner described in [Section 8.9.1](#).

Renal response at each visit may be analyzed in the same manner described in [Section 8.9.1](#).

8.10.4.2. Creatinine, Proteinuria, and eGFR

Proteinuria, measured by 24-hour urine protein excretion, and estimated glomerular filtration rate (eGFR) to all visits may be analyzed in the same manner described in [Section 8.8.1](#) using observed value.

8.10.5. Peripheral Neuropathy Endpoint Analyses

In addition to the secondary endpoint, for subjects in the Peripheral Neuropathy Evaluable Population, the NIS-LL total scores and the 3 deficit component scores (sensory function, reflexes, muscle strength) to all visits may be analyzed in the same manner described in [Section 8.9.2](#) using observed value.

8.10.6. Additional Time-to-Event Analyses

The following additional time-to event endpoints may be analyzed in the same manner described in [Section 8.7](#) for the primary endpoint.

8.10.6.1. Time to Cardiac Mortality or Cardiac Hospitalization

Time (months) to cardiac mortality or cardiac hospitalization, as adjudicated by the CEC, will be calculated as: (earliest date of cardiac hospitalization /cardiac death - the date of first study drug infusion + 1) / 30.4375. Only adjudicated events will be included in these analyses.

For cardiac mortality, all deaths adjudicated as “cardiac”, occurring after the first infusion of study drug will be included. Cardiac hospitalizations as defined for the primary endpoint will be used in this analysis.

The following censoring rules will apply:

- Subjects who die for any reason other than cardiac, will be censored at their date of death.
- Subjects who complete the study and experience a cardiac hospitalization on or after study day 1 but prior to study day 91, have no other cardiac hospitalizations on or after study day 91, and are not known to have died from a cardiac cause, will be censored at their last assessment (visit or phone call) known to be alive.
- Subjects who complete the study and do not experience any cardiac hospitalization and are not known to have died from cardiac cause will be censored at their last assessment (visit or phone call) known to be alive.
- Subjects who withdraw from the study or are lost to follow-up prior to experiencing a cardiac hospitalization on or after study day 91 or death will be censored at their last assessment (visit or phone call) where both vital status and hospitalization information was available.

In addition, the following sensitivity analyses may be conducted in the same manner:

- 1) Removing any time constraints on cardiac hospitalizations, i.e., including all cardiac hospitalizations regardless of when they occur.
- 2) Including only cardiac hospitalizations within the first 90 days after first study drug dosing.

8.10.6.2. Time to Cardiac Mortality

Time (months) to cardiac mortality, as adjudicated by the CEC, will be calculated as: $(\text{date of cardiac death} - \text{the date of first study drug infusion} + 1) / 30.4375$. Only adjudicated events will be included in analyses.

For cardiac mortality, all deaths adjudicated as “cardiac”, occurring after the first infusion of study drug will be included. Subjects who do not die will be censored at the date of last contact. If a subject dies for any reason other than cardiac, then the subject will be censored at their date of death.

8.10.6.3. Time to Cardiac Hospitalization

The following sensitivity analyses may be conducted in the same manner as specified for the primary endpoint ([Section 8.7](#)):

- 1) Removing any time constraints on cardiac hospitalizations, i.e., including all cardiac hospitalizations regardless of when they occur.
- 2) Including only cardiac hospitalizations within the first 90 days after first study drug dosing.

8.10.6.4. Time to Derived Organ Progression

The following time-to progression endpoints may be analyzed in the same manner described in [Section 8.7](#). 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 NT-proBNP progression calculated as: (date first assessed with progression (Section 2.3.2.3) - the date of first study drug infusion + 1) / 30.4375. Subjects who do not progress 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 2.3.3.1) - 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.

8.10.6.5. Time to First Derived Organ Response

The following time-to response endpoints may be analyzed in the same manner described in Section 8.7.

- Time (months) to first NT-proBNP response calculated as: (date first assessed with response (Section 2.3.2.3) - 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 2.3.3.1) - the date of first study drug infusion + 1) / 30.4375. Subjects who do not respond will be censored at the date of last proteinuria (measured by 24-hour urine total protein excretion), assessment.

8.10.7. Other Efficacy Endpoints

Below efficacy data will be presented in by-subject data listings:

- Echocardiogram Cardiac Parameters: Left ventricular ejection fraction (LVEF), Intraventricular septal at end diastole (LVSD), Left posterior wall at end diastole (LPWd)
- Cardiac Biomarker: Troponin T ($\mu\text{g/L}$)
- Kansas City Cardiomyopathy Questionnaire (KCCQ)
- Visual Analog Scale – Pain Intensity (VASPI)
- Liver size
- Eastern Cooperative Oncology Group (ECOG) performance, New York Heart Association (NYHA) Class, Mayo Clinic Stage, and Renal Stage
- Free light chains (sFLCs), serum and 24-hour urine protein electrophoresis (PEP), and serum and urine immunofixation electrophoresis (IFE)
- Disease-related symptoms
- Pharmacokinetics (PK)

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

9.1.1. Study Drug

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 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 summaries will include:

- The number of subjects exposed to NEOD001, the total PEY, and duration of exposure will be summarized using descriptive statistics.
- 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. The number of infusions received will be summarized using descriptive statistics. In addition, cumulative number of subjects receiving infusions at each visit will be presented.

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

9.1.2. Premedication

All subjects will be premedicated for each dose of study drug with 25 mg diphenhydramine (or an equivalent dose of a H1 antihistamine) and 650 mg acetaminophen (or an equivalent paracetamol dose) within 30-90 minutes prior to study drug administration. Pretreatment medications will be mapped to Anatomical Therapeutic Chemical (ATC) class and Preferred Name using the WHO Drug Dictionary, B2 Enhanced December 2015 and listed.

9.1.3. Standard of Care Chemotherapy

All subjects will receive concomitant standard of care chemotherapy, which must include bortezomib administered subcutaneously on a weekly basis for the initial, first-line chemotherapy regimen. Subsequent chemotherapy regimens may be prescribed as per standard of care at the Investigator's discretion (see protocol Section 7.1.5). Chemotherapy regimens including line of therapy, medication, date prescribed, and planned number of cycles will be listed.

9.2. Adverse Events

Verbatim terms on eCRFs will be mapped to PT and SOC 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 up to the ETD / EOS Visit or 28 days after date of last dose. 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.

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 missing or marked as CTCAE grade 3, 4, or 5)
- Related AEs (this is a subset of the AEs where relationship marked as “Related” or relationship is missing)
- AEs leading to Study Drug Withdrawal (this is a subset of the AEs where Action Taken with Study Treatment is checked as “Drug Discontinued”)
- 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 treatment

9.2.1. Types of Incidence Rates

9.2.1.1. Crude Incidence Rates

The crude rate for a particular AE is defined as the number of subjects with the AE divided by the number of subjects exposed to the study drug. All crude incidence tables will be repeated only for MedDRA PT, excluding MedDRA SOC.

9.2.1.2. Exposure-Adjusted Incidence Rates

Crude AE incidence will be corrected for differences in study drug exposure by using person-time in the denominator to calculate incidence rates. Adjusted incidence per 100 PEY is the number of subjects with an event for whom person-time is available divided by the total PEY for each treatment group and multiplied by 100. Each subject’s PEY will be calculated as the last infusion date minus the first infusion date plus 1 divided by 365.25 days/year. One PEY is the equivalent of one subject exposed to study drug for one 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.

9.2.2. Overall Summary of Adverse Events

An overall summary of crude AE incidences will be presented including the number and percent of subjects with at least one of:

- 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 \geq Grade 3
- Treatment-related TEAE leading to death
- TEAE leading to interruption of study treatment
- 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
- TEAE leading to study drug withdrawal

9.2.3. Treatment-Emergent Adverse Events

The crude incidences of TEAEs will be summarized by treatment group. In addition, the exposure-adjusted incidences of TEAEs will be summarized. The following summaries will be presented:

- Subject incidence of TEAEs by MedDRA SOC and PT
- Subject incidence of TEAEs by MedDRA SOC and PT occurring in $\geq 5\%$ of NEOD001 subjects with greater frequency than placebo
- Subject incidence of TEAEs by MedDRA SOC and PT occurring in $\geq 10\%$ of NEOD001 subjects with greater frequency than placebo
- Subject incidence of TEAEs by MedDRA SOC and PT occurring with greater frequency than placebo

9.2.4. Serious Adverse Events and Deaths

The crude incidences of serious TEAEs and deaths will be summarized by treatment group. In addition, the exposure-adjusted incidences of serious TEAEs and deaths will be summarized. The following summaries will be presented:

- Subject incidence of serious TEAEs by MedDRA SOC and PT
- Subject incidence of serious related TEAEs by MedDRA SOC and PT

9.2.5. Adverse Events Leading to Study Drug Withdrawal

AEs leading to study drug withdrawal are those AEs where Action Taken with Study Treatment is checked as “Drug Discontinued”. The crude incidences of AEs leading to study drug withdrawal will be summarized by treatment group. The following summaries will be presented:

- Subject incidence of TEAEs leading to study drug withdrawal by MedDRA SOC and PT.

9.2.6. Adverse Events of Special Interest

9.2.6.1. Infusion Associated Adverse Events

The crude incidence of infusion associated TEAEs by MedDRA SOC and PT will be summarized by treatment group. This is a subset of the AEs where the question “Was the event an infusion-associated adverse event?” is checked “Yes”. In addition, the exposure-adjusted incidences of TEAEs will be summarized.

If applicable, the crude incidence anaphylactic reaction, defined as the broad algorithmic standardized MedDRA query (SMQ) of “Anaphylactic reaction” will be summarized by treatment group.

9.3. FACT-GOG NTX

The Functional Assessment of Cancer Therapy – Gynecologic Oncology Group Neurotoxicity Subscale (FACT-GOG NTX) assesses subject-reported neurotoxicity symptoms and concerns that evaluate Activities of Daily Living (ADL) with an 11-item scale with a range of possible scores of 0 to 44. The FACT-GOG NTX score to all visits will be listed.

9.4. Clinical Laboratory Evaluations

Laboratory parameters include serum chemistry, hematology and coagulation.

All clinical laboratory data will be presented in by-subject data listings using standard international (SI) system of units. In addition, separate listings will be presented for any subject with a post-baseline CTCAE grade 3 or 4 laboratory value, or with a post-baseline value outside the normal range where CTCAE criteria cannot be applied to an analyte.

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

- INR Upper Limit of Normal (ULN) = 1.1
- eGFR LLN = 90 mL/min/1.73m²

9.4.1. Pregnancy Testing and Urinalysis Dipstick

All pregnancy test results and urinalysis dipstick results will be provided in a by-subject data listing.

9.5. Weight and BMI

Weight (kg), BMI (kg/m^2), and mBMI ($\text{kg}/\text{m}^2 \text{ g}/\text{L}$), defined as a subject's weight (kg) \times subjects squared height (meters) \times serum albumin (g/L), will be provided in a by-subject data listing.

9.6. 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.

9.7. Electrocardiograms

ECGs measurements will be made in triplicate, 5 to 10 minutes apart and assessed by a central reader. 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].

Overall interpretation results for ECGs and the investigator interpretation results are collected as normal, abnormal not clinically significant, and abnormal clinically significant.

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

9.8. Physical Examination

Physical examination findings will be included in a data listing.

9.9. Immunogenicity Analyses

Immunogenicity of NEOD001 will be assessed by anti-NEOD001 antibody levels. Serum anti-NEOD001 antibody levels will be listed.

10. CHANGES TO PROTOCOL PLANNED ANALYSES

10.1. Changes from Protocol Planned Analyses

The following describes the changes to any protocol planned analyses:

- 1) The protocol describes a Modified Intent-to-Treat (MITT) Population, which has been updated to the Intent-to-Treat (ITT) Population within this analysis plan.
- 2) The Safety Population is described in the protocol as only including randomized subjects, however, should a subject be dosed prior to randomization or without randomization, all subjects treated regardless of randomization will be included in the Safety Population. In addition, subjects will be analyzed as randomized. For any subject who receives a treatment different than that to which they were randomized, their AEs will be listed separately.
- 3) An Efficacy Evaluable Population was added.
- 4) The interim futility analysis was removed.

- 5) For the primary endpoint, cardiac hospitalizations occurring ≥ 91 days after a subject's first infusion of study drug through the last subject's last visit (LSLV) will be included.
- 6) The first key secondary endpoint, NT-proBNP best response from baseline to Month 9 was moved to the third key secondary endpoint.
- 7) The secondary endpoints for population subsets have been changed to efficacy subset populations to evaluate the following additional secondary endpoints:
 - i. For renal evaluable subjects, renal best response from baseline through the Month 9 visit
 - ii. For peripheral neuropathy evaluable subjects, change from baseline at the Month 9 in the NIS-LL total score
 - iii. For hepatic evaluable subjects, hepatic best response from baseline through the Month 9 visit
- 8) Two previous secondary endpoints have been changed to exploratory endpoints to assess the utility of these endpoints in AL amyloidosis:
 - i. For subjects with painful peripheral neuropathy due to AL amyloidosis, change in the Visual Analog Scale – Pain Intensity (VASPI) score from baseline to Month 9 of treatment
 - ii. Change from baseline to Month 9 in the Kansas City Cardiomyopathy Questionnaire (KCCQ)
- 9) The following secondary endpoints, that are subsets of the primary endpoint, will be analyzed as components of the primary endpoint:
 - i. Time to cardiac hospitalization (occurring ≥ 91 days after a subject's first infusion of study drug administered)
 - ii. Time to all-cause mortality
- 10) The following secondary endpoint will be analyzed as exploratory time-to-event endpoint:
 - i. Time to cardiac mortality or cardiac hospitalization (occurring ≥ 91 days after a subject's first infusion of study drug administered)
- 11) The protocol includes the following cardiac parameters from echocardiogram: left ventricular strain, atrial size, and atrial function. The following cardiac parameters were collected and will be summarized: LVEF = Left ventricular ejection fraction, IVSd = Intraventricular septal at end diastole, and LPWd = Left posterior wall at end diastole.
- 12) Additional exploratory endpoints and analyses have been included.
- 13) Subgroup analyses for ethnicity were removed.

10.2. Changes Due to Discontinuation of the NEOD001 Program

Based on the results from a separate Phase 2b PRONTO study (NEOD001-201) in the same indication, which did not meet its primary or secondary endpoints, the DMC was requested to

review an unplanned interim efficacy and futility analysis of the ongoing VITAL study (NEOD001-CL002). The unplanned interim efficacy and futility analysis was conducted using a Lan-DeMets spending function with non-binding futility and Pocock monitoring (stopping) boundaries based on 103 adjudicated events. The analysis needed to yield a HR of less than 0.664 for efficacy and greater than 0.739 for futility. The interim analysis HR was 0.84, leading the DMC to recommend the discontinuation of the VITAL study for futility. It was therefore decided to discontinue all development of NEOD001, including the VITAL study as well as the open label extension studies.

Due to the discontinuation of the NEOD001 program, the following changes were made to any protocol planned analyses:

- 1) The Efficacy Evaluable Population was removed.
- 2) All subgroup analyses were removed.
- 3) Hepatic related analyses were removed.
- 4) Most exploratory endpoints and analyses were removed.
- 5) Safety analyses were removed except the summary tables described in Section 9.2 for TEAEs and SAEs

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12. APPENDICES

APPENDIX 1: ORGAN RESPONSE AND PROGRESSION CRITERIA

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

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

1 Modified from Table 2 in [Comenzo 2012](#).

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

3 [Palladini 2014](#).

4 [Coelho 2012](#).

APPENDIX 2: STRATIFICATION DETAILS

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

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

Source: [Kumar 2012](#).

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

eGFR = estimated glomerular filtration rate.

Source: [Palladini 2014](#).

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

Assessments	Months 3, 6, 9, 12 Day 1 (±5) ¹	Every Third Month After Month 12 ² (e.g., Months 15, 18, 21) Day 1 (±5)	Every 3 Months after Last Visit
SF-36v2 ³	X		
KCCQ ³	X		
FACT-GOG NTX ^{3,4}	Per Protocol 7.4 & Table 2		
Echocardiogram	Months 6 and 12 ⁵		
Liver Imaging (CT)	Months 6 and 12 ⁶		
12-lead Triplicate ECG ⁷	X		
Symptom-Directed PE ⁸	X		
ECOG PS & NYHA Class	X		
NIS-LL ⁹	Per Protocol 7.4 & Table 2		
VASPI ¹⁰	Per Protocol 7.4 & Table 2		
Local Laboratory			
Serum Pregnancy (WOCBP)	X ¹¹		
Central Laboratory¹²			
Hematology & Chemistry	X		
Amylase	X		
Coagulation – PT/INR, PTT, & Indices ¹³	X		
Complements C ₃ , C ₄	X		
Troponin T	X		
NT-proBNP	X		
Serum Free Light Chains (sFLCs)	X		
Serum IFE/PEP	X ¹⁴		
Urinalysis	X		
Urine Sample for Quantitative/Renal Biomarkers ¹⁵	X		
24-hour Urine Collection for:			
Urine Protein Excretion ¹⁶	Months 3 and 9		
Urine IFE/PEP ¹⁶	Months 3 and 9 ¹⁷		
6-Minute Walk Test (6MWT)	X	X ¹⁸	
Bioanalytical Laboratory			
Anti-NEOD001 Antibody Sample ¹⁹	X		
Vital Signs	X ²⁰	X ¹⁸	
Adverse Event Assessment	X	X ¹⁸	
Concomitant Medications	X	X ¹⁸	
Health Status & Hospitalizations		X ¹⁸	
Vital Status Phone Call			X ²¹

BP = blood pressure; CT = computed tomography; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; ETD = Early Treatment Discontinuation; FACT-GOG NTX = Functional Assessment of Cancer Therapy – Gynecologic Oncology Group Neurotoxicity Subscale; HR = heart rate; IFE = immunofixation electrophoresis; KCCQ = Kansas

City Cardiomyopathy Questionnaire; NGAL = neutrophil gelatinase-associated lipocalin; NIS-LL = Neuropathy Impairment Score – Lower Limbs; NT-proBNP = N-terminal pro B-type natriuretic peptide; NYHA = New York Heart Association; PE = physical exam; PEP = protein electrophoresis; RBP = retinol-binding protein; RR = respiratory rate; 6MWT = 6-minute walk test; SF-36v2 = SF-36v2 Health Survey; VASPI = Visual Analog Scale – Pain Intensity; WOCBP = women of childbearing potential.

1. If a subject discontinues study drug prior to the end of the study, but is willing to continue to participate in study visits, the subject should have an ETD Visit within 28-35 days after the last study drug administration (per protocol section 7.1.6) and then have assessments performed every third month (i.e., Months 3, 6, 9, and 12, or whatever remains of these visits). **The most important visit is the Month 9-Day 1 Visit, so if a subject is unwilling to continue visits every third month, every effort should be made for the subject to return and complete the Month 9-Day 1 Visit on schedule.** All visits after the ETD Visit should occur on schedule, that is, at the time when the visit would have occurred had the subject remained on study drug.
2. If subject is willing to return to the study site, otherwise, subjects will receive vital status phone calls per [Footnote 21](#).
3. Administer questionnaires in the following order prior to the performance of any other study assessments on the day they are administered: SF-36v2 ([Appendix 5](#)), KCCQ ([Appendix 6](#)), and FACT-GOG NTX ([Appendix 7](#)).
4. Administer the FACT-GOG NTX ([Appendix 7](#)).
5. Perform echocardiograms within 10 days prior to Day 1 of Months 6 and 12. To be eligible for the additional cardiac imaging analysis, the subject must have had a 4-chamber view, 2-dimensional echocardiogram with Doppler.
6. For subjects with liver involvement at Screening (*Exception*: not required in Germany), perform *scheduled* repeat CT imaging of the abdomen for liver measurement at Months 6 and 12 and *unscheduled* repeat CT imaging as needed per protocol Section 7.6.
7. ECG to be performed in triplicate.
8. Symptom-directed PE should be as clinically indicated and also include weight, and assessment of macroglossia, submandibular nodes/fullness, adenopathy, ecchymoses, liver/spleen size (palpable +/-), ascites (+/-), and edema (which should be quantified on a scale of 0-4+).
9. Administer NIS-LL ([Appendix 8](#)).
10. Administer VASPI ([Appendix 9](#)).
11. Obtain local laboratory serum pregnancy test 90 (± 5) days after the last study drug administration.
12. Collect central laboratory samples before 6MWT, if being performed on the same day.
13. Collect citrated plasma samples at each time point; per [Appendix 10](#), samples will be frozen for potential analysis of coagulation indices at a later date.
14. Perform serum IFE/PEP at each visit. If a subject's first on-study hematologic complete response was assessed at the previous visit, perform serum IFE/PEP (and 24-hour urine IFE/PEP) at least 28 days after the initial assessment of response to confirm response.
15. Urine sample will be collected per protocol Section 7.3 and frozen for potential analysis of quantitative/renal biomarkers (i.e., urine albumin/creatinine ratio, urine NGAL, and urine RBP) at a later date.
16. The 24-hour urine protein excretion and 24-hour urine IFE/PEP tests will be performed using the same 24-hour urine collection sample, when required at the same visit.
17. If a subject's first on-study hematologic complete response was assessed at the previous visit, perform 24-hour urine IFE/PEP (and serum IFE/PEP) at least 28 days after the initial assessment of response to confirm response. Repeat every odd-numbered month (i.e., Months 3 and 9 to correspond with 24-hour urine protein excretion collection) to assess for continuing response or progression. If the initial response confirmation needs to occur on an even-numbered month, perform an additional 24-hour urine collection.
18. After Month 12, if the subject is willing to return to the study site, perform or collect the following every third month (e.g., Months 15, 18, 21): 6MWT (which includes BP and HR pre- and post-6MWT administration), adverse events, concomitant medications, overall health status, as well as details of any hospitalizations.
19. Collect if an earlier sample established the presence of anti-NEOD001 antibodies or if a subject discontinued treatment due to a suspected immunologic reaction.
20. Collect BP, HR, RR, and temperature any time during visit.
21. Conduct a vital status phone call per protocol Section 7.1.8 approximately 3 months after the subject's last visit and approximately every 3 months thereafter.

APPENDIX 4: HEMATOLOGIC RESPONSE AND PROGRESSION CRITERIA

Response Subcategory	Response Criteria
Complete Response (CR)	<ul style="list-style-type: none"> • Normalization of free light chain levels and ratio, negative serum and urine immunofixation
Very Good Partial Response (VGPR)*	<ul style="list-style-type: none"> • Reduction in the dFLC to <40 mg/L (<4.0 mg/dL)
Partial Response (PR)*	<ul style="list-style-type: none"> • A greater than 50% reduction in the dFLC
No Response (NR)	<ul style="list-style-type: none"> • Less than a PR
Progression	<ul style="list-style-type: none"> • From CR: any detectable monoclonal protein or abnormal free light chain ratio (light chain must double)
	<ul style="list-style-type: none"> • From PR, 50% increase in serum M protein to > 0.5 g/dL or 50% increase in urine M protein to > 200 mg/day (a visible peak must be present) or free light chain increase of 50% to > 10 mg/dL (100 mg/L)

dFLC = difference between involved and uninvolved free light chains.

*Only applicable for subjects with dFLC > 50 mg/L (5 mg/dL) at study entry.

Source: [Comenzo 2012](#).

APPENDIX 5: SF-36V2 HEALTH SURVEY

<p>SF-36v2® Health Survey © 1992, 1996, 2000, 2010 Medical Outcomes Trust and QualityMetric Incorporated.</p> <p>All Rights Reserved.</p> <p>SF-36® is a registered trademark of Medical Outcomes Trust. (SF-36v2® Health Survey Standard, United States (English))</p>
<p>Your Health and Well-Being</p> <p>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!</p> <p>For each of the following questions, please select the one box that best describes your answer.</p>
<p>In general, would you say your health is:</p> <p>Excellent Very good Good Fair Poor</p>
<p><u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?</p> <p>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</p>

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

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

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 6: 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.

- 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	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Showering/Bathing	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Walking 1 block on level ground	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Doing yardwork, housework or carrying groceries	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Climbing a flight of stairs without stopping	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Hurrying or jogging (as if to catch a bus)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

- 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
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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

It has <i>extremely</i> limited my enjoyment of life	It has limited my enjoyment of life <i>quite a bit</i>	It has <i>moderately</i> limited my enjoyment of life	It has <i>slightly</i> limited my enjoyment of life	It has <i>not limited</i> my enjoyment of life at all
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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 I felt that way I occasionally I rarely felt that I never felt that
 all of the time most of the time felt that way way 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	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Working or doing household chores	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Visiting family or friends out of your home	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Intimate relationships with loved ones	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

APPENDIX 7: FUNCTIONAL ASSESSMENT OF CANCER THERAPY – GYNECOLOGIC ONCOLOGY GROUP NEUROTOXICITY SUBSCALE (FACT-GOG NTX)

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

<u>ADDITIONAL CONCERNS</u>		Not at all	A little bit	Some-what	Quite a bit	Very much
NTX 1	I have numbness or tingling in my hands.....	0	1	2	3	4
NTX 2	I have numbness or tingling in my feet.....	0	1	2	3	4
NTX 3	I feel discomfort in my hands.....	0	1	2	3	4
NTX 4	I feel discomfort in my feet.....	0	1	2	3	4
NTX 5	I have joint pain or muscle cramps	0	1	2	3	4
HII2	I feel weak all over	0	1	2	3	4
NTX 6	I have trouble hearing.....	0	1	2	3	4
NTX 7	I get a ringing or buzzing in my ears.....	0	1	2	3	4
NTX 8	I have trouble buttoning buttons	0	1	2	3	4
NTX 9	I have trouble feeling the shape of small objects when they are in my hand	0	1	2	3	4
An6	I have trouble walking.....	0	1	2	3	4

Instructions for Healthcare Professionals:

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

NCI-CTCAE for Peripheral Neuropathy and Neuropathic Pain

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

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

APPENDIX 8: NEUROPATHY IMPAIRMENT SCALE – LOWER LIMBS (NIS-LL)



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

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

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

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

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

Performed by (Print Name): _____

 Signature Date: ____ / ____ / ____
 dd mmm yyyy



APPENDIX 9: VISUAL ANALOG SCALE – PAIN INTENSITY (VASPI)

prothena

VISUAL ANALOG SCALE – PAIN INTENSITY

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

●—————●

No Pain **Worst Imaginable Pain**

SAMPLE

APPENDIX 10: COAGULATION INDICES

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

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 11: EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG)
PERFORMANCE STATUS**

Grade	Eastern Cooperative Oncology Group
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Source: [Oken 1982](#).

APPENDIX 12: NEW YORK HEART ASSOCIATION (NYHA) FUNCTIONAL CLASSIFICATION

NYHA Class	Symptoms
I	Cardiac disease, but 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 subjects.

NYHA = New York Heart Association.
Source: [American Heart Association 2015](#).