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Statistical Analysis Plan for Protocol NEOD001-OLE251

Open-label Extension Study to Evaluate the Long-term Safety and Tolerability of NEOD001 in Subjects with Light Chain (AL) Amyloidosis

Investigational Product:	NEOD001
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Sponsor:	Prothena Therapeutics Limited Adelphi Plaza, Upper George's Street Dún Laoghaire, Co. Dublin A96 T927, Ireland
Sponsor Representative:	Prothena Biosciences Inc 331 Oyster Point Boulevard South San Francisco, CA 94080 USA
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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Term
6MWT	6-minute walk test
AE	adverse event
AL	amyloid light chain
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
BP	blood pressure
C	Celsius
CI	confidence interval
cm	centimeter
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DOB	date of birth
DOIC	date of informed consent
eCRF	electronic case report form
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eGFR	estimated glomerular filtration rate
EOI	end of infusion
EOS	end of study
FLC	free light chain
g/24 hours	grams per day (24 hours)
g	gram
HR	heart rate
ICH	International Council for Harmonisation
IFE	immunofixation electrophoresis
in	inches
IQR	interquartile range
IV	intravenous

Abbreviation	Term
kg	kilogram
L	liter
lb	pounds
m	meter
m^2	meters squared
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mg/dL	milligrams per deciliter
min	minimum
mL	milliliters
mmHg	millimeters of mercury
ng	nanogram
ng/L	nanograms per liter
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
PE	physical examination
PEP	protein electrophoresis
PK	pharmacokinetic
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
RR	respiratory rate or time between 2 consecutive R waves
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SF-36v2	Short Form-36 version 2 Health Survey

Abbreviation	Term
sFLC	serum free light chains
SI	Système International unit
SOC	system organ class
TEAE	treatment-emergent adverse event
temp	temperature
ULN	upper limit of normal
vs	versus
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-OLE251 (Open-label Extension [OLE] Study to Evaluate the Long-term Safety and Efficacy of NEOD001 in Subjects with Light Chain [AL] Amyloidosis Who were previously enrolled in Study NEOD001-201 (PRONTO)). The purpose of this plan is to provide specific guidelines from which the analyses will proceed. Any deviations from this statistical analysis plan (SAP) will be documented in the clinical study report (CSR).

2. INFORMATION FROM THE STUDY PROTOCOL

2.1. Study Objective

The objective of this study is to evaluate the long-term safety and efficacy of NEOD001 in subjects with AL amyloidosis who completed Study NEOD001-201 (PRONTO).

Safety and efficacy endpoints are detailed in Section 8 and Section 9.

2.2. Study Design

2.2.1. Overall Study Design

This is a global, multicenter, Phase 2b, open-label extension study of subjects with AL amyloidosis who completed Study NEOD001-201. Subjects in this study may receive concomitant chemotherapy.

Subject screening will occur during the 28 days prior to the first administration of study drug (i.e., Month 1-Day 1 Visit), which may overlap with the last visit in Study NEOD001-201. If all eligibility requirements are met, the subject will be enrolled and Screening assessments will be completed. Screening assessments are listed in Table 1 .

Study visits will occur every 28 days based on scheduling from Month 1-Day 1. A ±5-day window is allowed for visits starting after Month 1. Subjects may receive up to 36 infusions of study drug. Subjects who discontinue study drug before the End of Study (EOS) Visit should have an Early Treatment Discontinuation (ETD) Visit 30 (±5) days after their final administration of study drug.

2.2.2. Study Drug

Study drug consists of NEOD001. The NEOD001 dose is 24 mg/kg (not to exceed 2500 mg) and will be administered once every 28 (a ±5-day window is allowed for visits starting after Month 1) over 60 (±10) minutes unless a longer infusion duration was established for the individual subject in Study NEOD001-201. The length of the infusion may be extended over a longer period of time when it is clinically indicated. 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 study drug solution into the IV bag, such that the total IV bag volume will be 250 mL.

Please refer to the protocol for complete product details.

2.2.3. Study Procedures

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

Table 1: Schedule of Study Procedures

	Assessment or Procedure	Screening[1] Days -28 through -1: <60 days since last visit in Study NEOD001-201	Screening[1] Days -28 through -1: ≥60 days since last visit in Study NEOD001-201	Treatment[2] Monthly Day 1 (±5 days)[3]	Termination EOS/ETD[4]
	Written Informed Consent	X	X		
	Eligibility Review	X	X		
Clinical	Medical History[5]	X	X		
Clinical	Prior/Concomitant Medications/Therapy[6]	X	X	X	X
Clinical	Adverse Event Assessment[7]	X	X	X	X
Clinical	Physical Exam[8]	X	X	X	X
Clinical	Vital Signs[9]	X	X	X	X
Clinical	ECOG PS/NYHA Class[10]		X	Every 6 months	X
Clinical	NIS-LL[11]	X	X	Every 6 months	X
Clinical	VASPI[12]	X	X	Every 6 months	X
Clinical	SF-36v2[13]	X	X	Every 6 months	X
Clinical	KCCQ[14]	X	X	Every 6 months	X
Clinical	6MWT[15,16]	X, X[17]	X, X[17]	Every 6 months[18]	X
Clinical	ECG (12-lead triplicate)	X	X	Every 3 months[19]	X
Laboratory[20]	Hematology & Chemistry (including amylase and creatine kinase)[21]	X	X	X	X
Laboratory[20]	Coagulation – PT/INR, PTT	X	X	X	X
Laboratory[20]	Coagulation – other indices[22]			Months 1, 12	X
Laboratory[20]	Troponin T	X	X	X	X
Laboratory[20]	NT-proBNP[15]	X	X	X	X
Laboratory[20]	Pregnancy (WOCBP)[23]	X	X	X	X, X[24]
Laboratory[20]	sFLCs		X	Every 6 months	X
Laboratory[20]	Serum IFE & PEP[25]		X	Every 6 months	X
Laboratory[20]	Urinalysis – Dipstick[26]		X	Every 6 months	X
Laboratory[20]	24-hour Urine Collection:				
Laboratory[20]	Urine IFE & PEP[24]		X	Every 6 months	X
Laboratory[20]	Urine Protein Excretion		X	Every 6 months	X
	Serum NEOD001 Sample[27]			Every 6 months[28]	X
	Anti-NEOD001 Serum Sample[29]	X	X	Every 3 months[28]	X
	Study Drug Infusion[30]			X	
	Vital Status Phone Call				Every 3 months[31]

BP = blood pressure; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EOI = end of infusion; EOS = End of Study; ETD = Early Treatment Discontinuation; HR = heart rate; ICF = informed consent form; IFE = immunofixation electrophoresis; KCCQ = Kansas City Cardiomyopathy Questionnaire; nAb = neutralizing antibody; NIS-LL = Neuropathy Impairment Score – Lower Limbs; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; PEP = protein electrophoresis; PK = pharmacokinetic; PT/INR = prothrombin time/international normalized

ratio; PTT = partial thromboplastin time; RR = respiratory rate; 6MWT = 6-Minute Walk Test; SF-36v2 = Short Form-36 Health Survey version 2; VASPI = Visual Analog Scale – Pain Intensity; vWF = von Willebrand Factor; WOCBP = women of childbearing potential. Rescreening is allowed once per subject. Only repeat tests that did not meet eligibility requirements.

1. Individual test results that do not meet eligibility requirements may be repeated; full rescreening is allowed once per subject. Laboratory tests results from Study NEOD001-201 that were performed within 28 days of Month 1-Day 1 may be used for screening in this study.
2. See Protocol sections 6.1.2 and 6.4 for details regarding timing (e.g., pre- vs. postdose) and order of assessments, respectively.
3. Study visits will occur every 28 days based on scheduling from Month 1-Day 1. A ±5-day window is allowed for visits starting after Month 1. The predose assessments for each visit may be performed within the 3 days before the visit unless a different timeframe is specified in protocol section 6.1.
4. Conduct the EOS Visit 30 (±5) days after last administration of study drug. Subjects who discontinue study drug before the end of the study should have an ETD Visit 30 (±5) days after their final administration of study drug. The assessments shown for EOS/ETD should also be conducted for any unscheduled visit (i.e., a visit not specified by the protocol) as clinically indicated or if deemed necessary.
5. Medical History - Obtain medical history since the subject's last visit in Study NEOD001-201 (including all major hospitalizations and surgeries), as well as the subject's current medical status and therapy for AL amyloidosis.
6. Record all prior/concomitant medications taken or received by a subject within the 28 days prior to the Month 1-Day 1 Visit through the EOS/ETD Visit, and any changes to concomitant medications during the study.
7. Adverse events will be collected from the time that the ICF is signed through 30 days after the last dose of study drug or last study visit, whichever is later.
8. **Screening and EOS/ETD:** conduct a complete physical examination per protocol section 6.5.1.3. **All Other Visits:** conduct a directed physical examination per protocol section 6.5.1.3.
9. Vital signs (HR, BP, RR, and body temperature) - collect after the subject has been at rest for ≥5 minutes; within a visit, assess in the same position for all time points. **Month 1:** Within 30 minutes before start of dosing, at EOI (+5 minutes), 30 (±5) minutes after EOI, and 60 (±10) minutes after EOI. **All Other Months:** Within 30 minutes before start of dosing, at EOI (+5 minutes), and 60 (±10) minutes after EOI.
10. See Appendix 3 (ECOG) and Appendix 4 (NYHA).
11. See Appendix 5; NIS-LL is for all subjects who had peripheral neuropathy in Study NEOD001-201.
12. See Appendix 6; VASPI is for subjects who had painful peripheral neuropathy in Study NEOD001-201.
13. See Appendix 7 SF-36v2 should be administered before performing any other study assessments on the same calendar day it is administered.
14. See Appendix 8 ; administer KCCQ after the SF-36v2, but before conducting any other assessments on the same calendar day it is administered.
15. NT-proBNP should be drawn before conducting 6MWT if being performed on the same calendar day.
16. Collect blood pressure and heart rate pre- and post-6MWT administration.
17. Two pretreatment 6MWTs are required before the first administration of study drug, with a minimum of 4 days between the two tests. The first Screening 6MWT is required to be performed between Days -28 and -5, at least 4 days prior to the second Screening 6MWT, which should be performed within 2 days prior to Month 1-Day 1 (i.e., on Day -2 or Day -1).
18. The postbaseline 6MWTs may be administered on the same calendar day that study drug is administered as long as the NT-proBNP sample is drawn before conducting the 6MWT and the 6MWT is completed before initiation of the study drug infusion.
19. Perform ECGs centrally within 30 minutes before start of dosing and within 15 minutes after EOI.
20. All laboratory tests to be done centrally, unless otherwise noted. Please refer to Laboratory Manual for details. Laboratory tests conducted within 28 days of Month 1-Day 1 may be used for screening.
21. Hematology and chemistry per Appendix 9. Within 3 days before the first day of a new regimen of chemotherapy, conduct an unscheduled central laboratory collection (including hematology, chemistry, PT/INR.
22. Collect citrated plasma samples, which will be frozen for potential analysis of coagulation indices at a later date; see Appendix 10. **Month 1:** EOS/ETD results from Study NEOD001-201 will serve as baseline for this study. Collect sample for vWF activity and antigen assays before dosing on Month 1-Day 1 if they were not tested at EOS/ETD in Study NEOD001-201. **Month 12:** Subjects with defects identified at EOS/ETD in Study NEOD001-201: collect sample and test analytes that were abnormal. All other subjects: collect sample. **EOS/ETD:** Subjects with defects identified at Month 12: collect sample and test analytes that were abnormal. All other subjects: collect sample. **Unscheduled Samples:** collect sample in case of relevant serious adverse events. At any time, if defects are identified, additional analytes will be evaluated, as indicated.
23. Urine pregnancy tests (local) for WOCBP: **Screening:** within 28 days before Month 1-Day 1; **Monthly:** preinfusion; **EOS/ETD:** any time during visit. A positive urine pregnancy test (local laboratory) is to be confirmed with a serum pregnancy test (central laboratory).
24. 90 (±5) days after last study drug administration (any time during visit) perform urine pregnancy test (local) for WOCBP.
25. The serum and urine PEP must be conducted before the NEOD001 infusion, if being performed on the same calendar day.
26. Urinalysis dipstick per Appendix 9.
27. NEOD001 serum samples (for population PK analysis): **Every 6 months (±1 month):** within 2 hours before infusion and within 4 hours after EOI; **EOS/ETD:** any time during visit.
28. Collect additional samples as clinically indicated, such as when significant toxicity occurs per protocol section 5.4.2.

29. Anti-NEOD001 serum samples: **Screening:** any time during visit; **Every 3 months:** preinfusion; **EOS/ETD:** any time during visit.
30. Administer over 60 (±10) minutes unless a longer infusion duration was established for the individual subject in Study NEOD001-201 or during a previous infusion on this study. A minimum of 21 days between doses is required. Subjects should be closely monitored per protocol section 5.3 following completion of the study drug infusion. If chemotherapy is administered on the same day as NEOD001, it must be administered after the NEOD001 observation period.
31. Conduct vital status telephone call approximately 3 months after last study visit and approximately every 3 months thereafter for up to 5 years, death, or subject withdraws consent, whichever occurs first.

2.2.4. Definition of Baseline

2.2.4.1. PRONTO Baseline

The PRONTO Baseline for the 6MWT distance (meters), as defined in the PRONTO SAP, is the longest distance walked prior to the first study drug infusion in the original parent study (NEOD001-201). For all other efficacy and safety parameters, PRONTO Baseline will be defined as the last non-missing assessment prior to the first study drug infusion in the original parent study.

2.2.4.2. OLE Baseline

The OLE Baseline for the 6MWT will use the PRONTO Baseline for 6MWT. Otherwise, OLE Baseline is defined as the last assessment prior to first infusion in the OLE.

2.3. Study Endpoints

2.3.1. Safety Endpoints

Safety evaluations performed during the study include:

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

2.3.2. Efficacy Endpoints

The following are the efficacy endpoints.

2.3.2.1. NT-proBNP (Cardiac) Endpoints

The following endpoints will be evaluated in the NEOD001 Safety Population and OLE Safety Population (see Section 5).

For these subjects, cardiac response, as assessed by N-terminal pro-brain natriuretic peptide (NT-proBNP), categories are defined as (modified from Table 2 in Comenzo, 2012; Appendix 2):

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

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

- Cardiac best response from PRONTO and OLE baselines (see Section 2.2.4), as assessed by NT-proBNP response criteria. Best response will be over the course of the study.
- Cardiac response from PRONTO and OLE baselines (see Section 2.2.4), as assessed by NT-proBNP response criteria, at each visit
- Change and percent change from PRONTO and OLE baselines (see Section 2.2.4) to each visit in NT-proBNP

2.3.2.2. Quality of Life Endpoint – SF-36v2

The SF-36v2 is a 36-item self-report instrument that measures generic health-related quality of life in 8 specific dimensions plus 1 additional question that asks respondents to rate the amount of change experienced in their health in general (Maruish, 2011). It allows for the scoring of 2 component summary indices: the Physical Component Summary (PCS) score and the Mental Component Summary (MCS) score. The SF-36v2 is scored as 8 subscales representing separate domains of functional health and well-being:

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

Responses to items allow for direct calculation of subscales for each of the 8 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 8-scale profile.

- Change and percent change from PRONTO and OLE baselines in SF-36v2 PCS to each visit

2.3.2.3. Functional Endpoint - 6MWT Distance

The 6MWT is a practical simple test that requires a minimum walking length of 25 m but no exercise equipment or advanced training for technicians. The walking track or area should be the same for all tests for a subject. This test measures the distance that a subject can quickly walk on a flat, hard surface in a period of 6 minutes.

- Change and percent change from PRONTO and OLE baselines in the 6MWT distance (meters) to each visit

2.3.2.4. Renal Endpoints

The following endpoints will be evaluated in the Renal Evaluable Population (see Section 5).

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

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

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

- Renal best response from PRONTO and OLE baselines (see Section 2.2.4). Best response will be evaluated over the course of the study
- Renal response from PRONTO and OLE baselines (see Section 2.2.4) at each visit
- Change and percent change from PRONTO and OLE baselines (see Section 2.2.4) to each visit in creatinine, proteinuria, and estimated glomerular filtration rate (eGFR)

2.3.2.5. Peripheral Neuropathy Endpoint - NIS-LL Total Score

- Change and percent change from PRONTO and OLE baselines (see Section 2.2.4) to each visit in NIS-LL total score will be evaluated in the Peripheral Neuropathy Evaluable Population (see Section 5).

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

Any deaths after the first infusion of study drug (i.e. study day 1) through the study's last subject last visit (LSLV). Time (months) to event will be calculated as: (date of death - the date of first study drug infusion + 1) / 30.4375. Subjects will be censored at their last assessment known to be alive prior to LSLV.

2.3.2.7. Other Efficacy Data

Below are the other efficacy data collected in NEOD001-OLE251 study:

- Visual Analog Scale – Pain Intensity (VASPI)
- Kansas City Cardiomyopathy Questionnaire (KCCQ)
- Eastern Cooperative Oncology Group (ECOG) performance
- Free light chains (sFLCs), serum and 24-hour urine protein electrophoresis (PEP), and serum and urine immunofixation electrophoresis (IFE)
- Severity of disease-related symptoms including any changes from baseline
- Pharmacokinetics (PK)

3. SAMPLE SIZE JUSTIFICATION

Not applicable as this is an extension study for subjects who completed Study NEOD001-201.

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 in the OLE 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 discontinue due to "lost to follow-up," this reason will be included in the table with a count of 0. Percentages based on frequency counts will be presented to one decimal place, and values less than 1% will be presented as "<1%." Values less than 100% but greater than 99% will be presented as ">99%."

For continuous variables, the number of subjects, mean, standard deviation (SD), median, 25th 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 to 2 decimal places more than the raw data. In general, the number of decimal places should not exceed 3 decimal places unless appropriate. Confidence intervals (CIs) will be provided and will be rounded to 1 decimal place, unless otherwise specified, in the table and listing shell.

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

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. Partial Dates and Unknown Times

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

- 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.
- Start Dates (e.g., event date, 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.

All data recorded on the case report form will be included in data listings that will accompany the CSR.

4.4. Data Conventions

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

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

4.5. Standard Calculations

Variables requiring calculation will be derived using the following formulas:

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

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

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

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

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

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

- Age – Age is calculated as the number of years from the date of birth (*DOB*) to the specified date, e.g., date of informed consent (*DOIC*).

  age (years) = (DOIC –DOB + 1) / 365.25

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

  height (cm) = height (in) × 2.54

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

  weight (kg) = weight (lb) / 2.205

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

  temp (degrees Celsius) = 5 / 9 × (temp [degrees Fahrenheit] – 32)

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

  BMI (kg/m^2) = weight (kg) / ([height (cm)/100]^2)

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

  Change = post baseline value – baseline value

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

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

4.6. Analysis Visit Windows

Each visit will be denoted by its "month" and "day" such that the first dose day is denoted as Month 1-Day 1; subsequent months will use sequential numbers (e.g., the second dose is administered on Month 2-Day 1). Each infusion is scheduled to be every 28 days (±5 days) based on the first infusion date. For reporting purposes, the nominal visits will be used for the by-visit analyses. Details of the protocol defined visits and visit windows are given in the protocol and Table 1. In the event of unscheduled visits, re-test assessments, or ETD assessments, these will be reassigned to a scheduled visit for analysis purposes according to Tables 2, 3, 4 and 5. below. If multiple visits occur within a single visit window, after reassignment of unscheduled visits and ETD visits, then the visit closest to the target day of the visit window will be used in the analysis. If there is a tie, the later visit will be used in the analysis. Unscheduled assessments that do not collect time will not be mapped to any scheduled visit/timepoint.

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

4.6.1. PRONTO Visit Windows

PRONTO visit windows, a defined in PRONTO SAP, will be used to map the data collected in parent study (NEOD001-201).

Table 2 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 in parent study.

Table 2: PRONTO 1-Month Interval Visit Windows (Days)

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

Months	Target Study Day [a]	Analysis Window Study Day [a]	
		Low	High
PRONTO Month 12	308	295	319 [EEOS Low – 1]
PRONTO EEOS[c]	338	320 [Month 12 Low + 30 – 5]	

[a] Study day will be calculated from first dose date in parent study.
[b] PRONTO Baseline is defined in Section 2.2.4.
[c] PRONTO EEOS is defined as the visit occurring 30 (-5) days after the Month 12 infusion in parent study.

Table 3 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 in parent study.

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

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

[a] Study day will be calculated from first dose date in parent study.
[b] PRONTO Baseline is defined in Section 2.2.4.1
[c] PRONTO EEOS is defined as the visit occurring 30 (-5) days after the Month 12 infusion in parent study.

4.6.2. OLE Therapy Visit Windows

Table 4 defines the visit windows for assessments taken at 1-month intervals to be established with respect to relative day from the start of NEOD001 therapy in the OLE.

Table 4: OLE Therapy 1-Month Interval Visit Windows (Days)

Months	Target Study Day[a]	Analysis Window Study Day[a]	
		Low	High
OLE Baseline[b]	1	Closest visit to Day 1, prior to first OLE NEOD001 dose	
OLE Month 2	28	14	42 [= 28 + 28/2]
OLE Month 3	56	43 [= (28 + 28/2) + 1]	70 [= 56 + 28/2]
OLE Month x	28*x	(x-2)*28 + 28/2 + 1	(x-1)*28 + 28/2

OLE = open-label extension.
[a] Study day will be calculated from first OLE dose date.
[b] OLE Baseline is defined in Section 2.2.4.2.

Table 5 defines the visit windows for assessments taken at 3-month intervals to be established with respect to relative day from the start of NEOD001 therapy in the OLE.

Table 5: OLE Therapy 3-Month Interval Visit Windows (Days)

Months	Target Study Day[a]	Analysis Window Study Day[a]	
		Low	High
OLE Baseline[b]	1	Closest visit to Day 1, prior to first OLE NEOD001 dose	
OLE Month 3	56	14	98 [= 56 + 84/2]
OLE Month 6	168	99 [= (56 + 84/ 2) +1]	182 [= (140 + 84/2)]
OLE Month x	28*x	(x-4)*28 + 84/2 + 1	(x-1)*28 + 84/2

OLE = open-label extension.
[a] Study day will be calculated from first OLE dose date.
[b] OLE Baseline is defined in Section 2.2.4.

5. ANALYSIS POPULATIONS

The NEOD001 Safety Population will include all subjects who received any amount of NEOD001 in the original parent study (NEOD001-201).

The OLE Safety Population will include all subjects who received any amount of NEOD001 in the OLE study.

The Renal Evaluable Population will include subjects who were in the Renal Evaluable Population in the original parent study (NEOD001-201), defined as subjects who had proteinuria >0.5g/24 hours (measured by 24-hour urine total protein excretion), at baseline and at least one post-baseline assessment of proteinuria in NEOD001-201.

The Peripheral Neuropathy Evaluable Population will include subjects who were in the in the Peripheral Neuropathy Evaluable Population in the original parent study (NEOD001-201), defined as subjects who had ascending sensorimotor neuropathy due to AL amyloidosis etiologies at screening, had a baseline Neuropathy Impairment Score–Lower Limbs (NIS-LL) total score of 2 or greater and at least one post-baseline NIS-LL total score in NEOD001-201.

6. EXAMINATION OF SUBGROUPS

No prespecified evaluation of subgroups will be performed.

7. STUDY POPULATION

7.1. Subject Disposition

Subject disposition will be tabulated for all screened subjects and will include:

- the number of subjects dosed in the original parent study (NEOD001-201; NEOD001 Safety Population)
- the number of subjects screened in the OLE
- the number screened but not enrolled in the OLE
- the number enrolled in the OLE (OLE Safety Population)
- the number in each organ evaluable population
- the number who discontinued treatment early in the OLE and reason(s) for discontinuation of treatment as recorded on the OLE eCRF
- the number who withdraw from OLE study prior to completing the study and reason(s) for withdrawal as recorded on the OLE eCRF

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 and baseline characteristics from as reported on the OLE Demographics eCRF will be summarized for the OLE Safety Population.

Demographic variables will include the following:

- Age at informed consent including the subgroups <65 vs ≥65 years
- 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, ≥20 - <25, ≥25 - <30, ≥30 kg/m^2
- Both conventional BMI and modified BMI (mBMI [$kg/m^2 \times g/L$], defined as subject's weight (kg)/subjects squared height (meters) × serum albumin (g/L)) will be presented.

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

The following disease histories from the original parent study (NEOD001-201) will be summarized for the OLE Safety Population:

- Age at AL amyloidosis diagnosis
- Duration (months) since AL amyloidosis diagnosis
- Number of prior regimens for amyloidosis
- Duration (months) since last reported therapy for amyloidosis
- Response to last reported therapy for amyloidosis (CR, VGPR, PR, NR)
- Best response to previously reported therapy (CR, VGPR, PR, NR)
- Duration (months) since best response to previously reported therapy for amyloidosis
- Number of derived involved organs (1or 2 organs: renal, peripheral neuropathy) as defined in Section 5
- Number of physician assessed involved organs: The Investigator also assessed other organ involvement including gastrointestinal, autonomic nervous system, lung, soft tissue/lymphatic, or other. (1, 2, 3, 4, or 5 organs)
- Total number of involved organs (derived plus physician assessed)
- Screening and Baseline NT-proBNP (ng/L)
- Baseline 6MWT distance (meters)
- Renal Stage (Appendix 11): I, II, III; I/II, III; I, II/III
- Chronic Kidney Stage: 1, 2, 3, 4, 5
- NYHA Class (Appendix 4): I, II, III, IV; I/II vs III/IV
- Baseline FLC Ratio: Low (<0.26), Normal (0.26 – 1.65), High (>1.65)

No inferential statistical comparisons will be performed.

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

7.4. General Medical History

Medical history verbatim terms as recorded on the OLE eCRFs will be mapped to preferred terms (PTs) and system organ classes (SOCs) using MedDRA version 19.0.

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

7.5. Prior and New Concomitant Medications

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

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

Prior and new concomitant medications will be presented in a by-subject data listing.

7.6. Protocol Deviations

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

All protocol deviations will be collected by the clinical research associates and presented in a by-subject data listing.

7.7. Chemotherapy

Chemotherapy regimens may 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 for OLE Safety Population.

7.8. Concurrent Procedures

Data will be collected for concurrent procedures will be mapped to PTs and SOCs using MedDRA version 19.0. and will include name of procedure, ongoing status, indication, relationship to an AE or medical history, and frequency of the procedure. Concurrent procedures will be displayed in a subject data listing only for OLE Safety Population.

8. EFFICACY ANALYSES

All recorded efficacy endpoint data will be presented in by-subject data listings for the OLE Safety Population.

Analyses will be produced in both NEOD001 Safety Population and OLE Safety Population, unless otherwise specified. Data, visit window, and treatment group to be used for each population as below:

1. NEOD001 Safety Population:
    - Data: Pooled data from parent and OLE study
    - Visit window: PRONTO visit window for data in parent study, OLE therapy visit window for OLE data with exclusion of OLE Baseline.
    - Treatment: Placebo and NEOD001 subjects received in NEOD001-201 study and Overall
2. OLE Safety Population:
    - Using data from OLE study only
    - Visit window: OLE therapy visit window
    - Treatment: NEOD001

Analyses in Renal Evaluable Population or Peripheral Neuropathy Evaluable Population will be presented in the same manner described above for NEOD001 Safety Population and OLE Safety Population.

Baseline in all efficacy analyses refers to PRONTO Baseline and OLE Baseline, unless otherwise specified.

8.1. Adjustments for Covariates

For analyses of change from baseline, restricted maximum likelihood (REML) based mixed-effect model for repeated measures (MMRM) or analysis of covariance (ANCOVA) models will be used and the corresponding baseline value will be used as a covariate in the model.

8.2. Handling of Dropouts or Missing Data

For the SF-36v2, missing data conventions for partially completed questionnaires are specified in Section 2.3.2.2.

The following methods will be implemented to address missing data for relevant efficacy endpoint analyses.

8.2.1. Time to All-Cause Mortality

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

8.2.2. Responder Endpoints

For analyses of best response, a subject missing response status will be considered as a non-responder for 2-category response (response, non-response), or progressed for a 3-category response (response, stable, progression).

For analysis for response 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.

8.3. Interim Analyses and Data Monitoring

Not applicable.

8.4. Multicenter Studies

This is a multicenter study and data collected from all study centers will be listed.

8.5. Multiple Comparisons/Multiplicity

No adjustments for multiplicity will be made.

8.6. NT-proBNP (Cardiac) Endpoint Analyses

8.6.1. Best Response from Baseline

Best response will be derived from Baseline. All visits after the first infusion of study drug will be included. The number and percentage, with associated two-sided exact (Clopper-Pearson) 95% CIs, of subjects in each category of best response (response, nonresponse) will be presented. Refer to Section 8 for details about course of the study and relative first infusion of study drug for each set of analyses.

Cardiac response as 3 categories (response, stable, and progression) will be presented in the same manner described above.

8.6.2. Response at Each Visit

Response from baseline at each visit will be analyzed in the same manner described Section 8.6.1.

8.6.3. NT-proBNP Endpoint: Change from Baseline

Change from baseline will be analyzed using a REML based MMRM model including a fixed effect for categorical time point 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. Estimates of least-square (LS) means, standard errors (StdErr), and 95% CIs will be presented at each visit.

Descriptive statistics for NT-proBNP, change from baseline, and percent change from baseline will be presented by visit.

8.7. Quality of Life Endpoint: SF-36V2

PCS score, change from baseline, and percentage change from baseline will be analyzed in the same manner described in Section 8.6.3.

8.8. Functional Endpoint: 6WMT Distance

Subjects will be ranked at each visit ordered from worst to best, based on the completed distance. No imputations for missing data will be made.

Descriptive statistics for 6MWT distance, change from baseline, and percent change from baseline will be presented by visit. The change from baseline at each visit in 6MWT distance will be analyzed using a rank ANCOVA model including the ranked baseline value as a covariate. Estimates of least-square (LS) means, standard errors (StdErr), and 95% CIs will be presented by at each visit.

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

Descriptive statistics for observed value, change from baseline, and percent change from baseline will also be presented by visit.

8.9. Renal Endpoint Analyses

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

8.9.1. Best Renal Response from Baseline

Best renal response will be analyzed in the same manner described Section 8.6.1.

8.9.2. Renal Response at Each Visit

Renal response at each visit will be analyzed in the same manner described Section 8.6.1 .

8.9.3. Creatinine, Proteinuria and eGFR: Change from Baseline

Change from baseline in creatinine, proteinuria and eGFR will be analyzed in the same manner described in Section 8.6.3.

8.10. Peripheral Neuropathy Endpoint: Change from Baseline in NIS-LL Total Score

Change from baseline in NIS-LL will be evaluated in the Peripheral Neuropathy Evaluable Population, in the same manner described in Section 8.6.3.

8.11. All-Cause Mortality (Overall Survival)

Overall survival, time to all-cause mortality, will be calculated in days as the date of death minus the date of first NEOD001 infusion plus 1. Subjects will be censored at their last assessment known to be alive prior to LSLV. Refer to Section 8 for details about course of the study and relative first infusion of study drug for each set of analysis.

Kaplan-Meier (KM) estimates of the distribution of the time-to-event will be tabulated. The tabulation will include the KM estimate of the medians, 25th and 75th quartiles, and corresponding 95% CIs, if estimable. The number and percent of subjects censored and with events will be presented.

8.12. Other Efficacy Data

Below efficacy data will be presented in by-subject data listings for the OLE Safety Population.

- Visual Analog Scale – Pain Intensity (VASPI)
- Kansas City Cardiomyopathy Questionnaire (KCCQ)
- Eastern Cooperative Oncology Group (ECOG) performance
- Free light chains (sFLCs), serum and 24-hour urine protein electrophoresis (PEP), and serum and urine immunofixation electrophoresis (IFE)
- Severity of disease-related symptoms including any changes from baseline
- Pharmacokinetics (PK)

9. SAFETY ANALYSES

All recorded safety endpoint data will be presented in by-subject data listings for the OLE Safety Population. TEAE summaries will be presented for All Treated Subjects. Extent of exposure will be summarized for NEOD001 Safety Population and OLE Safety Population.

No inferential comparison of safety endpoints will be performed.

9.1. Extent of Exposure

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

9.2. Use of Premedication

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

Premedication data will be presented in a by-subject data listing.

9.3. Adverse Events

Verbatim terms on the OLE Adverse Event 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).

All AE summaries will be restricted to treatment-emergent adverse events (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 30 days after date of last dose or last study visit, whichever is

later. If it cannot be determined whether the AE is treatment emergent due to a partial onset date, then it will be counted as such.

To assess the long-term treatment effects overall and relative to shorter term treatment, TEAE incidence will be summarized separately by the original parent study (NEOD001-201) and OLE study (NEOD001-OLE251) as shown in Table 6. TEAEs collected during original parent study will be summarized by actual treatment subjects received. TEAEs that start on or after the first dose of OLE study will be summarized by treatment group subjects received in parent study. Overall summary will also be presented for NEOD001-OLE251.

Table 6: Treatment Group Schema

NEOD001-201		**NEOD001-OLE251**		
NEOD001 (N=xx)	Placebo (N=xx)	NEOD001-201 NEOD001 (N=xx)	NEOD001-201 Placebo (N=xx)	Overall (N=xx)

Each AE summary will be presented according to Table 6 for All Treated Subjects. Summaries that are displayed by SOC and PT will be ordered by descending order of NEOD001-OLE251 overall incidence of SOC and PT within each SOC.

- An overall summary of 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
  - Fatal TEAEs (outcome="Fatal" or severity=CTCAE Grade 5)
  - Treatment-related TEAE
  - Treatment-related serious TEAE
  - Treatment-related TEAE of CTCAE ≥Grade 3
  - TEAE leading to infusion interruption
  - TEAE leading to dose reduction
  - TEAE leading to dose being held
  - TEAE leading to prolongation of infusion time (>2.5 hours)
  - Infusion associated TEAE as determined by the Investigator
  - TEAE leading to study drug withdrawal
- Subject incidence of TEAEs by MedDRA SOC and PT
- Subject incidence of serious TEAEs by MedDRA SOC and PT

The following listings will be presented by subject for OLE Safety Population:

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

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/1.73m^2

9.4.1. Pregnancy Testing and Urinalysis Dipstick

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 (kg/m^2 g/L), defined as a subject's weight (kg) ÷ subjects squared height (meters) × 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 include, 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. Subjects whose interpretation shifts from normal to abnormal clinically significant or not clinically significant will be listed separately including description of the abnormality and any associated comments.

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

9.8. Physical Examination

Physical examination findings entered on the eCRF will be listed.

9.9. Immunogenicity

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

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

1. All safety analyses were removed except AE overview, TEAEs and SAEs.
2. The below efficacy analyses were removed:
    - Change from baseline in troponin T
    - Change from baseline in the Short Form-36 Health Survey version 2 (SF-36v2) Mental Component Score (MCS) and the 8 subscales
    - Progression-free survival
    - For renal-evaluable subjects:
        - Time to eGFR:
        - Time to any worsening in CKD Stage
        - Time to 40% reduction in eGFR
        - Time to doubling of creatinine
    - For peripheral neuropathy-evaluable subjects:
        - Peripheral neuropathy best response
        - Peripheral neuropathy response
        - For subjects with painful peripheral neuropathy in Study NEOD001-201 (i.e., baseline Visual Analog Scale – Pain Intensity [VASPI] score >0) change from baseline in the VASPI score
    - For hepatic-evaluable subjects:
        - Hepatic response
        - Hepatic best response from baseline
        - Frequency and duration of hospitalizations over the course of the study
    - Change from baseline in the Kansas City Cardiomyopathy Questionnaire (KCCQ) subscores and overall summary score
    - Time to progression for each organ (cardiac/NT-proBNP, renal, peripheral neuropathy, hepatic) separately and to any organ progression
    - Eastern Cooperative Oncology Group (ECOG) Performance Status and New York Heart Association (NYHA) Class at each visit including any changes from baseline
    - Change from baseline in serum free light chains (sFLCs), serum and 24-hour urine protein electrophoresis (PEP), and serum and urine immunofixation electrophoresis (IFE)
    - Severity of disease-related symptoms including any changes from baseline

11. REFERENCES

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12. APPENDICES

APPENDIX 1. HEMATOLOGIC RESPONSE AND PROGRESSION CRITERIA

Response Subcategory	Response Criteria
Complete Response (CR)	Normalization of free light chain levels and ratio, negative serum and urine immunofixation
Very Good Partial Response (VGPR)*	Reduction in the dFLC to <40 mg/L (<4.0 mg/dL)
Partial Response (PR)*	A greater than 50% reduction in the dFLC
No Response (NR)	Less than a PR
Progression	From CR: any detectable monoclonal protein or abnormal free light chain ratio (light chain must double)
	From PR, 50% increase in serum M protein to > 0.5 g/dL or 50% increase in urine M protein to > 200 mg/day (a visible peak must be present) or free light chain increase of 50% to > 10 mg/dL (100 mg/L)

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

APPENDIX 2. ORGAN RESPONSE AND PROGRESSION CRITERIA

Organ	Response	Progression
Heart/Cardiac[a,b]	NT-proBNP response (>30% and >300 ng/L decrease in subjects with baseline NT-proBNP ≥650 ng/L) OR NYHA class response (≥2 class decrease in subjects with baseline NYHA class III or IV)[b]	NT-proBNP progression (>30% and >300 ng/L increase)[c]
Renal[d]	≥30% decrease in proteinuria or drop of proteinuria below 0.5 g/24 hours in the absence of renal progression	≥25% decrease in eGFR
Peripheral Nerve[e]	NIS-LL increase from baseline of <2 points	NIS-LL increase from baseline of ≥2 points

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

a Modified from Table 2 in Comenzo 2012.
b NYHA class not considered for primary efficacy endpoint analyses.
c Subjects with progressively worsening renal function cannot be scored for NT-proBNP progression.
d Palladini 2014.
e Coelho 2012.

APPENDIX 3. 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 4. NEW YORK HEART ASSOCIATION (NYHA) FUNCTIONAL CLASSIFICATION

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

Source: American Heart Association, 2015.

APPENDIX 5. NEUROPATHY IMPAIRMENT SCALE – LOWER LIMBS

prothena

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

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

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

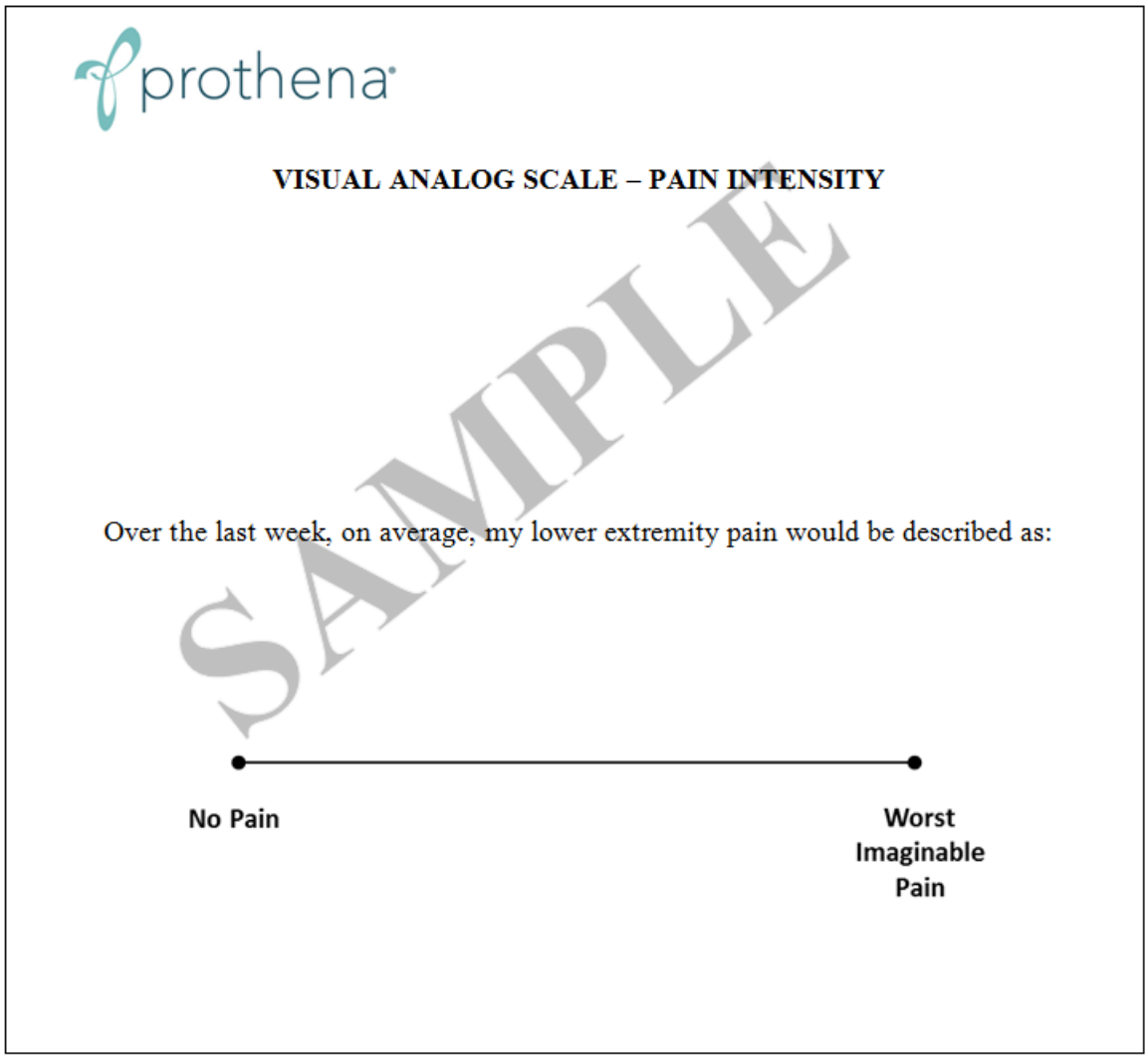
Assessment	*Right*	*Left*	*Sum*
Muscle Weakness - Score each assessment as: 0 - normal, 1 - 25% weakened, 2 - 50% weakened, 3 - 75% weakened, 4 - paralysis			
Hip Flexion (iliopsoas)			
Hip Extension (gluteus max.)			
Knee Flexion (biceps femoris)			
Knee Extension (quadriceps)			
Ankle Dorsiflexors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

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

Performed by (Print Name): _____

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

APPENDIX 6. VISUAL ANALOG SCALE – PAIN INTENSITY (VASPI)



APPENDIX 7. SF-36V2 HEALTH SURVEY

Your Health and Well-Being

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

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

In general, would you say your health is:

Excellent
Very good
Good
Fair
Poor

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

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

APPENDIX 8. KANSAS CITY CARDIOMYOPATHY QUESTIONNAIRE (KCCQ)

The KC Cardiomyopathy Questionnaire

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

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

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

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

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

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

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

Original US English

APPENDIX 9. LABORATORY TESTS

<table>
<tr>
<td colspan="2">Serum Chemistry:
ALP (E)[a]
ALT (E)
AST (E)
Bilirubin - total (E) and direct
GGT
BUN
LDH
Creatinine (E)
Glucose
Cholesterol
Triglycerides
Calcium
Phosphate
Protein - total
Albumin
Sodium
Potassium
Chloride
Bicarbonate
Magnesium
Amylase
Creatine kinase
Uric acid
Estimated glomerular filtration rate (E)[e]
Estimated creatinine clearance
Cystatin C</td>
<td>Hematology:
Hemoglobin (E)
Hematocrit
RBC
WBC
Neutrophils (absolute [E], %)
Lymphocytes (absolute, %)
Monocytes (absolute, %)
Eosinophils (absolute, %)
Basophils (absolute, %)
Platelet count (E)</td>
</tr>
<tr>
<td colspan="2"></td>
<td>Other[b]:
Serum anti-NEOD001 antibodies[c]
Serum NEOD001 concentration
Serum FLCs[d]
24-hr urine protein excretion & total volume
Serum & 24-hr urine PEP
Serum & urine IFE</td>
</tr>
<tr>
<td colspan="2"></td>
<td>Inflammatory Biomarkers[b]:
IL-6
IL-8
TNF-alpha
INF-gamma
Complements C3, C4, and CH50
CRP
SAA (A-SAA)
Tryptase</td>
</tr>
<tr>
<td>Urinalysis - Dipstick:
Color & clarity
Specific gravity
pH
Protein
Glucose
Ketones
Bilirubin
Urobilinogen
Blood
Nitrite
Leukocyte esterase
Microscopic</td>
<td>Urinalysis - Quantitative Analysis/Renal Biomarkers[f]:
Urine albumin/creatinine ratio
Urine NGAL
Urine RBP</td>
<td>Cardiac Biomarkers:
Troponin T
NT-proBNP

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

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

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

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

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

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

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

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

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

APPENDIX 10. COAGULATION INDICES

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

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

APPENDIX 11. RENAL STAGE

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

eGFR = estimated glomerular filtration rate.
RCSource: Palladini 2014.