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Official Title:	A Phase 2b Open-label Extension 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)
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Document Date:	09 January 2017

CLINICAL RESEARCH PROTOCOL

Study Title:	A Phase 2b Open-label Extension 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)
Protocol Number:	NEOD001-OLE251
Investigational Product:	NEOD001
US IND Number:	122,912
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Indication:	Light Chain (AL) Amyloidosis
Sponsor:	Prothena Therapeutics Limited Adelphi Plaza, Upper George's Street Dun Laoghaire, Co. Dublin A96 T927, Ireland
Sponsor Representative:	Prothena Biosciences Inc 331 Oyster Point Boulevard South San Francisco, California 94080 USA
Sponsor's Chief Medical Officer:	[redacted]
Development Phase:	2b
Date of Original Protocol:	09 January 2017

SPONSOR PROTOCOL APPROVAL PAGE

Protocol Title:	A Phase 2b Open-label Extension 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)
Protocol Number:	NEOD001-OLE251
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Declaration of Sponsor

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

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

[redacted]

[redacted]
Chief Medical Officer

[redacted]
Date

INVESTIGATOR SIGNATURE PAGE

Protocol Title:	A Phase 2b Open-label Extension 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)
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Date of Original Protocol:	09 January 2017

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

Investigator Signature Date

Investigator Name (Print)

Please **sign, date, and return** this form to your Study Monitor. Please **retain** a copy for your study files.

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NEOD001-OLE 251 PROTOCOL SYNOPSIS

Title	A Phase 2b Open-label Extension 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)
Phase	2b
Planned Number of Study Sites	Approximately 40 sites globally
Objective	The objective of this study is to evaluate the long-term safety and efficacy of NEOD001 in subjects with AL amyloidosis who have completed Study NEOD001-201.
Study Design	This is a global, multicenter, Phase 2b, open-label extension study of subjects with AL amyloidosis who had a hematologic response (Appendix 1) to first-line treatment for their amyloidosis (e.g., chemotherapy, autologous stem cell transplant [ASCT]) and 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 (Table 1) will be completed. 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 who discontinue study drug before the End of Study (EOS) Visit should have an Early Treatment Discontinuation (ETD) Visit 30 (±5) days after their final administration of study drug.
Number of Subjects	Approximately 100 subjects will be enrolled.
Study Drug, Dose, and Mode of Administration	Study drug consists of NEOD001 24 mg/kg (dose not to exceed 2500 mg). NEOD001 will be administered as an intravenous (IV) infusion once every 28 days (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. A minimum of 21 days between doses is required. Subjects should be closely monitored per Section 5.3 following completion of the study drug infusion.
Control Group	Not applicable

Estimated Treatment Duration	Each subject's study participation may be up to 38 months or until the study is terminated (per Section 4.6), whichever occurs first. The study consists of a Screening Phase (1 month), Treatment Phase (36 months), and EOS Visit (30 [±5] days after the last dose).
Subject Eligibility Criteria	**Inclusion Criteria** (subjects must meet ***all*** of the following criteria): 1. Completed the EOS Visit in Study NEOD001-201 2. Adequate bone marrow reserve, hepatic and renal function, as demonstrated by: o Absolute neutrophil count (ANC) $\geq 1.0 \times 10^9$/L o Platelet count $\geq 75 \times 10^9$/L o Hemoglobin ≥9 g/dL o Total bilirubin ≤2 × upper limit of normal (ULN) o Aspartate aminotransferase (AST) ≤3 × ULN o Alanine aminotransferase (ALT) ≤3 × ULN o Alkaline phosphatase (ALP) ≤5 × ULN (except for subjects with hepatomegaly and isozymes specific to liver, rather than bone) o Estimated glomerular filtration rate (eGFR) ≥25 mL/min/1.73 m^2 as estimated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, or measured GFR ≥25 mL/min/1.73 m^2 3. Systolic blood pressure 80-180 mmHg 4. Women of childbearing potential (WOCBP) must have a negative pregnancy test during Screening and must agree to use highly effective physician-approved contraception (Appendix 2) from Screening to 90 days following the last study drug administration 5. Male subjects must be surgically sterile or must agree to use highly effective physician-approved contraception (Appendix 2) from Screening to 90 days following the last study drug administration 6. Ability to understand and willingness to sign an informed consent form (ICF) prior to initiation of any study

	procedures **Exclusion Criteria** (subjects must ***not meet any*** of the following criteria): 1. Any new medical contraindication or clinically significant abnormality on physical, neurological, laboratory, vital signs, or electrocardiographic (ECG) examination (e.g., atrial fibrillation; ***with the exception*** of subjects for whom the ventricular rate is controlled) that precludes continuation or initiation of treatment with NEOD001 or participation in the study 2. Symptomatic orthostatic hypotension that in the medical judgment of the Investigator would interfere with subject's ability to safely receive treatment or complete study assessments 3. Myocardial infarction, uncontrolled angina, uncontrolled ventricular arrhythmias, or ECG evidence of acute ischemia, within 6 months prior to the Month 1-Day 1 Visit 4. Severe valvular stenosis (e.g., aortic or mitral stenosis with a valve area <1.0 cm^2) or severe congenital heart disease 5. ECG evidence of acute ischemia or active conduction system abnormalities ***with the exception*** of any of the following: o First degree atrioventricular (AV) block o Second degree AV block Type 1 (Mobitz Type 1/ Wenckebach type) o Right or left bundle branch block o Atrial fibrillation with a controlled ventricular rate (uncontrolled [i.e., >110 bpm] ventricular rate is not allowed [determined by an average of three beats in Lead II or 3 representative beats if Lead II is not representative of the overall ECG]) 6. Has not recovered (i.e., equivalent to a Common Terminology Criteria for Adverse Events [CTCAE] ≥Grade 2) from the clinically significant toxic effects of prior anticancer therapy. ***Exception:*** subjects who have received treatment with a proteasome inhibitor such as bortezomib may have CTCAE Grade 2 neuropathy. 7. Received any of the following within the specified time frame prior to the Month 1-Day 1 Visit:

	○ Oral or IV antibiotics, antifungals, or antivirals within 1 week, ***with the exception*** of prophylactic oral agents. Note: In the event that a subject requires the chronic use of antivirals, Medical Monitor permission is required for entry into the study. ○ Hematopoietic growth factors, transfusions of blood or blood products within 1 week ○ Chemotherapy, radiotherapy, HDAC inhibitors, or other plasma cell directed therapy within 2 weeks ○ ASCT within 4 weeks (i.e., ASCT is allowed if it occurred ***before*** enrollment in Study NEOD001-201 or ***after*** completion of Study NEOD001-201 if it was at least 4 weeks before Month 1-Day 1 of this study) ○ Major surgery within 4 weeks (or within 2 weeks following consultation with and approval of Medical Monitor) ○ Planned organ transplant during the study ○ Any investigational agent, other than NEOD001, within 4 weeks ○ Any experimental imaging agent directed at amyloid within 2 weeks 8. Active malignancy ***with the exception*** of any of the following: ○ Adequately treated basal cell carcinoma, squamous cell carcinoma, or in situ cervical cancer ○ Adequately treated Stage I cancer from which the subject is currently in remission and has been in remission for ≥2 years ○ Low-risk prostate cancer with Gleason score <7 and prostate-specific antigen <10 mg/mL ○ Any other cancer from which the subject has been disease-free for ≥2 years 9. History of Grade ≥3 infusion-related adverse events (AEs) or hypersensitivity to NEOD001 10. History of severe allergy to any of the components of

	NEOD001 such as histidine/L-Histidine, Trehalose, or Polysorbate 20 11. Currently known uncontrolled bacterial, viral, fungal, HIV, hepatitis B, or hepatitis C infection 12. Women who are breastfeeding 13. Any condition which could interfere with, or the treatment for which might interfere with, the conduct of the study or which would, in the opinion of the Investigator, unacceptably increase the subject's risk by participating in the study 14. Unable or unwilling to adhere to the study-specified procedures and restrictions 15. Subject is under legal custodianship
Study Procedures and Assessments	See Schedule of Assessments (Table 1)
Endpoints	*Safety Endpoints:* • Long-term safety and tolerability as assessed by vital signs, 12-lead ECGs, routine clinical laboratory assessments, and AEs • Immunogenicity *Efficacy Endpoints:* • N-terminal pro-brain natriuretic peptide (NT-proBNP): o Response (Appendix 3) o Best response from baseline o Change from baseline • Change from baseline in troponin T • Change from baseline in the Short Form-36 Health Survey version 2 (SF-36v2) Physical Component Score (PCS), Mental Component Score (MCS), and the 8 subscales • Change from baseline in the 6-Minute Walk Test (6MWT) distance (meters) • Progression-free survival • For renal-evaluable subjects: o Renal response (Appendix 3)

	○ Renal best response from baseline ○ Change from baseline in creatinine, proteinuria, and eGFR ○ Time to eGFR: ▪ ≤15 mL/min/1.73 m^2 (Chronic Kidney Disease [CKD] Stage 5) ▪ <30 mL/min/1.73 m^2 (CKD Stage 4) ▪ <60 mL/min/1.73 m^2 (CKD Stage 3) ○ Time to any worsening in CKD Stage ○ Time to 40% reduction in eGFR ○ Time to doubling of creatinine • For peripheral neuropathy-evaluable subjects: ○ Change from baseline in Neuropathy Impairment Score–Lower Limbs (NIS-LL) total score ○ Peripheral neuropathy best response ○ Peripheral neuropathy response (Appendix 3) ○ 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 (Appendix 3) ○ Hepatic best response from baseline • Time to all-cause mortality (overall survival) • 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 • Pharmacokinetics (PK)
Statistical Considerations and Methods	*Analysis Populations:* All analyses will be based on the Safety Population, defined as all subjects who receive any amount of study drug. Select analyses will use efficacy subsets, defined as: • Renal Evaluable Population: subjects who had renal involvement in Study NEOD001-201 • Peripheral Neuropathy Evaluable Population: subjects who had peripheral nerve involvement in Study NEOD001-201 • Hepatic Evaluable Population: subjects who had hepatic involvement in Study NEOD001-201 *Safety Analyses:* Safety will be assessed through changes in vital signs, 12-lead ECGs, laboratory test results, and summaries of AEs. All treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) will be summarized. *Efficacy Analyses:* Response rates will be summarized including 95% confidence intervals. The distributions of time-to-event endpoints (progression-free survival, overall survival) will be summarized using the Kaplan-Meier method. All quantitative endpoints, except 6MWT distance, defined as the change from baseline will be analyzed using linear mixed models for repeated measurements (MMRM). The dependent variable will be the change from baseline at each time point. The model will include fixed effects for time point and treatment-by-time interaction. The baseline value of the corresponding endpoint will be included as a covariate and the unstructured covariance model will be used. The denominator degrees of freedom will be estimated using the Kenward-Roger approximation. The 6MWT distance change from baseline will be analyzed using a Wilcoxon signed rank test.

Sample Size Justification	Not applicable as this is an open-label extension study for subjects who completed Study NEOD001-201.
Sponsor	Prothena Therapeutics Limited

Table 1 Schedule of Assessments

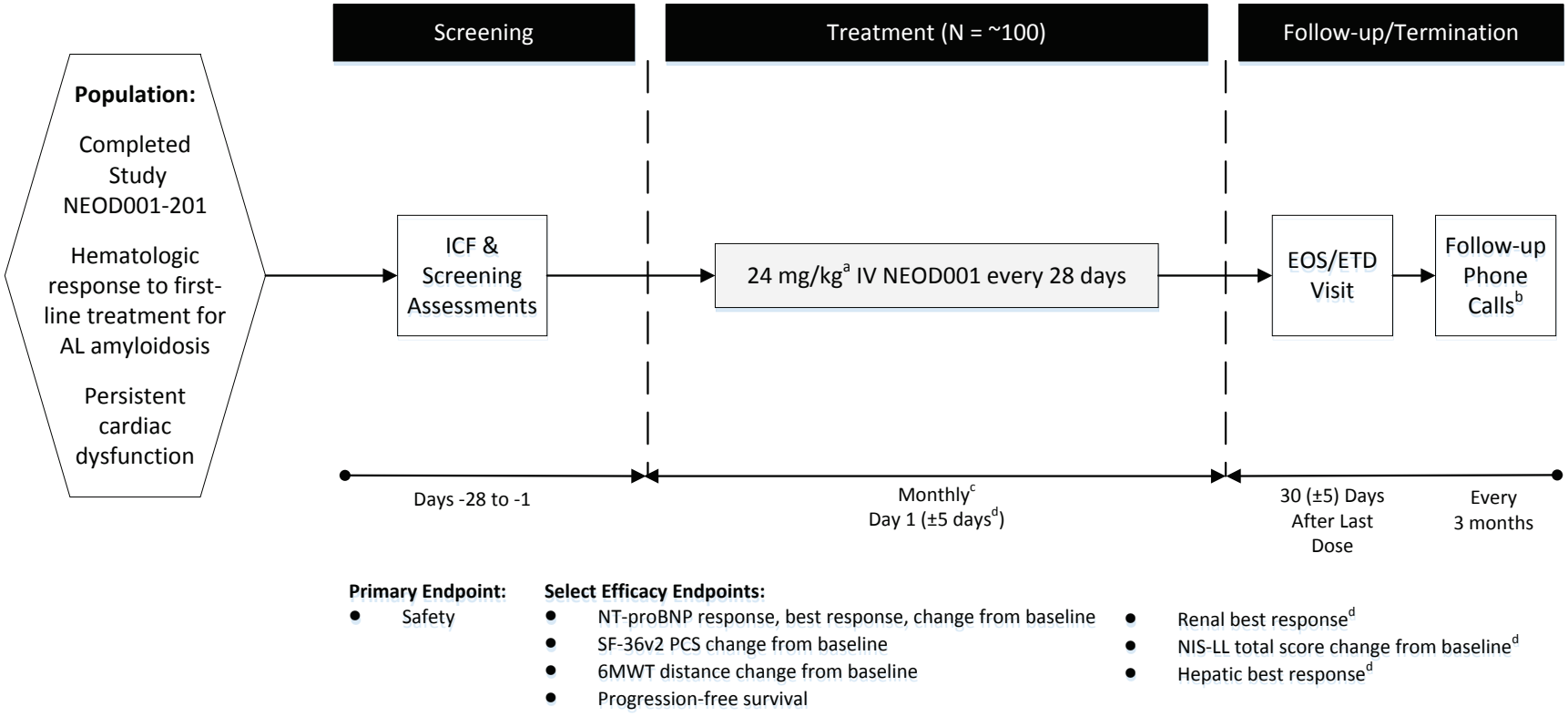
	Assessment or Procedure	Screening[1] Days -28 through -1: <60 days since last visit in Study NEOD001-201	Screening[1] Days -28 through -1: ≥60 days since last visit in Study NEOD001-201	Treatment[2] Monthly Day 1 (±5 days)[3]	Termination EOS/ETD[4]
	Written Informed Consent	X	X		
	Eligibility Review	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.

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 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 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 Section 6.5.1.3. **All Other Visits:** conduct a directed physical examination per 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 4 (ECOG) and Appendix 5 (NYHA).
11. See Appendix 6; NIS-LL is for all subjects who had peripheral neuropathy in Study NEOD001-201.
12. See Appendix 7; VASPI is for subjects who had painful peripheral neuropathy in Study NEOD001-201.
13. See Appendix 8; SF-36v2 should be administered before performing any other study assessments on the same calendar day it is administered.
14. See Appendix 9; 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 10. Within 3 days before the first day of a new regimen of chemotherapy, conduct an unscheduled central laboratory collection (including hematology, chemistry, PT/INR, and PTT).

22. Collect citrated plasma samples, which will be frozen for potential analysis of coagulation indices at a later date; see Appendix 11. **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 10.
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 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 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.

Figure 1 NEOD001-OLE251 Design



EOS/ETD = End of Study/Early Treatment Discontinuation; ICF = informed consent form; IV = intravenous; NIS-LL = Neuropathy Impairment Score–Lower Limbs; NT-proBNP = N-terminal pro-brain natriuretic peptide; PCS=Physical Component Score; SF-36v2 = Short Form-36 Health Survey version 2; 6MWT = 6-Minute Walk Test.

a Maximum dose not to exceed 2500 mg.
b 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.
c For up to 36 months or until the study is terminated, whichever occurs first.
d ±5-day window applicable to Months 2+.
e In Efficacy Subset Populations: Renal-evaluable subjects, peripheral neuropathy-evaluable subjects, and hepatic-evaluable subjects, respectively.

GLOSSARY OF TERMS

Abbreviation/Acronym	Definition
AA	Amyloid A
ADA(s)	Anti-drug antibody(ies)
ADCP	Antibody-dependent cellular phagocytosis
ADL	Activities of daily living
AE(s)	Adverse event(s)
AEF	Amyloid-enhancing factor
ALP	Alkaline phosphatase
AL	Amyloid light chain
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ASCT	Autologous stem cell transplant
A-SAA	Acute phase serum amyloid A
AST	Aspartate aminotransferase
AV	Atrioventricular
BP	Blood pressure
BPM	Beats per minute
BSA	Bovine serum albumin
BUN	Blood urea nitrogen
CA	Competent Authority
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CR	Complete response
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
D	Aspartic acid
DLTs	Dose-limiting toxicities

Abbreviation/Acronym	Definition
E	Glutamic acid
ECG	Electrocardiogram
ECL	Electrochemiluminescent
ECOG PS	Eastern Cooperative Oncology Group performance status
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EOI	End of infusion
EOS	End of Study
ETD	Early Treatment Discontinuation
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
HR	Heart rate
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Institutional Ethics Committee
IFE	Immunofixation electrophoresis
Ig	Immunoglobulin
IgG1	Immunoglobulin G1
IL-6	Interleukin-6
IRB	Institutional Review Board
IV	Intravenous or intravenously
KCCQ	Kansas City Cardiomyopathy Questionnaire
LDH	Lactate dehydrogenase
MCS	Mental Component Score
MMRM	Mixed models for repeated measurements

Abbreviation/Acronym	Definition
nAb	Neutralizing antibody
NIS-LL	Neuropathy Impairment Score–Lower Limbs
NOAEL	No-observable-adverse-effect-level
NR	No response
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
PCD	Plasma cell dyscrasia
PCS	Physical Component Score
PEP	Protein electrophoresis
PK	Pharmacokinetic(s)
PR	Partial response
PT/INR	Prothrombin time/international normalized ratio
PTT	Partial thromboplastin time
RR	Respiratory rate
SAA	Serum amyloid A
SAE(s)	Serious adverse event(s)
SC	Subcutaneous(ly)
SF-36v2	Short Form-36 Health Survey version 2
sFLC	Serum free light chain
6MWT	6-Minute Walk Test
TEAE(s)	Treatment-emergent adverse event(s)
TRIAD	Transgenic Rapidly Inducible Amyloid Disease
ULN	Upper limit of normal
US(A)	United States (of America)
USP	United States Pharmacopeial Convention
VASPI	Visual Analog Scale – Pain Intensity
VGPR	Very good partial response

Abbreviation/Acronym	Definition
vWF	von Willebrand Factor
WFI	Water for injection
WOCBP	Women of childbearing potential
WT	Wild-type

1 INTRODUCTION

1.1 Light Chain (AL) Amyloidosis

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

Approximately three-fourths of AL amyloidosis patients present with 1 or 2 major organ systems involved (e.g., cardiac, renal, hepatic, peripheral nervous system, autonomic nervous system, gastrointestinal tract, soft tissues) while a quarter of patients present with >2 systems involved (Palladini et al, 2005; Gertz et al, 2010). AL amyloidosis is most commonly associated with cardiac and/or renal dysfunction, with overt restrictive cardiomyopathy observed in approximately 50% of all cases, and subclinical cardiac involvement detected in almost every case at autopsy or on endomyocardial biopsy (Falk and Dubrey, 2010).

AL amyloidosis has two important disease components. The first component is the plasma cell dyscrasia (PCD), which results in the overproduction of immunoglobulin light chain, and the second component is the impact of the soluble and insoluble amyloid on organ structure and function, leading to the clinical manifestations of the disease. Currently, there are no approved treatments for AL amyloidosis and no existing treatments that directly neutralize the toxic soluble aggregates or remove the deposited misfolded amyloid that are thought to cause organ dysfunction (Falk and Dubrey, 2010). The current standard of care for patients with AL amyloidosis is aimed at reducing or eliminating the bone marrow disorder, the PCD. The most aggressive treatment options include autologous stem cell transplant (ASCT) and high-dose chemotherapy for those patients who can tolerate it. Other treatment regimens include combinations of drugs often used to treat hematological malignancies including melphalan, prednisone, dexamethasone, and proteasome inhibitors (e.g., bortezomib), in an attempt to reduce light chain production.

The incidence of treatment-related mortality following ASCT is high, although variable and treatment center dependent, with the greatest mortality occurring in patients with cardiac involvement (Falk and Dubrey, 2010). Falk and colleagues noted that although complete hematologic responses could be achieved in approximately 40% of treated patients (Falk and Dubrey, 2010), the rate of any organ function improvement or stabilization (“organ response”) after achieving hematologic response from ASCT or chemotherapy regimens is highly variable (Cibeira et al, 2011; Cohen et al, 2007; Michael et al, 2010). Hematologic response in the absence of organ benefit provides limited, if any, clinical benefit to patients with AL amyloidosis

(Kaufman et al, 2015), underscoring that the major determinant of morbidity and mortality is end organ damage.

Unlike other hematologic disorders such as multiple myeloma, the morbidity and mortality of AL amyloidosis is related to organ dysfunction rather than the PCD. In all patients with AL amyloidosis, disease outcome is highly dependent on the severity of organ involvement, especially cardiac involvement; and prognosis can be defined by N-terminal pro-brain natriuretic peptide (NT-proBNP). NT-proBNP was chosen as the primary endpoint for the Phase 2b Study NEOD001-201 because it is a clinically validated cardiac functional biomarker of injury and dysfunction and decreasing NT-proBNP levels predict lower mortality rates (Comenzo et al, 2012). NT-proBNP can also be used for early assessment of cardiac response, allowing treatment modification (Palladini et al, 2014). In Study NEOD001-001, the Phase 1/2 study of NEOD001 in subjects with AL amyloidosis, monthly infusions of NEOD001 resulted in clinically meaningful reductions in NT-proBNP (Gertz et al, 2016).

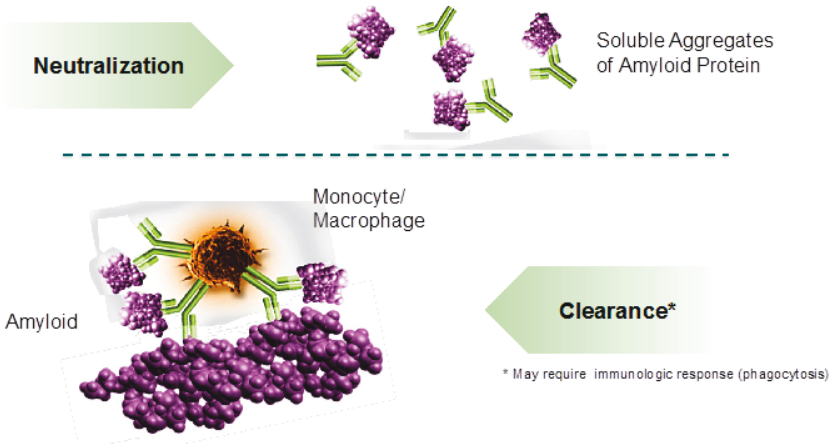
AL amyloidosis is a rare disorder. NEOD001 was designated as an Orphan Medicinal Product in the European Union on 08 February 2013 for the treatment of AL amyloidosis and in the US on 17 February 2012 for the treatment of AA amyloidosis and AL amyloidosis.

1.2 Background on NEOD001

Prothena Therapeutics Limited (Prothena) is developing NEOD001, a humanized immunoglobulin G1 (IgG1), kappa version of 2A4, the parent murine monoclonal antibody. NEOD001 and 2A4 bind specifically and with nanomolar affinity to a cryptic epitope only exposed on AL amyloid fibrils and soluble aggregates, but not available for binding on normally folded light chains that compose immunoglobulins (Ig) or on free non-amyloid light chain in circulation. NEOD001, administered by intravenous (IV) infusion, is proposed for use to target the misfolded light chain protein in subjects with AL amyloidosis. Refer to the current NEOD001 Investigator's Brochure for detailed nonclinical and clinical information.

The proposed mechanism of action for NEOD001 is thought to be two-pronged (Figure 2). The first is the direct interaction of NEOD001 with misfolded, soluble light chain aggregates resulting in the neutralization of these cytotoxic moieties. The second is the clearing of insoluble toxic light chain amyloid deposited in organs/tissues via an antibody-dependent cellular phagocytosis (ADCP) mechanism. It is believed that NEOD001 binds (opsonizes) amyloid deposits, and signals monocytes/macrophages to initiate the phagocytosis process that ultimately removes the amyloid deposits from affected organs. Both mechanisms may contribute to potential clinical benefit.

Figure 2 Proposed Mechanism of Action for NEOD001



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

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

1.2.1 Nonclinical Safety

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

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

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

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

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

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

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

A special immunogenicity/toxicity study was conducted to explore whether the mortality observed following IV dosing of 2A4 in the TRIAD mouse can be observed with an unrelated, but immunogenic protein. Nontransgenic/wild-type (WT) mice and H2/hIL-6 transgenic mice (no AEF administered) were treated once weekly by IV administration with 2A4 at 4 mg/kg. The nontransgenic mice showed no systemic effects; however, the IL-6 overproducing mice developed profound signs (decreased motor activity, hunched posture, ataxia, cold to touch) immediately after dosing on Days 15 and 22, replicating what was observed in the TRIAD mouse safety studies above. Mortality and moribundity occurred post dosing on Day 22. Another group of H2/hIL-6 transgenic mice was treated once weekly by IV administration with BSA at 50 mg/kg. A similar clinical course occurred although signs began one week earlier; i.e., after dosing on Day 8 (the second dose). Again, mortality was observed in some animals after dosing on Day 22. This study demonstrates the importance of elevated IL-6 in the morbidity and mortality observed in this model and further demonstrates that the mortality is not unique to 2A4 but can be seen with other proteins that are immunogenic in this mouse model.

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

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

1.2.2 Clinical Experience

The safety and tolerability of NEOD001 have been investigated in the Phase 1/2 study (Study NEOD001-001) in the US, and are being investigated in the following ongoing global studies:

- Phase 1/2 open-label extension study (Study NEOD001-OLE001)
- Phase 2b study (Study NEOD001-201)
- Phase 3 study (Study NEOD001-CL002)

Study NEOD001-001 was an open-label, dose escalation study of the IV administration of single-agent NEOD001 in subjects with AL amyloidosis, which enrolled 27 subjects in the Escalation Phase in 7 cohorts (evaluating dose levels from 0.5 mg/kg to 24.0 mg/kg) and enrolled an additional 42 subjects in the Expansion Phase. The most frequently reported treatment-emergent adverse events (TEAEs) overall in Study NEOD001-001 (occurring in ≥10% of subjects [N=69], regardless of relationship to NEOD001) were fatigue, nausea, upper respiratory tract infection, peripheral edema, diarrhea, anemia, increased blood creatinine, dizziness, cough, constipation, headache, vomiting, dyspnea, pain in extremity, back pain, muscle spasms, rash, and urinary tract infection (Gertz et al, 2016). No confirmed anti-NEOD001 antibodies were detected. No dose-limiting toxicities (DLTs) or related serious adverse events (SAEs) were reported.

Efficacy data from the completed Study NEOD001-001 were reported by Gertz et al. (2016) and are summarized herein. Cardiac response was assessed by the clinically relevant cardiac biomarker, NT-proBNP, using Comenzo et al, 2012 criteria (Appendix 3). Thirty-six subjects were considered cardiac evaluable (i.e., baseline NT-proBNP ≥650 pg/mL). Among cardiac-evaluable subjects, 53% (n=19) met the criteria for cardiac best response and 47% (n=17) met cardiac best response category of stable disease. Renal response was defined according to Palladini et al (2014) criteria (Appendix 3). Thirty-six subjects were considered renal evaluable (i.e., baseline proteinuria ≥0.5 g/24 hours). Among renal-evaluable subjects, 64% (n=23) met the criteria for renal best response and 36% (n=13) met renal best response category of stable disease. Peripheral neuropathy response was defined according to Coelho et al (2012) criteria (Appendix 3). Eleven subjects in the Peripheral Neuropathy Expansion Cohort were considered peripheral neuropathy evaluable. Among peripheral neuropathy-evaluable subjects, 82% (n=9) met the criteria for neuropathy response (i.e., <2-point increase in Neuropathy Impairment Score–Lower Limbs [NIS-LL] score [88-point scale] from baseline) and 18% (n=2) were progressors. Two of the responders had complete resolution of peripheral neuropathy.

Eligible subjects from Study NEOD001-001 are being enrolled in Study NEOD001-OLE001, an open-label extension study to evaluate the long-term safety and tolerability of NEOD001 in subjects with AL amyloidosis. Subjects receive 24 mg/kg NEOD001 once every 28 days using the infusion duration established for the individual subject in Study NEOD001-001 or over 60 (±10) minutes.

Study NEOD001-201 (PRONTO) is an ongoing Phase 2b, multicenter, global, randomized, double-blind, placebo-controlled, two-arm, parallel group efficacy and safety study of NEOD001 as a single agent administered intravenously in adults with AL amyloidosis who had a hematologic response to first-line treatment for their amyloidosis (e.g., chemotherapy, ASCT) and have persistent cardiac dysfunction. Subjects are randomized in a 1:1 ratio to receive either NEOD001 (24 mg/kg) or placebo. Eligible subjects from Study NEOD001-201 may be enrolled in this open-label extension study (NEOD001-OLE251). As of 30 September 2016, 23 subjects were enrolled in Study NEOD001-201 and received 24 mg/kg NEOD001 or placebo (treatment remains blinded). One subject experienced a serious TEAE and no deaths were reported. A 64-year-old male experienced vasovagal syncope (characterized by bradycardia, hypotension, and syncope), which the Investigator assessed as Common Terminology Criteria for Adverse Events (CTCAE) Grade 3, serious, and related to study drug (treatment remains blinded). The subject recovered/resolved from the event of vasovagal syncope and discontinued the study on the day of the event.

Study NEOD001-CL002 (VITAL) is an ongoing Phase 3, multicenter, international, randomized, double-blind, placebo-controlled, two-arm efficacy and safety study in subjects with AL amyloidosis. Newly diagnosed subjects with AL amyloidosis are randomized in a 1:1 ratio to received either NEOD001 (24 mg/kg) plus standard of care or placebo plus standard of care, administered once every 28 days as a 1- to 2-hour IV infusion. All subjects are premedicated with 25 mg diphenhydramine (or an equivalent dose of an H1 antihistamine) and 650 mg acetaminophen (or an equivalent dose of paracetamol) within 30 to 90 minutes prior to the start of the infusion. As of 30 September 2016, 129 subjects were enrolled in the Phase 3 Study NEOD001-CL002 and received NEOD001 24 mg/kg plus standard of care OR placebo plus standard of care (treatment remains blinded). Sixty-five (50.4%) subjects experienced at least 1 serious TEAE, none of which were considered by the Investigator to be related to study drug treatment (blinded). As of the data lock point, 19 (14.7%) subjects had died; none of the deaths were considered by the Investigator to be related to study drug treatment (blinded). Five (3.9%) subjects had TEAEs that lead to study drug discontinuation.

Due to the limited number of infusion-site related reactions reported to date, premedication of subjects prior to the start of NEOD001 infusion is not required in the NEOD001-OLE001, NEOD001-201, and NEOD001-OLE251 protocols. As of 30 September 2016, 221 subjects had been dosed in the 4 completed or ongoing studies. In Study NEOD001-CL002 (VITAL), 129 subjects received a total of 534 infusions of blinded study drug (24 mg/kg NEOD001 plus standard of care or placebo plus standard of care). In Study NEOD001-201 (PRONTO), 23 subjects received a total of 51 infusions of blinded study drug (24 mg/kg NEOD001 or placebo). In Study NEOD001-001, 69 subjects received 994 infusions of NEOD001 (up to doses of 24 mg/kg) and 31 of these subjects had gone on to receive 59 infusions of 24 mg/kg NEOD001 in the open-label extension study (NEOD001-OLE001). In the completed Study NEOD001-001, 6 subjects experienced 9 infusion-site reactions were reported (6 subjects) and most (n=7; 78%) were classified as Grade 1. As noted above, 1 subject in the ongoing Study NEOD001-201 experienced an event of vasovagal syncope (characterized by bradycardia, hypotension, and syncope). Another aspect of safety monitoring in studies of NEOD001 has been a required postinfusion observation time ranging from 60 to 120 minutes. Studies NEOD001-201 and NEOD001-OLE251 allow for flexibility in monitoring time if no reactions are seen after the first 2 infusions, as described in Section 5.3.

Based on the data available to date, NEOD001 has been well tolerated as single-agent therapy in subjects with AL amyloidosis and no clinically significant safety signals have been identified.

1.3 Rationale for Study Conduct, Design, and Dose Selection

Study NEOD001-OLE251 is an open-label extension study, designed to allow subjects who completed Study NEOD001-201 to receive active treatment and to evaluate the long-term safety and efficacy of NEOD001 as a single agent in subjects with AL amyloidosis who were previously treated with PCD therapies. The selected dose of NEOD001, 24 mg/kg (dose not to exceed 2500 mg), was used in Study NEOD001-201 and will be continued in this study and the other ongoing studies of NEOD001.

NEOD001 is currently being studied in 3 other ongoing studies. Study NEOD001-201 is a double-blinded, randomized, controlled Phase 2b study designed to evaluate the efficacy and safety of NEOD001 as a single agent in patients with AL amyloidosis whose underlying PCD is stable but who still exhibit significant cardiac impairment. Study NEOD001-CL002 is a double-blinded, randomized, placebo-controlled Phase 3 study in patients with newly diagnosed AL amyloidosis disease who are receiving chemotherapy to treat the underlying PCD. In addition, Study NEOD001-OLE001, an open-label extension study for subjects previously enrolled in the Phase 1/2 Study NEOD001-001, allows subjects to receive NEOD001 and concomitant chemotherapy for treatment of their underlying PCD.

2 OBJECTIVES

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.

3 STUDY PLAN

3.1 Study Design

This is a global, multicenter, Phase 2b, open-label extension study of subjects with AL amyloidosis who had a hematologic response (Appendix 1) to first-line treatment for their amyloidosis (e.g., chemotherapy, ASCT) and completed Study NEOD001-201. Subjects in this study may receive concomitant chemotherapy (see Section 5.6.1).

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.

3.2 Endpoints

3.2.1 Safety Endpoints

- Long-term safety and tolerability as assessed by vital signs, 12-lead ECGs, routine clinical laboratory assessments, and AEs
- Immunogenicity

3.2.2 Efficacy Endpoints

- N-terminal pro-brain natriuretic peptide (NT-proBNP):
  - Response (Appendix 3)
  - Best response from baseline
  - Change from baseline
- Change from baseline in troponin T
- Change from baseline in the Short Form-36 Health Survey version 2 (SF-36v2) Physical Component Score (PCS), Mental Component Score (MCS), and the 8 subscales
- Change from baseline in the 6-Minute Walk Test (6MWT) distance (meters)
- Progression-free survival
- For renal-evaluable subjects:
  - Renal response (Appendix 3)

  - Renal best response from baseline
  - Change from baseline in creatinine, proteinuria, and eGFR
  - Time to eGFR:
    - ≤15 mL/min/1.73 m^2 (Chronic Kidney Disease [CKD] Stage 5)
    - <30 mL/min/1.73 m^2 (CKD Stage 4)
    - <60 mL/min/1.73 m^2 (CKD Stage 3)
  - Time to any worsening in CKD Stage
  - Time to 40% reduction in eGFR
  - Time to doubling of creatinine

- For peripheral neuropathy-evaluable subjects:
  - Change from baseline in NIS-LL total score
  - Peripheral neuropathy best response
  - Peripheral neuropathy response (Appendix 3)
  - 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 (Appendix 3)
  - Hepatic best response from baseline

- Time to all-cause mortality (overall survival)
- 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
- Pharmacokinetics (PK)

3.3 Number of Sites and Subjects

This is a global, multicenter study in approximately 40 sites and 100 subjects.

3.4 Randomization and Blinding

Not applicable.

3.5 Safety Monitoring Committee

Not applicable.

3.6 Estimated Treatment Duration

Each subject's study participation may be up to 38 months or until the study is terminated (per Section 4.6), whichever occurs first. The study consists of a Screening Phase (1 month), Treatment Phase (36 months), and EOS Visit (30 [±5] days after the last dose).

3.7 Definition of End of Study

The study is expected to be completed approximately 3 years after the last subject is enrolled. The study is considered completed with the last assessment for the last subject participating in the study or if the study is terminated, whichever occurs first, see Section 4.6.

4 SELECTION, DISCONTINUATION, AND WITHDRAWAL OF SUBJECTS

4.1 Inclusion Criteria

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

1. Completed the EOS Visit in Study NEOD001-201

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

    - Absolute neutrophil count (ANC) $\geq 1.0 \times 10^9$/L
    - Platelet count $\geq 75 \times 10^9$/L
    - Hemoglobin ≥9 g/dL
    - Total bilirubin ≤2 × upper limit of normal (ULN)
    - Aspartate aminotransferase (AST) ≤3 × ULN
    - Alanine aminotransferase (ALT) ≤3 × ULN
    - Alkaline phosphatase (ALP) ≤5 × ULN (except for subjects with hepatomegaly and isozymes specific to liver, rather than bone)
    - Estimated glomerular filtration rate (eGFR) ≥25 mL/min/1.73 m^2 as estimated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, or measured GFR ≥25 mL/min/1.73 m^2

3. Systolic blood pressure (BP) 80-180 mmHg

4. Women of childbearing potential (WOCBP) must have a negative pregnancy test during Screening and must agree to use highly effective physician-approved contraception (Appendix 2) from Screening to 90 days following the last study drug administration

5. Male subjects must be surgically sterile or must agree to use highly effective physician-approved contraception (Appendix 2) from Screening to 90 days following the last study drug administration

6. Ability to understand and willingness to sign an informed consent form (ICF) prior to initiation of any study procedures

4.2 Exclusion Criteria

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

1. Any new medical contraindication or clinically significant abnormality on physical, neurological, laboratory, vital signs, or ECG examination (e.g., atrial fibrillation; ***with the exception*** of subjects for whom the ventricular rate is controlled) that precludes continuation or initiation of treatment with NEOD001 or participation in the study

2. Symptomatic orthostatic hypotension that in the medical judgment of the Investigator would interfere with subject's ability to safely receive treatment or complete study assessments

3. Myocardial infarction, uncontrolled angina, uncontrolled ventricular arrhythmias, or ECG evidence of acute ischemia, within 6 months prior to the Month 1-Day 1 Visit

4. Severe valvular stenosis (e.g., aortic or mitral stenosis with a valve area <1.0 cm^2) or severe congenital heart disease

5. ECG evidence of acute ischemia or active conduction system abnormalities ***with the exception*** of any of the following:

    - First degree atrioventricular (AV) block
    - Second degree AV block Type 1 (Mobitz Type 1/Wenckebach type)
    - Right or left bundle branch block
    - Atrial fibrillation with a controlled ventricular rate (uncontrolled [i.e., >110 bpm] ventricular rate is not allowed [determined by an average of three beats in Lead II or 3 representative beats if Lead II is not representative of the overall ECG])

6. Has not recovered (i.e., equivalent to a CTCAE ≥Grade 2) from the clinically significant toxic effects of prior anticancer therapy. ***Exception:*** subjects who have received treatment with a proteasome inhibitor such as bortezomib may have CTCAE Grade 2 neuropathy.

7. Received any of the following within the specified time frame prior to the Month 1-Day 1 Visit:

    - Oral or IV antibiotics, antifungals, or antivirals within 1 week, ***with the exception*** of prophylactic oral agents. Note: In the event that a subject requires the chronic use of antivirals, Medical Monitor permission is required for entry into the study.
    - Hematopoietic growth factors, transfusions of blood or blood products within 1 week
    - Chemotherapy, radiotherapy, HDAC inhibitors, or other plasma cell directed therapy within 2 weeks
    - ASCT within 4 weeks (i.e., ASCT is allowed if it occurred ***before*** enrollment in Study NEOD001-201 or ***after*** completion of Study NEOD001-201 if it was at least 4 weeks before Month 1-Day 1 of this study)
    - Major surgery within 4 weeks (or within 2 weeks following consultation with and approval of Medical Monitor)
    - Planned organ transplant during the study
    - Any investigational agent, other than NEOD001, within 4 weeks

- Any experimental imaging agent directed at amyloid within 2 years

8. Active malignancy ***with the exception*** of any of the following:

   - Adequately treated basal cell carcinoma, squamous cell carcinoma, or in situ cervical cancer

   - Adequately treated Stage I cancer from which the subject is currently in remission and has been in remission for ≥2 years

   - Low-risk prostate cancer with Gleason score <7 and prostate-specific antigen <10 mg/mL

   - Any other cancer from which the subject has been disease-free for ≥2 years

9. History of Grade ≥3 infusion-related AEs or hypersensitivity to NEOD001

10. History of severe allergy to any of the components of NEOD001 such as histidine/ L-histidine, Trehalose, or Polysorbate 20

11. Currently known uncontrolled bacterial, viral, fungal, HIV, hepatitis B, or hepatitis C infection

12. Women who are breastfeeding

13. Any condition which could interfere with, or the treatment for which might interfere with, the conduct of the study or which would, in the opinion of the Investigator, unacceptably increase the subject's risk by participating in the study

14. Unable or unwilling to adhere to the study-specified procedures and restrictions

15. Subject is under legal custodianship

4.3 Early Treatment Discontinuation

If the subject discontinues study drug prior to the EOS Visit, they should return for an ETD Visit 30 (±5) days after their final administration of study drug as per Section 6.1.3. If a subject fails to return for the scheduled visit, a documented effort must be made to determine the reason. If the subject cannot be reached by telephone after 2 attempts, a certified letter will be sent to the subject (or the subject's legally authorized representative, if appropriate) requesting contact with the Investigator. This information will be recorded in the study records.

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

- Need for organ transplant

- A suspected NEOD001-related clinically significant immunologic reaction – collect additional serum samples, if possible, during the period following the treatment stoppage to allow for the determination of the persistence of anti-NEOD001 antibodies. At a minimum, samples should be collected at the ETD Visit and 3 months after the ETD Visit, if the subject agrees to return to the clinic.

- Occurrence of an AE or clinically significant laboratory abnormality that, in the opinion of the Investigator, warrants the subject's permanent discontinuation from study drug treatment; the Medical Monitor should be notified as soon as possible of any discontinuation of study drug due to an AE

- Suspected or confirmed pregnancy or nursing during study treatment period. Female subjects whose pregnancy test is positive at the ETD Visit must be followed to term or until termination of the pregnancy (Section 7.4.2).

After the ETD Visit, vital status follow-up phone calls should be made per Section 6.3.

4.4 Early Termination from the Study

Early termination occurs if the subject fails to complete the entire study, through the EOS Visit. Subjects may withdraw their consent to participate in this study at any time without prejudice. The Investigator must withdraw from the study any subject who requests to be withdrawn. A subject's participation in the study may be discontinued at any time at the discretion of the Investigator in accordance with his/her clinical judgment. The Sponsor or its designee should be notified in a timely manner of all subject discontinuations. When possible, the tests and evaluations listed for the ETD Visit should be carried out.

Early termination from the study may occur if:

- In the opinion of the Investigator, the subject cannot safely participate in the procedures required by the protocol

- Subject withdraws consent

- Subject is unwilling or unable to comply with the study requirements

- Subject is lost to follow-up

Vital status will be collected within legal and ethical boundaries for all screened subjects 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 subjects who withdrew participation from the study. If vital status is determined, the subject will not be considered lost to follow-up.

4.5 Replacement of Subjects

As this is an open-label study for subjects who completed Study NEOD001-201, no subjects will be replaced.

4.6 Termination of the Clinical Study, Investigator, or Study Site

The Sponsor reserves the right to terminate the study, participation of an individual Investigator, or a study site at any time for any reason. Conditions that may warrant termination include, but are not limited to:

- Clinical or administrative reasons
- Discovery of an unexpected, relevant, and/or unacceptable risk to subjects
- Sponsor's discontinuation of further development of the study drug
- Study drug becomes commercially available
- Failure of the Investigator to comply with the protocol, the requirements of the Institutional Ethics Committee/Institutional Review Board (IEC/IRB) or Competent Authority (CA), the Sponsor's procedures, or Good Clinical Practice (GCP) guidelines
- Inadequate recruitment of subjects by the Investigator

According to the study contract, the Investigator also reserves the right to terminate participation in the study.

5 TREATMENT OF SUBJECTS

5.1 Study Drug

Study drug consists of NEOD001.

5.1.1 Formulation and Packaging of NEOD001

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

5.1.2 Shipping, Storage, and Handling of NEOD001

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

If a study staff member becomes aware that the NEOD001 has not been properly handled (e.g., supply arrived at room temperature or was not placed in refrigerator upon receipt), follow the procedure outlined in the Pharmacy Manual or immediately contact the Study Monitor (contact information available in the Study Manual). In such an event, NEOD001 should be quarantined in a 2°C to 8°C refrigerator and must not be administered to any subject until the drug has been approved for use.

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

Refer to Section 5.3 and the Pharmacy Manual for further details about shipping, storage and handling of NEOD001.

5.2 Accountability and Return of Study Supplies

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

All study drugs provided by the Sponsor or provided at the study center should be retained at the site until otherwise instructed in writing by the Sponsor. Upon completion of the study or termination of the investigational site, all unused vials of study drug supplied by the Sponsor can be destroyed locally as per local institutional guidelines and a copy of the destruction certificate supplied to the Sponsor or may be shipped to a depot designated by the Sponsor. Refer to the Pharmacy Manual for additional information.

5.3 Dosage, Preparation, and Administration

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

Each vial of 500 mg of NEOD001 will be reconstituted with 9.6 mL sterile WFI to a concentration of 50 mg/mL resulting in a buffered, isotonic, preservative-free solution with a total extractable volume of 10 mL. Study drug will be prepared in a 250 mL IV bag of 0.9% saline. The equivalent volume of reconstituted NEOD001 will be withdrawn prior to transferring the drug solution into the IV bag, such that the total IV bag volume will be 250 mL. Refer to the Pharmacy Manual for complete information on preparing and administering the study drug.

The Pharmacy Staff at each site will be responsible for preparing the study drug.

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

NEOD001 will be administered once every 28 days (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. A minimum of 21 days between doses is required. The length of the infusion may be extended over a longer period of time if and when it is clinically indicated.

NEOD001 contains no antimicrobial preservatives. Once reconstituted, storage of study drug, inclusive of dilution and administration, should be limited to 24 hours under refrigerated conditions or 4 hours at room temperature. If it is anticipated that the infusion will extend beyond 4 hours, the reconstituted study drug should be split into multiple bags to ensure that no amount of reconstituted study drug will be at room temperature for longer than 4 hours (i.e., from the time of reconstitution of the vial to end of the infusion of a bag). The additional bag(s) should remain refrigerated until ready for use. The volume contained in the administration tubing should be completely flushed using 30 mL of 0.9% Sodium Chloride Injection (USP) after administration of study drug. The infusion line should NOT be used for blood draws.

Postdose Monitoring Period: All subjects will be closely monitored after completion of the study drug infusion as follows:

- If it has been <60 days since the subject's last visit in Study NEOD001-201, the subject should be monitored according to the observation time established for the individual subject in Study NEOD001-201

- If it has been ≥60 days since the subject's last visit in Study NEOD001-201, the subject should be monitored for 90 (±10) minutes for at least the first two infusions

- Beginning with the third infusion, the Investigator may decrease the monitoring time to no less than 60 minutes, if no infusion-related reactions were observed in the previous infusions and allowed per the IRB/IEC

- The Investigator may increase the 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.

5.4 Dosage Adjustments

5.4.1 Withholding of Study Drug

Subjects with symptomatic orthostatic hypotension and/or systolic BP <85 mmHg, which in the medical judgment of the Investigator would interfere with subject's ability to safely receive study drug, will have study drug withheld until the next scheduled monthly administration, but should still have all other study visit assessments completed. If study drug is withheld and subsequently rescheduled, central laboratory assessments required for that visit will need to be repeated if they were drawn >7 days prior to the rescheduled dosing date. A symptom-directed physical exam and vital signs need to be repeated prior to each dosing.

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

In the event of a suspected systemic infusion-related and/or hypersensitivity AE, the infusion should be immediately discontinued and appropriate supportive therapy should be administered per institutional practice, which may include, but is not limited to, epinephrine, IV fluids, corticosteroids, vasopressors, oxygen, bronchodilators, antihistamines, or acetaminophen/paracetamol. Subjects should be evaluated and carefully monitored until there is complete resolution of the AE (i.e., all hypersensitivity signs and symptoms have resolved). In addition to the institution's recommended assessments, blood samples should be obtained in the event of a suspected systemic infusion-related and/or hypersensitivity AE for assessment of the following: cytokine levels (IL-6, IL-8, TNF-alpha, and INF-gamma) complements C3, C4, and CH50; C-reactive protein (CRP), serum amyloid A/acute phase serum amyloid A (SAA/A-SAA); tryptase (serial levels: within 30 to 120 minutes of onset AND at 48 to 72 hours); serum NEOD001; and anti-NEOD001 antibody levels. If possible, samples should be collected while the acute symptoms persist.

For subjects with a Grade 2 infusion-related AE, if it is appropriate to restart the infusion, the infusion rate should be decreased by 50% (e.g., if the infusion was previously administered over 60 minutes, the new rate should be based on administering 250 mL over at least 90 minutes). If the subject is to receive additional infusions in subsequent weeks, the rate of these infusions should be discussed with and agreed upon prospectively by the Investigator and the Medical Monitor. In addition, for all subsequent infusions, maximal premedication must be administered according to institutional practice and should include an H1 blocker, an H2 blocker, an antipyretic such as acetaminophen/paracetamol and a steroid (e.g., 25-50 mg hydrocortisone IV).

If a subject experiences a Grade 3 infusion-related and/or hypersensitivity AE, the infusion should not be restarted. The decision to continue dosing this subject at their next scheduled administration should be discussed with the Medical Monitor. If the decision is made to proceed with subsequent dosing, **both** the dose and infusion rate will be reduced by 50% from the original dose (i.e., 12.5 mg/kg in 250 mL) and infusion rate (e.g., over at least 90 minutes [if the previous infusion time was 60 minutes]). In addition, maximal premedication must be administered according to institutional practice and should include an H1 blocker, an H2 blocker, an antipyretic such as acetaminophen/paracetamol and a steroid (e.g., 25-50 mg hydrocortisone IV). Subjects who have an infusion-related and/or hypersensitivity AE at the subsequent scheduled study drug administration must have study drug permanently discontinued and have an ETD Visit per Section 6.1.3.

Subjects who experience a Grade 4 infusion-related and/or hypersensitivity AE must have study drug permanently discontinued and have an ETD Visit per Section 6.1.3.

5.4.3 Dose Reductions

Dose reductions may be allowed in the event that an observed AE is believed to be related to study drug, and upon consultation between the Investigator and the Medical Monitor, is considered to be manageable by a 50% reduction in dose. The duration of the dose reduction will be at the Investigator's discretion.

5.5 Treatment Compliance

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

5.6 Prior and Concomitant Medication/Therapy

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

5.6.1 Allowed Concomitant Medication/Therapy

- Radiation therapy for the treatment of local amyloid deposits
- Concomitant chemotherapy:
    - The Investigator may prescribe chemotherapy as per standard of care
    - Monthly doses of NEOD001 should not be delayed or skipped due to adjustments made to chemotherapy dosing
    - If bortezomib is administered, antiviral prophylaxis is required

- Particular care must be taken to accurately report chemotherapy administration, including missed or delayed doses, and dose reductions

- Blood samples for local laboratory assessments must be collected per institutional practice prior to administration of chemotherapy

- Within 3 days before the first day of a new regimen of chemotherapy, conduct an unscheduled laboratory collection (including hematology, chemistry, prothrombin time/international normalized ratio [PT/INR], and partial thromboplastin time [PTT])

- If chemotherapy is administered on the same day as NEOD001, the chemotherapy must be administered after the NEOD001 observation period and postdose vital sign measurements

- Medications such as anti-emetics required for prophylaxis of emesis for the subsequent chemotherapy should be given after the ECG has been completed.

- Calcium channel blockers (if on stable dose)

- Steroids

5.6.2 Prohibited Concomitant Medication/Therapy

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

- Myeloablative chemotherapy with ASCT

- Organ transplant

- Histone deacetylase (HDAC) inhibitors

- Experimental imaging agent directed at amyloid

- Gadolinium contrast agents are only permitted in exceptional circumstances. If a patient requires the use of gadolinium contrast agents, contact the Medical Monitor

6 STUDY PROCEDURES

6.1 Evaluations by Visit

6.1.1 Screening Period: Days -28 to -1

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

Screening evaluations and procedures will be performed within 28 days prior to the first study drug administration on Month 1-Day 1. Individual test results that do not meet eligibility requirements may be repeated; full rescreening is allowed once per subject.

6.1.1.1 Assessments for Subjects Whose Previous Visit in Study NEOD001-201 was Within 60 Days of Screening

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

- Signed ICF
- Review inclusion and exclusion criteria to assess eligibility
- Medical History - Obtain 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
- Prior and concomitant medications/therapy taken or received by a subject within the 28 days prior to the Month 1-Day 1 Visit
- Assessment of AEs
- Complete physical examination - including height (per Section 6.5.1.3)
- Vital signs (HR, BP, RR, and body temperature; per Section 6.5.1.2) - collect after the subject has been at rest for ≥5 minutes
- NIS-LL (Appendix 6 and Section 6.5.2.5)
    - Note: NIS-LL is for all subjects who had peripheral neuropathy in Study NEOD001-201
- VASPI (Appendix 7 and Section 6.5.2.5)
    - Note: VASPI is for subjects with painful peripheral neuropathy in Study NEOD001-201
- SF-36v2 (Appendix 8)
    - Note: Administer SF-36v2 before conducting any other assessments on the same calendar day it is administered

- KCCQ (Appendix 9)
    - Note: Administer KCCQ after the SF-36v2, but before conducting any other assessments on the same calendar day it is administered
- 6MWT (Section 6.5.2.3); also collect HR and BP pre- and post-6MWT administration
    - Notes: Two pretreatment 6MWTs are required before the first administration of study drug, with a minimum of 4 days in between the two tests. The first Screening 6MWT is required to be performed between Days -28 and -5, at least 4 days prior to the second Screening 6MWT, which should be performed within 2 days prior to Month 1-Day 1 (i.e., on Day -2 or Day -1). NT-proBNP should be drawn before conducting 6MWT if being performed on the same calendar day.
- 12-lead ECG performed in triplicate (perform centrally)
- Laboratory Assessments (central laboratory, unless otherwise noted) – Note: 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:
    - Hematology and chemistry (including amylase and creatine kinase) per Appendix 10
    - Coagulation - PT/INR, PTT
    - Troponin T
    - NT-proBNP
        - Note: NT-proBNP should be drawn before 6MWT if being performed on the same calendar day
    - Urine pregnancy test for WOCBP
        - Note: Women with tubal ligations are considered to be of childbearing potential but women who are surgically sterile (hysterectomy) or postmenopausal ≥2 years are not considered to be of childbearing potential
- Other Assessments (see Laboratory Manual):
    - Anti-NEOD001 serum sample

6.1.1.2 Assessments for Subjects Whose Previous Visit in Study NEOD001-201 was ≥60 Days from Screening

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

- Signed ICF
- Review inclusion and exclusion criteria to assess eligibility

- Medical History - Obtain 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

- Prior and concomitant medications/therapy taken or received by a subject within the 28 days prior to the Month 1-Day 1 Visit

- Assessment of AEs

- Complete physical examination - including height (per Section 6.5.1.3)

- Vital signs (HR, BP, RR, and body temperature; per Section 6.5.1.2) - collect after the subject has been at rest for ≥5 minutes

- Eastern Cooperative Oncology Group performance status (ECOG PS) (Appendix 4)

- NYHA class (Appendix 5)

- NIS-LL (Appendix 6)

    - Note: NIS-LL is for all subjects who had peripheral neuropathy in Study NEOD001-201

- VASPI (Appendix 7)

    - Note: VASPI is for subjects who had painful peripheral neuropathy in Study NEOD001-201

- SF-36v2 (Appendix 8)

    - Note: Administer SF-36v2 before conducting any other assessments on the same calendar day it is administered

- KCCQ (Appendix 9)

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

- 6MWT (Section 6.5.2.3); also collect HR and BP pre- and post-6MWT administration

    - Notes: Two pretreatment 6MWTs are required before the first administration of study drug, with a minimum of 4 days between the two tests. The first Screening 6MWT is required to be performed between Days -28 and -5, at least 4 days prior to the second Screening 6MWT, which should be performed within 2 days prior to Month 1-Day 1 (i.e., on Day -2 or Day -1). NT-proBNP should be drawn before conducting 6MWT if being performed on the same calendar day.

- 12-lead ECG performed in triplicate (perform centrally)

- Laboratory Assessments (central laboratory, unless otherwise noted):
  - Hematology and chemistry (including amylase and creatine kinase) per Appendix 10
  - Coagulation - PT/INR, PTT
  - Troponin T
  - NT-proBNP
    - Note: NT-proBNP should be drawn before 6MWT if being performed on the same calendar day
  - Urine pregnancy test for WOCBP
    - Note: Women with tubal ligations are considered to be of childbearing potential but women who are surgically sterile (hysterectomy) or postmenopausal ≥2 years are not considered to be of childbearing potential
  - sFLCs
  - Serum immunofixation electrophoresis (IFE) and protein electrophoresis (PEP)
  - Urinalysis - dipstick per Appendix 10
  - 24-hour urine collection for:
    - Urine IFE and PEP
    - Urine protein excretion
- Other Assessments (see Laboratory Manual):
  - Anti-NEOD001 serum sample

6.1.2 Treatment Period: Monthly X-Day 1 (±5 days starting with Month 2)

Study visits will occur every 28 days based on scheduling from Month 1-Day 1. A ±5-day window is allowed for visits starting after Month 1. A minimum of 21 days between doses is required. When chemotherapy is administered on same day as NEOD001, it must be administered after the NEOD001 observation period.

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

An unscheduled central laboratory collection (i.e., hematology, chemistry, PT/INR, and PTT) will be conducted within 3 days before the first day of a new regimen of chemotherapy. An unscheduled sample will be taken in case of a relevant serious adverse event. If defects are identified, additional analytes will be evaluated, as indicated.

Prior to Study Drug Infusion:

The following assessments will be done monthly, unless otherwise specified, prior to dosing on Day 1. The predose assessments may be performed within the 3 days before the visit unless a different timeframe is specified:

- Concomitant medications/therapies
- Assessment of AEs
- Directed physical examination (per Section 6.5.1.3)
- Vital signs (HR, BP, RR, and body temperature; per Section 6.5.1.2) – within 30 minutes before start of dosing, after subject has been at rest ≥5 minutes; assess in same position for all time points
- ECOG PS (Appendix 4) – every 6 months
- NYHA class (Appendix 5) – every 6 months
- NIS-LL (Appendix 6) – every 6 months
    - Note: NIS-LL is for all subjects who had peripheral neuropathy in Study NEOD001-201
- VASPI (Appendix 7) – every 6 months
    - Note: VASPI is for subjects who had painful peripheral neuropathy in Study NEOD001-201
- SF-36v2 (Appendix 8) – every 6 months
    - Note: administer SF-36v2 before performing any other study assessments on the same calendar day it is administered
- KCCQ (Appendix 9) – every 6 months
    - Note: Administer after the SF-36v2, but prior to conducting any other assessments on the same calendar day it is administered

- 6MWT (Section 6.5.2.3) – every 6 months – also collect HR and BP pre- and post-6MWT administration
    - Notes: NT-proBNP should be drawn before conducting 6MWT if being performed on the same calendar day. If the 6MWT is conducted on the same calendar day as the study drug infusion, the 6MWT must be completed before initiation of the infusion
- 12-lead ECG in triplicate (perform centrally) – within 30 minutes before start of dosing – every 3 months
- Laboratory Assessments (central laboratory, unless otherwise noted):
    - Hematology and chemistry (including amylase and creatine kinase) per Appendix 10
    - Coagulation - PT/INR, PTT
    - Other coagulation indices – Month 1, Month 12 - per Appendix 11
        - **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:** *For subjects with defects identified at EOS/ETD in Study NEOD001-201:* collect sample and test analytes that were abnormal. *All other subjects:* collect sample. If defects are identified, additional analytes will be evaluated, as indicated.
    - Troponin T
    - NT-proBNP
        - Note: NT-proBNP should be drawn before conducting 6MWT if being performed on the same calendar day
    - Urine pregnancy test (WOCBP only)
    - sFLCs – every 6 months
    - Serum IFE and PEP – every 6 months
    - Urinalysis - dipstick per Appendix 10 – every 6 months
    - 24-hour urine collection - every 6 months for:
        - Urine IFE and PEP
        - Urine protein excretion

- Other Assessments (see Laboratory Manual):
    - NEOD001 serum sample – within 2 hours before infusion – every 6 months (±1 month)
    - Anti-NEOD001 serum sample – preinfusion – every 3 months

Study Drug Administration:

Subjects who present with symptomatic orthostatic hypotension and/or systolic BP <85 mmHg, which in the medical judgment of the Investigator would interfere with the subject's ability to safely receive treatment, will have study drug withheld until the next scheduled monthly administration, but should still have all other study visit assessments completed. If study drug is withheld and subsequently rescheduled, central laboratory assessments required for that visit will need to be repeated if they were drawn >7 days prior to the rescheduled dosing date. A symptom-directed physical exam and vital signs need to be repeated prior to each dosing.

- Month 1-Day 1:
    - Administer study drug IV over 60 (±10) minutes unless a longer infusion duration was established for the individual subject in Study NEOD001-201. See Section 5.3 for information on dosage, preparation, and administration of study drug.
- All Other Months-Day 1:
    - If the Month 1-Day 1 infusion was well tolerated without infusion-associated AEs, administer NEOD001 IV over 60 (±10) minutes unless a longer infusion duration was established for the individual subject during Study NEOD001-201. See Section 5.3 for information on dosage, preparation, and administration of study drug; if needed, see Section 5.4 for dose adjustment instructions.

Assessments After Infusion:

- Monitor subjects per Section 5.3 following completion of the study drug infusion
- Routine medications should not be administered for at least 15 minutes after the completion of the NEOD001 infusion and, if possible, should be delayed until completion of the postinfusion vital sign and ECG assessments
- Vital signs (HR, BP, RR, and body temperature; per Section 6.5.1.2) – after subject has been at rest ≥5 minutes; assess in same position for all time point
    - Month 1-Day 1:
        - At end of infusion (EOI) (+5 minutes)
        - 30 (±5) minutes after EOI
        - 60 (±10) minutes after EOI

- All Other Months:
  - EOI (+5 minutes)
  - 60 (±10) minutes after EOI

- 12-lead ECG in triplicate (perform centrally) – every 3 months:
  - Within 15 minutes after EOI

- Other Assessments (see Laboratory Manual):
  - NEOD001 serum sample within 4 hours after EOI – every 6 months (±1 month)
  - Collect additional blood samples if a significant toxicity is observed (e.g., a systemic infusion-related reaction, anaphylaxis, hypersensitivity reaction; Section 5.4.2) and if possible, samples should be collected while the acute symptoms persist

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

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

A final visit should occur 30 (±5) days after the last administration of NEOD001. The assessments shown for EOS/ETD should also be conducted for any unscheduled visit (i.e., a visit not specified by the protocol) as clinically indicated or if deemed necessary.

- Concomitant medications/therapy
- Assessment of AEs
- Complete physical examination (per Section 6.5.1.3)
- Vital signs (HR, BP, RR, and body temperature; per Section 6.5.1.2) - after subject has been at rest ≥5 minutes
- ECOG PS (Appendix 4)
- NYHA class (Appendix 5)
- NIS-LL (Appendix 6)
  - Note: NIS-LL is for all subjects who had peripheral neuropathy in Study NEOD001-201
- VASPI (Appendix 7)

  - Note: VASPI is for subjects who had painful peripheral neuropathy in Study NEOD001-201

- SF-36v2 (Appendix 8)
  - Note: Administer SF-36v2 before conducting any other assessments on the same calendar day it is administered
- KCCQ (Appendix 9)
  - Note: Administer after the SF-36v2, but prior to conducting any other assessments on the same calendar day it is administered
- 6MWT (Section 6.5.2.3); also collect HR and BP pre- and post-6MWT administration
  - Note: NT-proBNP should be drawn before conducting 6MWT if being performed on the same calendar day
- 12-lead ECG performed in triplicate (perform centrally)
- Laboratory Assessments (central laboratory, unless otherwise noted):
  - Hematology and chemistry (including amylase and creatine kinase) per Appendix 10
  - Coagulation - PT/INR, PTT
  - Other coagulation indices per Appendix 11 - *For subjects with defects identified at Month 12:* collect sample and test analytes that were abnormal. *All other subjects:* collect sample. If defects are identified, additional analytes will be evaluated, as indicated.
  - Troponin T
  - NT-proBNP
    - Note: NT-proBNP should be drawn before conducting 6MWT if being performed on the same calendar day
  - Urine pregnancy test (WOCBP only); see also Section 6.2
  - sFLCs
  - Serum IFE and PEP
  - Urinalysis - dipstick per Appendix 10
  - 24-hour urine collection for:
    - Urine IFE and PEP

  - Urine protein excretion

- Other Assessments (see Laboratory Manual):
  - NEOD001 serum sample
  - Anti-NEOD001 serum sample

6.2 90-day Postdose Pregnancy Test

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

6.3 Vital Status Follow-Up Phone Call

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.

6.4 Order of Assessments of Specific Tests

SF-36v2:

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

KCCQ:

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

6MWT:

- Questionnaires should be administered and clinical laboratory samples, including NT-proBNP, should be drawn prior to administering the 6MWT, if being performed on the same calendar day.

- Postbaseline 6MWTs must be completed before the study drug infusion is initiated, if being performed on the same calendar day.

ECGs:

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

Concomitant Medications:

- Routine medications should not be administered for at least 15 minutes after the completion of the NEOD001 infusion and, if possible, should be delayed until completion of the postinfusion vital sign and ECG assessments

- For subject receiving chemotherapy, medications such as anti-emetics required for prophylaxis of emesis for the subsequent chemotherapy should be given after the ECG has been completed

- If chemotherapy is administered on the same day as NEOD001, the chemotherapy must be administered after the NEOD001 observation period and postdose vital sign measurements

6.5 Methods of Assessment

6.5.1 Safety

6.5.1.1 Clinical Laboratory Evaluations

A central laboratory will be used for analysis of hematology, chemistry (including amylase), PT/INR, PTT, cardiac biomarkers, sFLCs, serum IFE/PEP, urinalyses, and 24-hour urine collection for urine IFE/PEP and urine protein excretion. Local urine pregnancy testing will be conducted as shown in Table 1. A positive urine pregnancy test (local laboratory) is to be confirmed with a serum pregnancy test (central laboratory). Local pregnancy test results will be collected via an eCRF and in the clinical database.

Local laboratory results may be obtained at the Investigator's discretion for subject management when necessary for obtaining results on a more immediate basis. Local laboratory results should also be obtained and reviewed for a safety assessment prior to each administration of chemotherapy. Results will be reviewed prior to dosing at each month's Day 1 visit to confirm that continued dosing is appropriate. Results from local laboratory tests (***Exception***: pregnancy tests) will not be collected via an eCRF or the clinical database.

Other Coagulation Indices: Citrated plasma samples will be collected and frozen for potential analysis of coagulation indices at a later date. These analyses may include but may not be limited to the indices listed in Appendix 11.

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

Bioanalytical Samples: A bioanalytical laboratory will be used for the analysis of serum NEOD001 and anti-NEOD001 samples (Sections 6.5.3 and 6.5.4).

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

6.5.1.2 Vital Signs

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

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

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

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

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

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

6.5.1.3 Physical Examination

Any unfavorable changes in physical examination findings considered by the Investigator as clinically significant will be documented on the eCRF as an AE. Other results of the physical examinations will not be collected via an eCRF or the clinical database. Physical examinations must be performed by the Investigator or a medically qualified delegate.

A **complete** physical examination includes height (Screening only), weight, and examination of the following: general appearance; head, ears, eyes, nose, and throat; neck; skin; cardiovascular system; respiratory system; gastrointestinal system; and nervous system. A **directed** physical examination includes weight and other components, which will be as clinically indicated. At **all visits**, the following are to be assessed: macroglossia, submandibular nodes/fullness, adenopathy, ecchymoses, liver/spleen size (palpable +/-), ascites (+/-), and edema (which should be quantified on a scale of 0-4+).

6.5.1.4 12-Lead ECGs

The ECGs will be performed centrally. Measurements will be made in triplicate, 1 to 10 minutes apart and taken after the subject has rested in a supine position for ≥5 minutes. Heart rate, PQ/PR duration, QRS duration, QT duration, and QTcF - Fridericia's correction formula, and the Investigator's overall interpretation will be recorded. Refer to Section 6.4 for details regarding order of assessments in relation to conducting 12-lead ECGs.

6.5.2 Efficacy

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

See Appendix 3.

6.5.2.2 Short Form-36 Version 2 (SF-36v2)

See Appendix 8. Details will be provided separately.

6.5.2.3 Kansas City Cardiomyopathy Questionnaire (KCCQ)

See Appendix 9. Details will be provided in the Study Manual.

6.5.2.4 6-Minute Walk Test (6MWT)

Details regarding the requirements for proper administration of the 6MWT are described in the Study Manual. As part of the 6MWT, BP and HR will be collected pre- and post-6MWT administration.

6.5.2.5 Peripheral Neuropathy Assessment

Peripheral neuropathy will be assessed as follows:

- The Neuropathy Impairment Score in Lower Limbs (NIS-LL; Appendix 6) assesses lower limb reflexes, sensation, and motor strength and will be administered to subjects who had peripheral neuropathy in Study NEOD001-201

- The Visual Analog Scale – Pain Intensity (VASPI; sample tool in Appendix 7) assesses a subject's level of pain related to peripheral neuropathy and will be administered to subjects who had painful peripheral neuropathy in Study NEOD001-201. Details regarding administration of the VASPI are described in the Study Manual.

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

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

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

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

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

6.5.2.6 ECOG

See Appendix 4.

6.5.2.7 NYHA

See Appendix 5.

6.5.3 Pharmacokinetics

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

6.5.4 Immunogenicity

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

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

Refer to the Laboratory Manual for additional details.

7 ADVERSE EVENTS/SERIOUS ADVERSE EVENTS AND REPORTING

7.1 Adverse Events—Definition

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

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

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

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

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

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

7.2 Adverse Events—Severity Rating

Adverse events will be assessed according to CTCAE v4.0 (National Cancer Institute, 2009). Adverse events that do not have a corresponding CTCAE term will be assessed according to their impact on the participant's ability to perform daily activities as listed below. The severity of each AE should be characterized and then classified into one of five clearly defined categories as follows:

- **Grade 1 (mild):** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2 (moderate):** Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activity of daily living (e.g., preparing meals, shopping for groceries or clothes, using the telephone, managing money).
- **Grade 3 (severe):** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (e.g., bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).
- **Grade 4 (life threatening):** Life-threatening consequences; urgent intervention indicated.
- **Grade 5 (fatal):** Death related to AE.

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

7.3 Adverse Events—Causality Rating

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

Guidelines for "Related" Events

- There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
- There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.

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

Guidelines for "Not related" Events

- There is little evidence to suggest there is a causal relationship. There is another reasonable explanation for the event.

- An adverse event will be considered "not related" to the use of the product if any of the following tests are met:

    - An unreasonable temporal relationship between administration of the product and the onset on the AE (e.g., the event occurred either before, or too long after administration of the product for it to be considered product-related)

    - A causal relationship between the product and the AE is biologically implausible (e.g., death as a passenger in an automobile accident)

    - A clearly more likely alternative explanation for the AE is present (e.g., typical adverse reaction to a concomitant drug and/or typical disease-related event)

Consider the Following When Assessing Causality

- Temporal associations between the agent and the event

- Effect of dechallenge and/or rechallenge

- Compatibility with known class effect

- Known effects of concomitant medications

- Preexisting risk factors

- A plausible mechanism

- Concurrent illnesses

7.4 Serious Adverse Events and Unexpected Adverse Events

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

- Is fatal

- Is life-threatening

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

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

Definition of Hospitalization
Hospitalization is defined by the Sponsor as a full admission to the hospital for diagnosis and treatment. This includes prolongation of an existing inpatient hospitalization.

Examples of visits to a hospital facility that do not meet the serious criteria for hospitalization include:

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

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

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

Definition of Disability

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

Definition of Medically Significant
Important medical events (medically significant events) that may not result in death, be life-threatening or require hospitalization may be considered to be an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and/or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are a new diagnosis of cancer, intensive treatment in an emergency room or at home for allergic bronchospasm, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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

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

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

7.4.1 Elective Procedures and Surgeries

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

- A prescheduled elective procedure or a routinely scheduled treatment is not to be considered an SAE, even if the subject is hospitalized, provided the site stipulates that:
    - The condition requiring the prescheduled elective procedure or routinely scheduled treatment was present before and did not worsen or progress between the subject's consent to participate in the clinical trial and the time of the procedure or treatment
    - The prescheduled elective procedure or routinely scheduled treatment is the sole reason for admission and intervention
- An untoward medical event occurring during the prescheduled elective procedure or routinely scheduled treatment should be recorded as an AE or a SAE. Any concurrent medications should also be recorded on the eCRF.

7.4.2 Other Reportable Information

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

7.4.3 Disease Progression and Death

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

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

7.4.4 Serious Adverse Events—Reporting

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

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

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

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

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

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

8 STATISTICAL METHODS AND CONSIDERATIONS

A statistical analysis plan, providing details about the specific planned analyses and hypothesis tests, will be prepared and approved by the Sponsor prior to study database lock.

Endpoints are listed in Section 3.2.

8.1 Analysis Populations

All analyses will be based on the Safety Population, defined as all subjects who receive any amount of study drug.

Select analyses will use efficacy subsets, defined as:

- Renal Evaluable Population: subjects who had renal involvement in Study NEOD001-201
- Peripheral Neuropathy Evaluable Population: subjects who had peripheral nerve involvement in Study NEOD001-201
- Hepatic Evaluable Population: subjects who had hepatic involvement in Study NEOD001-201

8.2 Analysis of Study Population and Subject Characteristics

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

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

Study drug administration data will be listed by study site, subject number, and visit; and any dose modifications will be flagged. Means and standard deviations will be used to summarize the total dose of NEOD001 received.

8.3 Analysis of Safety Endpoints

Safety will be assessed through changes in vital signs, 12-lead ECGs, laboratory test results, and summaries of AEs. All TEAEs and SAEs will be summarized.

Quantitative laboratory tests will be assigned toxicity grades based on CTCAE v4.0. Shifts in CTCAE toxicity grade of laboratory tests will be presented from baseline to worst value, last value, and at each postbaseline visit. Summaries will present the number and percentage of subjects with shifts in laboratory toxicity grade.

Descriptive statistics of the quantitative laboratory, vital sign, and ECG parameters will be presented by study visit, as well as the change from baseline.

8.4 Analysis of Efficacy Endpoints

Response rates will be summarized including 95% confidence intervals. The distributions of time-to-event endpoints (progression-free survival, overall survival) will be summarized using the Kaplan-Meier method.

All quantitative endpoints (except 6MWT distance) defined as the change from baseline will be analyzed using linear mixed models for repeated measurements (MMRM). The dependent variable will be the change from baseline at each time point. The model will include fixed effects for time point and treatment-by-time interaction. The baseline value of the corresponding endpoint will be included as a covariate and the unstructured covariance model will be used. The denominator degrees of freedom will be estimated using the Kenward-Roger approximation. The 6MWT distance change from baseline will be analyzed using a Wilcoxon signed rank test.

8.5 Analysis of Other Endpoints

8.5.1 Pharmacokinetics

Serum NEOD001 concentrations (sparse sampling) will be pooled with similar samples from other studies in a population PK analysis. Details will be provided in a separate document.

8.5.2 Immunogenicity

Serum anti-NEOD001 titers will be listed and correlated with clinical toxicity and serum NEOD001 concentrations (where available). Anti-NEOD001 antibody levels will be correlated with NEOD001 exposure level to assess potential dose concentration related associations when anti-NEOD001 antibody and corresponding PK data are available.

8.6 Determination of Sample Size

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

8.7 Handling of Dropouts and Missing Data

Observed data will be included in listings and summary tables. Sensitivity analyses imputing missing data may be conducted.

9 DATA RECORDING, RETENTION, AND MONITORING

9.1 Case Report Forms

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

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

9.2 Availability and Retention of Records

The Investigator must make study data accessible to the Sponsor, Study Monitor, other authorized representatives of the Sponsor and CA inspectors upon request. A file for each subject must be maintained at the clinical site that includes the signed ICF and the Investigator's copies of all source documentation related to that subject. The Investigator must ensure the reliability and availability of source documents from which the information on the eCRF was derived.

Investigators are required to maintain all study documentation, including documents created or modified in electronic format, for at least 15 years following the completion of the study unless local regulations or institutional policies require a longer retention period or the Investigator is otherwise notified in writing by the Sponsor. Essential documents should be retained until at least 2 years after the last approval of a marketing application in an International Council for Harmonisation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. The Investigator must not discard any records unless given written authorization by the Sponsor.

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

9.3 Quality Control and Quality Assurance

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

The Study Monitor is responsible for inspecting the eCRFs at regular intervals throughout the study to verify the following: adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The Monitor should have access to subject medical records and other study-related records needed to verify the entries on the eCRFs. The Investigator must agree to cooperate with the Monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

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

9.4 Subject Confidentiality

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

10 ETHICAL AND LEGAL ISSUES

10.1 Ethical Conduct of the Study

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

10.2 Regulatory Approval

The Sponsor or its designee will make the appropriate applications to the CA in each participating country for regulatory approval of the study and, if necessary, approval to import Investigational Product. The study will not start until the required regulatory approvals have been obtained in the appropriate jurisdiction.

10.3 Ethics Committee Approval

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

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

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

10.4 Subject Informed Consent

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

The ICF documents the study-specific information the Investigator provides to the subject and the subject's agreement to participate. Among other things, the Investigator will fully explain in layman's terms the nature of the study, along with the aims, methods, potential risks, and any discomfort participation in the study may entail. The subject must personally sign and date the ICF before any study-related procedures are performed. The original and any amended, signed and dated ICF(s) must be retained in the subject's file at the study site and a copy of the signed ICF must be given to the subject.

10.5 Subject Compensation for Adverse Effects on Health

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

10.6 Protocol and ICF Amendments

Protocol amendments and amendments to the ICF must be made only with the prior approval of the Sponsor and/or its designee. The IRB/IEC or CA must be informed of all amendments and give approval for any amendments related to the safety of the subjects or the conduct of the trial (Section 10.3). The Investigator must send a copy of the approval letter from the IRB/IEC or CA to the Sponsor and/or designee. The Sponsor or its designee will also obtain the appropriate approval from the CA in each participating country for any substantial amendments before implementing the changes in that country.

10.7 Finance, Insurance, and Indemnity

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

10.8 Publication Policy

All publication rights are delineated in the Clinical Study Agreement.

11 REFERENCES

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12 APPENDICES

Appendix 1 Hematologic Response and Progression Criteria

Response Subcategory	Response Criteria
Complete Response (CR)	• Normalization of FLC 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 FLC 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 FLC increase of 50% to >10 mg/dL (100 mg/L)

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

Appendix 2 Examples of Highly Effective Contraception Methods

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

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

[1] Hormonal contraception may be susceptible to interaction with the Investigational Medicinal Product (IMP), which may reduce the efficacy of the contraception method.

[2] Contraception methods that in the context of this guidance are considered to have low user dependency.

[3] Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the women of childbearing potential (WOCBP) trial participant and that the vasectomised partner has received medical assessment of the surgical success.

[4] In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Source: Clinical Trial Facilitation Group, 2014.

Appendix 3 Organ Response and Progression Criteria

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

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

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

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

c Palladini et al, 2014.

d Coelho et al, 2012.

Appendix 4 Eastern Cooperative Oncology Group (ECOG) Performance Status

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

Source: Oken et al, 1982.

Appendix 5 New York Heart Association (NYHA) Functional Classification

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

Source: adapted from American Heart Association, 2016.

Appendix 6 Neuropathy Impairment Scale – Lower Limbs (NIS-LL)

prothena

Neuropathy Impairment Scale – Lower Limbs (NIS-LL)
NEOD001-OLE251

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 7 Visual Analog Scale – Pain Intensity (VASPI)

VISUAL ANALOG SCALE – PAIN INTENSITY

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

Appendix 8 Short Form-36 Health Survey Version 2 (SF-36v2)

Your Health and Well-Being

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

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

In general, would you say your health is:

Excellent
Very good
Good
Fair
Poor

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Not at all
A little bit
Moderately
Quite a bit
Extremely

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

How TRUE or FALSE is the following statement for you?

My health is excellent.

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

Appendix 9 Kansas City Cardiomyopathy Questionnaire (KCCQ)

The KC Cardiomyopathy Questionnaire

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

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

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

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

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

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

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

 Original US English

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

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

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

It has been ...

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

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

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

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

It has been ...

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

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

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

Original US English

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

It has been ...

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

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

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

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

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

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

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

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

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

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

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

Original US English

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

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

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

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

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

Original US English

Appendix 10 Laboratory Tests

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

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

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

Cardiac Biomarkers:
- Troponin T
- NT-proBNP

Coagulation:
- PT/INR
- PTT
- Other coagulation indices – see Appendix 11

Urinalysis - Dipstick:
- Color & clarity
- Specific gravity
- pH
- Protein
- Glucose
- Ketones
- Bilirubin
- Urobilinogen
- Blood
- Nitrite
- Leukocyte esterase
- Microscopic
- Pregnancy (WOCBP only) (E)[f]

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; (E) = may be used for eligibility; eGFR = estimated glomerular filtration rate; FLC = free light chain; GGT = gamma-glutamyl transpeptidase; IFE = immunofixation electrophoresis; LDH = lactate dehydrogenase; nAb = neutralizing antibody; 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; sFLC = serum free light chains; WBC = white blood cell; WOCBP = women of childbearing potential.

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

b See details in Section 5.4.2 regarding collection of samples for inflammatory biomarkers 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 nAb assay.

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

e GFR = 141 × min (Scr /κ, 1)α × max(Scr /κ, 1)-1.209 × 0.993Age × 1.018 [if female] × 1.159 [if black]
where: Scr = serum creatinine in mg/dL; κ = 0.7 for females, 0.9 for males; α = -0.329 for females, -0.411 for males; min = the minimum of Scr /κ or 1; max = the maximum of Scr /κ or 1. Measured GFR is allowed for eligibility purposes only; eGFR must be used throughout the study.

f A positive urine pregnancy test (local laboratory) is to be confirmed with a serum pregnancy test (central laboratory).

Appendix 11 Other Coagulation Indices

For each coagulation time point in Table 1 and Section 6.1.2, 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)	Fibrin Monomer
Partial Thromboplastin Time Mixing Studies	Fibrinogen Activity
D-dimer, quantitative	Fibrinogen Antigen
Euglobulin Lysis Time	High-Molecular Weight Kininogen
Factor II Activity	Prekallikrein
Factor IV Activity	Plasminogen Activator Inhibitor-1 Antigen
Factor V Activity	Plasminogen Activator Inhibitor-1 Activity
Factor VII Activity	Plasmin-antiplasmin Complex
Factor VIII Activity	Plasminogen Activity
Factor VIII Antigen Quantitation	Protein C Activity
Factor IX Activity	Protein S Antigen Free
Factor X Activity	Thrombin Time
Factor XI Activity	Tissue Plasminogen Activator Activity
Factor XII Activity	Tissue Plasminogen Activator Antigen
Factor XIII Activity	von Willebrand Factor (vWF) Activity (Ristocetin Cofactor)
	vWF Antigen
	vWF Multimers