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Official Title:	Open-label Extension Study to Evaluate the Long-term Safety and Tolerability of NEOD001 in Subjects with Light Chain (AL) Amyloidosis
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The protocol for Study NEOD001-OLE001 was amended one time.

Date of Original Protocol:	16 October 2015
Date of Protocol Amendment 1:	09 March 2017

The following key changes were made:

Overview of Major/Substantial Changes in Amendment 1:

- Extended study participation duration from 14 to 38 months or until the study is terminated, whichever occurs first
- Eliminated collection of archive samples
- Eliminated routine collection of citrated plasma samples for coagulation indices (samples only to be collected in cases of relevant serious adverse events)
- Reduced frequency of SF-36 and 6MWT from every 3 months to every 6 months
- Reduced postdose monitoring time beginning with the third infusion

CLINICAL RESEARCH PROTOCOL

Study Title:	**Open-label Extension Study to Evaluate the Long-term Safety and Tolerability of NEOD001 in Subjects with Light Chain (AL) Amyloidosis**
Protocol Number:	NEOD001-OLE001
Investigational Product:	NEOD001
IND Number:	113495
Indication:	AL Amyloidosis
Sponsor:	Prothena Therapeutics Limited Adelphi Plaza, Upper George's Street Dún Laoghaire, Co. Dublin A96 T927, Ireland
Sponsor Representative:	Prothena Biosciences Inc 331 Oyster Point Boulevard South San Francisco, CA 94080 USA
Sponsor's Chief Medical Officer:	[redacted]
Development Phase:	2
Date of Original Protocol:	16 October 2015
Date of Protocol Amendment 1:	09 March 2017

SPONSOR PROTOCOL APPROVAL PAGE

Protocol Title: A Phase 2 Open-label Extension Study to Evaluate the Long-term Safety and Tolerability of NEOD001 in Subjects with Light Chain (AL) Amyloidosis

Protocol Number:	NEOD001-OLE001
Sponsor:	Prothena Therapeutics Limited
Date of Original Protocol:	16 October 2015
Date of Protocol Amendment 1:	09 March 2017

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 Date

INVESTIGATOR SIGNATURE PAGE

Protocol Title: A Phase 2 Open-label Extension Study to Evaluate the Long-term Safety and Tolerability of NEOD001 in Subjects with Light Chain (AL) Amyloidosis

Protocol Number: NEOD001-OLE001

Sponsor: Prothena Therapeutics Limited

Date of Original Protocol: 16 October 2015

Date of Protocol Amendment 1: 09 March 2017

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

Investigator Signature Date

Investigator Print Name

Please return the form to Prothena or its designee. Contact details will be provided to the Investigator. Please retain a copy for your study files.

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PROTOCOL SYNOPSIS

Title	A Phase 2 Open-label Extension Study to Evaluate the Long-term Safety and Tolerability of NEOD001 in Subjects with Light Chain (AL) Amyloidosis
Study Phase	2
Indication	AL amyloidosis
Objectives	Primary: • To evaluate long-term safety and tolerability of NEOD001 Secondary: • To assess the immunogenicity of NEOD001 • To incorporate serum NEOD001 concentrations in a population pharmacokinetics (PK) analysis Exploratory: • To evaluate overall survival • To evaluate change in 6-Minute Walk Test (6MWT) • To evaluate general health-related quality of life using the Short Form-36 (SF-36)
Study Design	This is an open-label study for subjects previously enrolled and treated for at least 9 months in Study NEOD001-001.
Number of Sites and Subjects	Multicenter study in approximately 70 subjects
Estimated Study and Treatment Duration	A subject's study duration may be up to 38 months or until the study is terminated (per Section 4.5), whichever occurs first. The study consists of a Screening Phase (1 month), Treatment Phase (36 months), and the End of Study (EOS) Visit 30 (±5) days after the last dose.
Summary of Subject Eligibility Criteria	**Inclusion Criteria** (subject must meet ***all*** of the following): 1. Previously enrolled and treated for at least 9 months in Study NEOD001-001 2. Ability to understand and willingness to sign an informed consent form prior to initiation of any study procedures 3. Has adequate bone marrow reserve, hepatic and renal function, as demonstrated by: o Absolute neutrophil count (ANC) $\geq 1.0 \times 10^9$/L

	○ Platelet count ≥75 × 10^9/L ○ Hemoglobin ≥9 g/dL ○ Total bilirubin ≤2 times the upper limit of normal (× ULN) ○ Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) ≤3 × ULN ○ Estimated glomerular filtration rate ≥30 mL/minute 4. Seated systolic blood pressure 90 to 180 mmHg 5. ECOG Performance Status 0 to 2 6. Women of childbearing potential (WOCBP) must have a negative serum pregnancy test within 28 days prior to the first administration of study drug and agree to use highly effective physician-approved contraception (Appendix 1) from 30 days prior to the first study drug administration to 90 days following the last study drug administration 7. Male subjects must be surgically sterile or must agree to use highly effective physician-approved contraception (Appendix 1) from 30 days prior to the first study drug administration to 90 days following the last study drug administration
	Exclusion Criteria (subject must ***not*** meet any of the following): 1. Any new medical contraindication or clinically significant abnormality on physical, neurological, laboratory, vital signs, or electrocardiogram (ECG) examination (e.g., atrial fibrillation; ***with the exception*** of subjects for whom the ventricular rate is controlled) that precludes continued or initiation of treatment with NEOD001 or participation in the study 2. History of Grade ≥3 infusion-associated adverse events (AEs) or hypersensitivities to NEOD001 or any of its excipients 3. Treatment with any anticancer therapy (standard or investigational) within the 14 days prior to the first dose of study drug. In addition, subjects must have fully recovered (i.e., National Cancer Institute Common Terminology Criteria for Adverse Events [CTCAE] Grade 1 [***exception****:* subjects with prior bortezomib may have CTCAE Grade 2 neuropathy]) from the clinically significant toxic effects of

	that treatment 4. Received any of the following within the specified time frame prior to the first administration of study drug: o Hematopoietic growth factors, transfusions of blood or blood products within 1 week o Major surgery within 2 weeks o Radiotherapy within 2 weeks o Transplant within 8 weeks o Investigational drug other than NEOD001 within 4 weeks o Another experimental anti-amyloid therapy other than NEOD001 within 2 years 5. Uncontrolled symptomatic orthostatic hypotension 6. Myocardial infarction, uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia, within 6 months prior to the first dose of study drug 7. Uncontrolled infection 8. Secondary malignancy, ***with the exception of***: o Adequately treated basal cell carcinoma, squamous cell carcinoma, or in situ cervical cancer o Adequately treated stage I cancer from which the subject is currently in remission o Any other cancer from which the subject has been disease-free for ≥3 years 9. Uncontrolled human immunodeficiency virus (HIV), hepatitis B, or hepatitis C infection 10. Women who are lactating
Drug, Drug Dosage, Formulation, and Route of Administration	NEOD001 is supplied as a sterile, lyophilized dosage form in a 20/25-mL vial containing 500 mg NEOD001. Each vial will be reconstituted with 9.6 mL sterile water for injection (WFI) to a concentration of 50 mg/mL resulting in a buffered, isotonic, preservative-free solution. NEOD001, 24 mg/kg (not to exceed 2500 mg), will be administered once every 28 (±5) days using the infusion duration established in Study NEOD001-001 or over

	60 (±10) minutes. The length of the infusion may be extended over a longer period of time if and when it is clinically indicated per Section 5.3. If an infusion-related reaction occurs, for all subsequent dosing sessions the subject will be premedicated per Section 5.4.2.
Control Group	Not applicable
Procedures	See Schedule of Events Table 1. Of note, two pretreatment 6MWTs are required before the first administration of study drug, with a minimum of 4 days in between the two tests. The second test must be completed 1 to 2 days before the Month 1-Day 1 Visit. The SF-36 must be administered before performing any other study assessments on the day it is administered. The N-terminal pro B-type natriuretic peptide (NT-proBNP) must be drawn before conducting 6MWT, if performed on the same calendar day.
Endpoints	Primary: • Assessment of the safety and tolerability of NEOD001 as assessed by vital signs, duration of therapy, 12-lead ECGs, routine laboratory assessments, and frequency and severity of AEs Secondary: • Assessment of immunogenicity by measurement of anti-NEOD001 antibodies • Serum NEOD001 concentrations (sparse sampling) will be pooled with similar samples from other studies in a population PK analysis Exploratory: • Time to all-cause mortality from baseline in Study NEOD001-001 • Change from baseline (of this study) in the 6MWT • Change from baseline (of this study) in the SF-36

Statistical Considerations and Methods	Analysis Populations: The Safety Population, which will include all subjects who receive at least one NEOD001 infusion, will be used for all analyses. Safety Analyses: *Adverse Events* - AEs will be coded using the Medical Dictionary of Regulatory Activities (MedDRA). The incidence of treatment-emergent adverse events (TEAEs) occurring on or after treatment on Study Day 1 will be tabulated by MedDRA System Organ Class and Preferred Term, and by severity and relationship to treatment. TEAEs leading to discontinuation and serious adverse events (SAEs) will be summarized. *Clinical Laboratory Evaluations* - Descriptive statistics summarizing central laboratory data will be presented for all study visits. Changes from baseline to each study visit will also be summarized. *Additional Safety Assessments* - Additional safety assessments include vital signs and ECGs. Descriptive statistics of the vital sign and ECG parameters will be presented by study visit, as well as the change from baseline at each visit. Efficacy Analyses: Overall survival will be summarized using the Kaplan-Meier method. The change from baseline in the 6MWT will be summarized using the mean, standard deviation, median, and minimum and maximum values. Other Analyses: *Immunogenicity* - Serum anti-NEOD001 antibody titers will be listed. *Population PK* - 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) Determination of Sample Size: Not applicable as this is an extension study for subjects previously enrolled and treated for at least 9 months in Study NEOD001-001.
Sponsor	Prothena Therapeutics Limited

Table 1 Schedule of Events

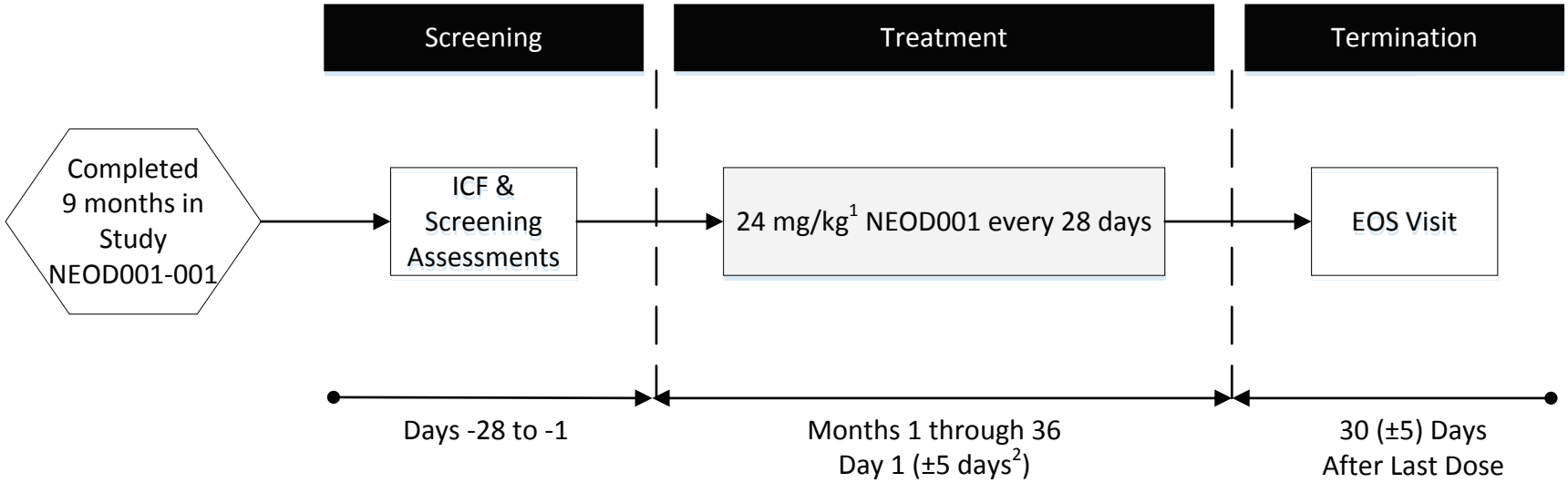
	Assessment or Procedure	Screening[1]		Treatment	Termination
		Days -28 to -1			
		<60 days since last visit in Study NEOD001-001	≥60 days since last visit in Study NEOD001-001	Months 1- 36 Day 1 (±5[2])	EOS[3] 30 (±5) days after last dose
	Written Informed Consent	X	X		
	Eligibility Review	X	X		
Clinical	Medical History[4]	X	X		
	Historical NT-proBNP Levels	X	X		
	Prior/Concomitant Medication/Therapy[5]	X	X	X	X
	Adverse Event Assessment[6]	X	X	X	X
	Physical Examination[7]	X	X	X	X
	Vital Signs[8]	X	X	X	X
	ECOG PS/NYHA Class		X	X	X
	Peripheral Neuropathy Assessment[9]	X	X	Every 3 months[10]	X
	SF-36 Health Survey[11]	X	X	Every 6 months[12]	X
	6MWT[13]	X[14]	X[14]	Every 6 months[12]	X
	Echocardiogram		X	Every 12 months[15]	X[16]
	ECG (12-lead in triplicate; local)	X	X	Every 3 months[10,17]	X
	Vital Status Telephone Call				Every 3 months[18]
Laboratory[21]	Hematology & Chemistry[19]	X	X	X	X
	Amylase	X	X	X	X
	Coagulation[20]	X	X	X	X
	Troponin T	X	X	X	X
	NT-proBNP[13]	X	X	X	X
	Pregnancy (WOCBP)[22]	X	X	X	X, X[23]
	Serum Free Light Chain		X	Every 3 months[10]	X
	SPEP & 24-hour UPEP[24]		X	Every 3 months[10,25]	X
	SIFE & UIFE		X	Every 3 months [10,25]	X
	Urinalysis (dip stick)[26]		X	Every 3 months[10]	X
	24-hr Urine Protein Excretion[24]		X	Every 3 months[10]	X
Other	Serum NEOD001 Sample[27]	X	X	Every 3 months[10]	X
	Serum anti-NEOD001 Antibody Sample[28]	X	X	Every 3 months[10]	X
	NEOD001 Infusion[29]			X	

ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EOI = end of infusion; EOS = End of Study; INR = international normalized ratio; NT-proBNP = N-terminal pro B-type natriuretic peptide; NYHA = New York Heart Association; PK = pharmacokinetic; PT = prothrombin time; PTT = partial thromboplastin time; SF-36 = Short form-36; SIFE = serum immunofixation electrophoresis; 6MWT = 6-Minute Walk Test; SPEP = serum protein electrophoresis; UIFE = urine immunofixation electrophoresis; UPEP = urine protein electrophoresis; WOCBP = women of childbearing potential.

1. Rescreening is allowed once per subject. Only repeat tests that did not meet eligibility requirements.
2. Day 1 assessments may be conducted ±5 days from Day 1, with the exception of Month 1-Day 1 (i.e., no window is allowed at Month 1).

3. Conduct the EOS Visit 30 (±5) days after last administration of study drug. Two additional evaluations are to be conducted beyond this time point, see Footnotes 18 and 23.
4. Obtain medical history since subject's last visit in Study NEOD001-001 (including all major hospitalizations and surgeries), as well as the subject's current medical status and prior therapies for AL amyloidosis. Adverse events that resolved prior to the subject's last visit in Study NEOD001-001 and prior to signing the ICF for this study should be assessed as possible medical history in this study.
5. Record all prior therapies for AL amyloidosis taken prior to signing ICF for this study and since last visit in Study NEOD001-001. 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 Visit, and any changes to concomitant medications during the study. See Study Manual for more information.
6. Adverse events will be collected from the time that the informed consent form is signed through 30 days after the last dose of study drug or last study visit, whichever is later. Record any adverse events that were ongoing from the subject's last visit in Study NEOD001-001 and at the time of the NEOD001-OLE001 Screening Visit.
7. Physical examination will include weight, height (Screening only), and examination of the following: general appearance; head, ears, eyes, nose, and throat; neck; skin; cardiovascular system; respiratory system; abdominal system; and nervous system. A complete physical examination will be done at Screening and EOS; at all other visits, the components of the physical examination will be as clinically indicated. However, at all time points the following should be assessed: macroglossia, submandibular nodes/fullness, adenopathy, ecchymoses, liver/spleen size (palpable +/-), ascites (+/-), and edema (which should be quantified on a scale of 0-4).
8. Vital signs include heart rate (HR), blood pressure (BP), respiratory rate (RR), and body temperature; assess per Section 6.3.2. **Month 1-Day 1:** Predose, halfway through infusion, immediately at EOI (+5 minutes), and 30 (±5) minutes and 60 (±10) minutes after EOI. **All Other Months-Day 1:** Predose, EOI (+5 minutes), and 60 (±10) minutes after EOI.
9. Peripheral neuropathy assessment: only for subjects previously enrolled in Cohort C of Study NEOD001-001.
10. Perform every 3 months (Months 3, 6, 9, 12, etc.).
11. Administer SF-36 before performing any other study assessments on the day it is administered (Appendix 2).
12. Perform every 6 months (Months 6, 12, 18, etc.).
13. NT-proBNP must be drawn before conducting 6MWT, if performed on the same calendar day. Collect blood pressure and heart rate pre- and post-6MWT administration.
14. Two pretreatment 6MWTs are required before the first administration of study drug, with a minimum of 4 days in between the two tests. The second test must be completed 1 to 2 days before the Month 1-Day 1 Visit.
15. Echocardiogram to be conducted every 12 months and may be conducted within 10 days before the visit.
16. Repeat echocardiogram at EOS if not performed within 60 days prior to visit.
17. For all post-Screening visits, ECGs are to be performed predose and within 15 minutes after the EOI.
18. Conduct telephone call approximately 3 months after subject's last study visit and approximately every 3 months thereafter for up to 5 years, death, or subject withdraws consent, whichever occurs first.
19. Hematology and chemistry per Appendix 3. At Screening, include Screen for Infectious Diseases per Appendix 3. 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).
20. Coagulation per Appendix 3. Collect unscheduled citrated plasma samples for subjects with relevant serious adverse event(s); if defects are identified, additional analytes will be analyzed, as indicated (see Appendix 4).
21. All laboratory tests to be done centrally, unless otherwise noted.
22. Perform pregnancy tests for WOCBP as follows: **Screening:** serum test (central) within 28 days before Month 1-Day 1; **Monthly starting with Month 2**: urine test (local) predose; **EOS:** serum test (central).A positive urine pregnancy test (local laboratory) is to be confirmed with a serum pregnancy test (central laboratory).
23. Perform serum pregnancy test (local; WOCBP only) 90 (±5) days after the last study drug administration.
24. Begin urine collections 24 hours prior to the study visit.
25. After Baseline, use to confirm initial within-study hematologic complete response only.
26. Urinalysis per Appendix 3.
27. NEOD001 serum samples (for population PK analysis): collect predose, at EOI (record the time, but the sample can be collected at any time after the infusion on Day 1), and at other times as clinically indicated, such as when significant toxicity occurs.
28. Anti-NEOD001 antibody samples: collect predose and at other times as clinically indicated, such as when significant toxicity occurs.
29. NEOD001 will be administered every 28 (±5) days. Subjects should be closely monitored for 90 (±10) minutes following completion of the study drug infusion. Beginning with the third infusion, the Investigator may decrease the postdose 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. If parenteral chemotherapy is administered on the same day as NEOD001, the chemotherapy must be administered **after** the observation period.

Figure 1 NEOD001-OLE001 Study Design



EOS = end of study; ICF = informed consent form.
[1] Maximum dose not to exceed 2500 mg.
[2] ±5-day window applicable to Months 2+.

GLOSSARY OF TERMS

Abbreviation/Acronym	Definition
AA	Amyloid A
ADA(s)	Anti-drug antibody(ies)
AE	Adverse event
AEF	Amyloid-enhancing factor
AL	Amyloid light chain
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ASCT	Autologous stem cell transplant
AST	Aspartate aminotransferase
BP	Blood pressure
BSA	Bovine serum albumin
BUN	Blood urea nitrogen
CTCAE	Common Terminology Criteria for Adverse Events
(E)	Eligibility (i.e., a test that may be used to determine eligibility)
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EOI	End of infusion
EOS	End of Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase
HIV	Human immunodeficiency virus
HR	Heart rate

Abbreviation/Acronym	Definition
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Institutional Ethics Committee
IFE	Immunofixation electrophoresis
IgG1	Immunoglobulin G1
INR	International normalized ratio
IRB	Institutional Review Board
IV	Intravenous(ly)
LDH	Lactate dehydrogenase
NT-proBNP	N-terminal pro B-type natriuretic peptide
NYHA	New York Heart Association
PCD	Plasma cell dyscrasia
PEP	Protein electrophoresis
PK	Pharmacokinetic(s)
PS	Performance status
PT	Prothrombin time
PTT	Partial thromboplastin time
QTc	Corrected QT interval
RBC	Red blood cell
RR	Respiratory rate
SAE	Serious adverse event
SFLC	Serum free light chain
SIFE	Serum immunofixation electrophoresis
6MWT	Six-Minute Walk Test
SPEP	Serum protein electrophoresis
TRIAD	Transgenic Rapidly Inducible Amyloid Disease
UIFE	Urine immunofixation electrophoresis

Abbreviation/Acronym	Definition
ULN	Upper limit of normal
UPEP	Urine protein electrophoresis
US	United States
WBC	White blood cell
WFI	Water for injection
WOCBP	Women of childbearing potential

1 INTRODUCTION

1.1 LIGHT CHAIN (AL) AMYLOIDOSIS

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

AL amyloidosis is a rare disorder. Although the exact incidence of AL amyloidosis in the United States (US) is unknown, a weighted average from 5 sources (Kyle et al, 1992; Simms et al, 1994; Kyle et al, 2002; Kyle et al, 2006; Junicon Study) estimates the incidence to be 7.6 new cases per million population per year, which is approximately 2300 new cases per year.

Approximately, two thirds of AL amyloidosis patients present with one or two major organ systems involved (e.g., cardiac, renal, gastrointestinal tract, hepatic, autonomic nervous system, peripheral nervous system, soft tissues) while a third of patients present with more than two systems involved (Kyle et al, 1992). AL amyloidosis is most commonly associated with cardiac and/or renal dysfunction, with overt restrictive cardiomyopathy observed in approximately 50% of all cases, and subclinical cardiac involvement detected in almost every case at autopsy or on endomyocardial biopsy (Falk and Dubrey, 2010).

AL amyloidosis has two important disease components. The first component is the plasma cell dyscrasia (PCD), which results in the overproduction of immunoglobulin light chain, and the second component is the impact of the soluble and insoluble amyloid on organ structure and function, leading to the clinical manifestations of the disease. While there are no approved treatments for AL amyloidosis, the current standard of care for these patients is aimed at reducing or eliminating the bone marrow disorder, the PCD. The most aggressive treatment options include autologous stem cell transplant (ASCT) and high-dose chemotherapy for those patients who can tolerate it. Other treatment regimens include combinations of drugs often used to treat hematological malignancies including melphalan, prednisone, dexamethasone and proteasome inhibitors (e.g., bortezomib), in an attempt to reduce light chain production. There are no currently approved treatments for AL amyloidosis, and none that directly target potentially toxic forms of the amyloidogenic proteins.

1.2 STUDY RATIONALE

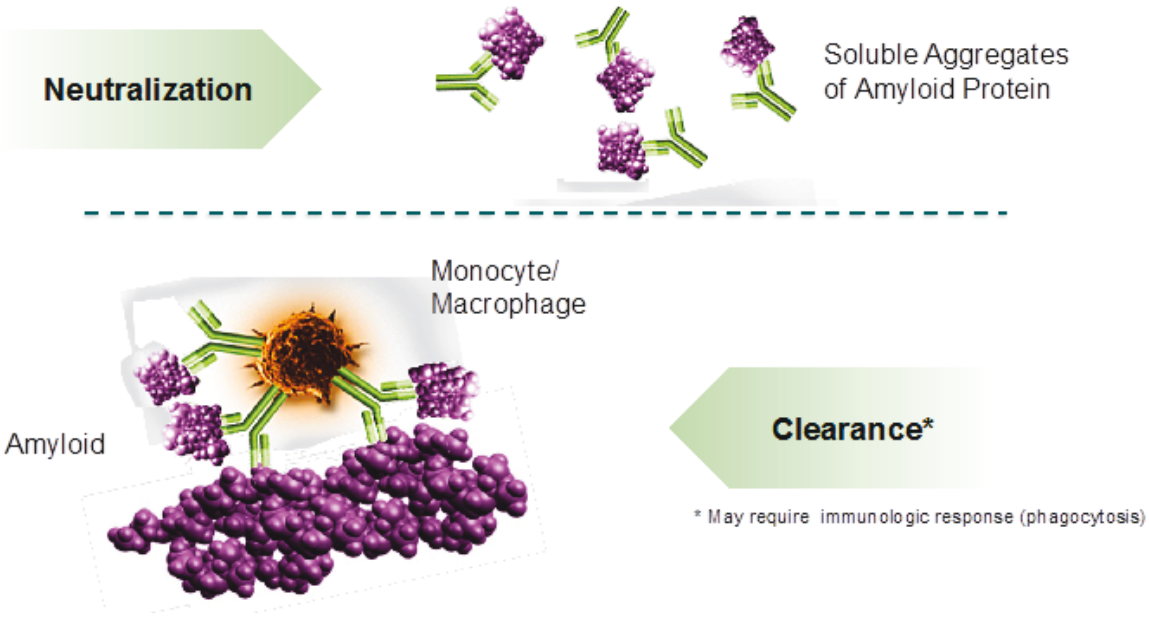
Unlike other hematologic disorders such as multiple myeloma, the morbidity and mortality of AL amyloidosis is almost entirely related to organ dysfunction and not hematologic parameters. One of the major determinants of prognostic outcome in AL amyloidosis patients is the extent of cardiac involvement; 75% of the deaths are due to cardiac amyloidosis (Merlini et al, 2011). The process of amyloid formation results in cellular injury, tissue damage, and organ dysfunction through mechanisms that are not completely understood. Because the current available treatment options are limited to treatment for the PCD component of the disease, the rate of organ function improvement or stabilization ("organ response") after achieving hematologic response from chemotherapy regimens is highly variable, ranging from 25% to 78% based on published information (Cibeira et al, 2011; Cohen et al, 2007; Michael et al, 2010). Furthermore, the incidence of treatment-related mortality following high dose melphalan and ASCT was 13% within the first 100 days in patients with AL amyloidosis (Skinner et al, 2004) and with the greatest mortality in patients with cardiac involvement. Though the ASCT approach is effective and results in rapid hematologic response, the average treatment-related mortality in four single-center studies ranged from 21% to 39% (Falk and Dubrey, 2010). Therefore, there is an urgent need to develop a treatment that can directly target the misfolded proteins to increase their clearance and to alleviate direct organ toxicity. Treatments that reduce or eliminate PCD in conjunction with treatments that target toxic soluble aggregates and insoluble amyloid may be of great clinical benefit in the treatment of AL amyloidosis.

1.3 BACKGROUND ON NEOD001

Prothena Therapeutics Limited (Prothena) is developing NEOD001, a humanized immunoglobulin G1 (IgG1), kappa version of 2A4, the parent murine monoclonal antibody, which is directed against a cryptic epitope on amyloid fibrils. NE0D001 specifically targets misfolded light chain aggregates and amyloid deposits. Nonclinical studies to date suggest little cross-reactivity of the antibody with normal immunoglobulins of the immune system. NEOD001, administered by intravenous (IV) infusion, is proposed for use to target the misfolded light chain protein in subjects with AL amyloidosis. See the current NEOD001 Investigator's Brochure for detailed nonclinical and clinical information.

The proposed mechanism of action for NEOD001 is thought to be two-pronged (Figure 2). First, is the direct interaction of NEOD001 with soluble aggregates resulting in the neutralization of the soluble, toxic aggregated moieties. The second is clearing the insoluble toxic amyloid deposited in organs/tissues. Here, it is believed that NEOD001 attaches to the amyloid deposits and the intact Fc portion of NEOD001 signals monocytes/macrophages to the area; and via phagocytosis, clearance of the insoluble, toxic deposits occurs (e.g., opsonization of the deposited amyloid). It is believed that both mechanisms may contribute to potential clinical benefit.

Figure 2 Proposed Mechanism of Action for NEOD001



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

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

1.3.1 Nonclinical Safety

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

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

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

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

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

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

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

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

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

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

1.3.2 Clinical Safety

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 a Phase 1/2 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, diarrhea, anemia, blood creatinine increased, dizziness, constipation, cough, headache, edema peripheral, vomiting, pain in extremity, back pain, dyspnea, edema, 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.

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 the open-label extension study (NEOD001-OLE251). As of the data lock point 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 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 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). In the completed Study NEOD001-001, 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. In addition to this study, 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. See the current NEOD001 Investigator's Brochure for detailed clinical information.

1.4 RATIONALE FOR STUDY CONDUCT AND DOSE SELECTION

The rationale for this study is to provide additional treatment with NEOD001 for subjects who complete Study NEOD001-001, and to continue to evaluate long-term safety and tolerability. All subjects in the current NEOD001 trials are being dosed at 24 mg/kg, which will be continued in this study.

2 OBJECTIVES

2.1 PRIMARY

- To evaluate long-term safety and tolerability of NEOD001

2.2 SECONDARY

- To assess the immunogenicity of NEOD001
- To incorporate serum NEOD001 concentrations in a population pharmacokinetic (PK) analysis

2.3 EXPLORATORY

- To evaluate overall survival
- To evaluate change in Six Minute Walk Test (6MWT)
- To evaluate general health-related quality of life using the Short Form-36 (SF-36)

3 STUDY PLAN

3.1 STUDY DESIGN

This is a multicenter, Phase 2, open-label extension study. The purpose of the study is to evaluate the long-term safety and tolerability of NEOD001 in subjects with AL amyloidosis who were previously enrolled and treated for at least 9 months in Study NEOD001-001.

3.2 STUDY ENDPOINTS

3.2.1 Primary

- Assessment of the safety and tolerability of NEOD001 as assessed by vital signs, duration of therapy, 12-lead electrocardiograms (ECGs), routine laboratory assessments, and frequency and severity of AEs

3.2.2 Secondary

- Assessment of immunogenicity by measurement of anti-NEOD001 antibodies
- Serum NEOD001 concentrations (sparse sampling) will be pooled with similar samples from other studies in a population PK analysis

3.2.3 Exploratory

- Time to all-cause mortality from baseline in Study NEOD001-001
- Change from baseline (of this study) in the 6MWT
- Change from baseline (of this study) in the SF-36

3.3 NUMBER OF SITES AND SUBJECTS

Multi-center study in approximately 70 subjects.

3.4 RANDOMIZATION AND BLINDING

Not applicable.

3.5 ESTIMATED STUDY AND TREATMENT DURATION

A subject's study duration may be up to 38 months or until the study is terminated (per Section 4.5), whichever occurs first. The study consists of a Screening Phase (1 month), Treatment Phase (36 months), and the End of Study (EOS) Visit 30 (±5) days after the last dose.

3.6 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 study visit for the last subject participating in the study or if the study is terminated, whichever occurs first, see Section 4.5.

4 SELECTION, DISCONTINUATION, AND WITHDRAWAL OF SUBJECTS

4.1 INCLUSION CRITERIA

Subject must meet ***all*** of the following:

1. Previously enrolled and treated for at least 9 months in Study NEOD001-001
2. Ability to understand and willingness to sign an informed consent form (ICF) prior to initiation of any study procedures
3. Has 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 times the upper limit of normal (× ULN)
   - Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) ≤3 × ULN
   - Estimated glomerular filtration rate ≥30 mL/minute
4. Seated systolic blood pressure (BP) 90 to 180 mmHg
5. ECOG PS 0 to 2
6. Women of childbearing potential (WOCBP) must have a negative serum pregnancy test within 28 days prior to the first administration of study drug and agree to use highly effective physician-approved contraception (Appendix 1) from 30 days prior to the first study drug administration to 90 days following the last study drug administration
7. Male subjects must be surgically sterile or must agree to use highly effective physician-approved contraception (Appendix 1) from 30 days prior to the first study drug administration to 90 days following the last study drug administration

4.2 EXCLUSION CRITERIA

Subject must ***not*** meet any of the following:

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 continued or initiation of treatment with NEOD001 or participation in the study
2. History of Grade ≥3 infusion-associated adverse events (AEs) or hypersensitivities to NEOD001 or any of its excipients

3. Treatment with any anticancer therapy (standard or investigational) within the 14 days prior to the first dose of study drug. In addition, subjects must have fully recovered (i.e., National Cancer Institute Common Terminology Criteria for Adverse Events [CTCAE] Grade 1 [***exception***: subjects with prior bortezomib may have CTCAE Grade 2 neuropathy]) from the clinically significant toxic effects of that treatment

4. Received any of the following within the specified time frame prior to the first administration of study drug:

    - Hematopoietic growth factors, transfusions of blood or blood products within 1 week
    - Major surgery within 2 weeks
    - Radiotherapy within 2 weeks
    - Transplant within 8 weeks
    - Investigational drug other than NEOD001 within 4 weeks
    - Another experimental anti-amyloid therapy other than NEOD001 within 2 years

5. Uncontrolled symptomatic orthostatic hypotension

6. Myocardial infarction, uncontrolled angina, uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia, within 6 months prior to the first dose of study drug

7. Uncontrolled infection

8. Secondary malignancy, ***with the exception of***:

    - 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
    - Any other cancer from which the subject has been disease-free for ≥3 years

9. Uncontrolled human immunodeficiency virus (HIV), hepatitis B, or hepatitis C infection

10. Women who are lactating

4.3 EARLY TREATMENT DISCONTINUATION

If the subject discontinues study drug prior to completing 36 months of treatment, they should return for an EOS 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:

- A suspected NEOD001-related immunologic reaction – collect additional serum samples, if possible, during the period following the treatment stoppage to allow for the determination of the persistence of anti-NEOD001 antibodies. Samples should be collected at the EOS Visit and 3 months after the EOS 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 EOS Visit must be followed to term or until termination of the pregnancy (Section 7.4.2).

- Subject requests to withdraw from the study treatment

- Subject requires or has taken medication prohibited by the protocol

4.4 EARLY TERMINATION FROM STUDY

Subject participation in this study will continue until EOS. 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 EOS 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 randomized subjects receiving at least one dose of study drug and will be searched in public sources. During the study close-out period, survival status will be collected within legal and ethical boundaries for all randomized subjects who withdrew participation from the study. If vital status is determined, the subject will not be considered lost to follow-up.

4.5 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, 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, 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.

4.6 REPLACEMENT OF SUBJECTS

As this is an open-label study for subjects previously enrolled and treated for at least 9 months in Study NEOD001-001, no subjects will be replaced.

5 TREATMENT OF SUBJECTS

5.1 STUDY THERAPY

5.1.1 Formulation, Packaging, and Labeling

The active study drug, NEOD001, is supplied as a sterile, lyophilized dosage form in a 20/25-mL vial containing 500 mg 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 labeling will comply with applicable regulatory requirements.

5.1.2 Shipping, Storage, and Handling

NEOD001 will be shipped to clinical sites in individual cartons (one vial per carton). Upon receipt, a study staff member will place the study drug in a refrigerator at a temperature ranging from 2°C to 8°C in a secure, locked location. Access to the study drug 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 study drug has not been properly handled (e.g., physical damage to carton/vial, temperature outside the 2°C to 8°C range in transit, or not stored at 2°C to 8°C in the clinic), follow the procedure outlined in the Pharmacy Manual or immediately contact the Study Monitor (contact information available in the Study Manual). In such an event, study drug should be quarantined in a 2°C to 8°C refrigerator and must not be administered to any subject until the drug has been approved for use.

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

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

5.2 ACCOUNTABILITY AND RETURN OF STUDY SUPPLIES

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

All study drug provided by the Sponsor 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 baseline 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 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.

The study drug will be administered once every 28 (±5) days at the infusion duration established in Study NEOD001-001 or over 60 (±10) minutes. The length of the infusion may be extended over a longer period of time as 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:

- Subjects will be closely monitored for possible infusion-associated AEs and/or hypersensitivities for approximately 90 (±10) minutes after completion of the study drug infusion to assess for possible infusion-associated AEs and/or hypersensitivities.

- Beginning with the third infusion, the Investigator may decrease the postdose 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 postdose 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 DOSE ADJUSTMENTS

5.4.1 Withholding of Study Drug

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

5.4.2 Management of Suspected Infusion-Related/Hypersensitivity Adverse Events

In the event of a suspected infusion-related and/or hypersensitivity AE, the infusion should be immediately discontinued and appropriate supportive therapy should be administered, which may include epinephrine, IV fluids, corticosteroids, vasopressors, oxygen, bronchodilators, antihistamines, or acetaminophen. Subjects should be evaluated and carefully monitored until there is complete resolution of the AE or hypersensitivity signs and symptoms. In addition to the institution's recommended assessments, blood samples should be obtained in the event of a suspected infusion-related and/or hypersensitivity AE for assessment of the following: tryptase, complements C3 and C4, serum NEOD001, and anti-NEOD001 antibody levels.

For subjects who have an infusion-related reaction, any subsequent infusion must be given with premedication. Within the 30-60 minutes before the start of each infusion, administer 25 mg diphenhydramine (or an equivalent H1 antihistamine) and 650 mg acetaminophen. All premedications will be recorded in the electronic case report forms (eCRFs).

For subjects with a Grade 2 infusion-related AE, if it is appropriate to restart the infusion, it should be done at 50% of the original rate (e.g., if the initial infusion is 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.

If a subject experiences a Grade 3 infusion-related and/or hypersensitivity AE, the infusion should not be restarted. The decision to continue dosing at the subject's next scheduled administration should be discussed with the Medical Monitor. If the decision is made to proceed with dosing, the dose will be reduced by 50%, in addition to a 50% reduction of the original infusion rate. 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 EOS 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 EOS Visit per Section 6.1.3.

5.4.3 Dose Reductions

Dose reductions may be allowed in the event that observed AEs are believed to be related to study drug, and which in consultation between the Investigator and the Medical Monitor, may be managed by a 50% reduction in dose. The duration of the dose reduction will be at the Investigator's discretion.

5.5 TREATMENT COMPLIANCE

Treatment compliance will be documented in the eCRF by recording the date, time, and whether or not each IV dose of study drug was completely infused.

5.6 PRIOR AND CONCOMITANT MEDICATION/THERAPY

Prior and concomitant medications include any drug (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 Visit, and any changes to concomitant medications during the study will be recorded in the appropriate eCRF. In addition, all prior therapies for AL amyloidosis taken prior to signing ICF for this study and since last visit in Study NEOD001-001 will be recorded. See Study Manual for more information.

5.6.1 Allowed Concomitant Medication/Therapy

The following are allowed during the study:

- Radiation therapy for the removal of local amyloid deposits
- Concomitant chemotherapy
    - The Investigator may prescribe chemotherapy as per standard of care
    - Particular care must be taken to accurately report chemotherapy administration, including missed or delayed doses, and dose reductions
    - If parenteral chemotherapy is administered on the same day as NEOD001, the chemotherapy must be administered after the 90-minute NEOD001 observation period
    - 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)
    - Routine medications should not be administered in the 15 minutes after the completion of the NEOD001 infusion. Medications such as anti-emetics required for prophylaxis of emesis for the subsequent chemotherapy should be given after the ECG has been done.

5.6.2 Prohibited Concomitant Medication/Therapy

The following are not allowed during the study:

- Other investigational agents

- Myeloablative chemotherapy with ASCT

- Gadolinium contrast agents are only permitted in exceptional circumstances. If a subject 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

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.

Rescreening is allowed once per subject. Repeat only tests that did not meet eligibility requirements. All laboratory evaluations to be done centrally, unless otherwise noted. Refer to the Central Laboratory Manual for complete instructions on collection of samples.

6.1.1.1 Assessments for Subjects Whose Previous Visit in Study NEOD001-001 was Within 60 Days of Screening

- Signed informed consent
- Review eligibility, including discontinuation of prior therapies according to the Exclusion Criteria
- Medical History - Obtain medical history since subject's last visit in Study NEOD001-001 (including all major hospitalizations and surgeries), as well as the subject's current medical status and prior therapies for AL amyloidosis. Adverse events that resolved prior to the subject's last visit in Study NEOD001-001 and prior to signing ICF for this study should be assessed as possible medical history in this study.
- Historical NT-proBNP levels – any NT-proBNP results available since participation in Study NEOD001-001 must be recorded
- Prior and concomitant medications/therapy (per Section 5.6)
- Assessment of AEs; record any AEs that were ongoing from the subject's last visit in Study NEOD001-001 and at the time of the NEOD001-OLE001 Screening Visit
- Complete physical examination - including height, weight, and examination of general appearance; head, ears, eyes, nose, and throat; neck; skin; cardiovascular system; respiratory system; abdominal system; and nervous system. The following should be assessed: macroglossia, submandibular nodes/fullness, adenopathy, ecchymoses, liver/spleen size (palpable +/-), ascites (+/-), and edema (which should be quantified on a scale of 0-4).
- Vital signs including heart rate (HR), BP, respiratory rate (RR), and body temperature (Section 6.3.2)
    - Note: subjects with uncontrolled hypotension or systolic BP <85 mmHg are not eligible for the study

- Peripheral Neuropathy Assessment (Section 6.3.5 and Appendix 5)
    - Note: only for subjects previously enrolled in Cohort C of Study NEOD001-001
- SF-36 Health Survey (Appendix 2)
    - Note: administer SF-36 before performing any other study assessments on the day it is administered
- 6MWT (Section 6.3.6): Two pretreatment 6MWTs are required before the first administration of study drug, with a minimum of 4 days in between the two tests. The second test must be completed 1 to 2 days before the Month 1-Day 1 Visit. Also collect HR and BP pre- and post-6MWT administration.
    - Note: NT-proBNP must be drawn before conducting 6MWT, if performed on the same calendar day
- 12-lead ECG in triplicate (perform locally)
- Laboratory Assessments:
    - Hematology, chemistry (including amylase), and Screen for Infectious Diseases per Appendix 3
    - Coagulation per Appendix 3; collect unscheduled citrated plasma samples for subjects with relevant SAEs; if defects are identified, additional analytes will be analyzed, as indicated (see Appendix 4)
    - Cardiac biomarkers per Appendix 3
    - Serum pregnancy tests (WOCBP only): Perform a serum pregnancy test (central) within 28 days before Month 1-Day 1 study drug administration
- Other Assessments (see Laboratory Manual):
    - Serum NEOD001 concentration
    - Serum anti-NEOD001 antibodies

6.1.1.2 Assessments for Subjects Whose Previous Visit in Study NEOD001-001 was ≥60 Days from Screening

- Signed informed consent
- Begin urine collection 24 hours prior to the study visit
- Review eligibility, including discontinuation of prior therapies according to the Exclusion Criteria

- Medical History - Obtain medical history since subject's last visit in Study NEOD001-001 (including all major hospitalizations and surgeries), as well as the subject's current medical status and prior therapies for AL amyloidosis. Adverse events that resolved prior to the subject's last visit in Study NEOD001-001 and prior to signing ICF in this study should be assessed as possible medical history in this study.

- Historical NT-proBNP levels – any NT-proBNP results available since participation in Study NEOD001-001 must be recorded

- Prior and concomitant medications/therapy (per Section 5.6)

- Assessment of AEs; record any AEs that were ongoing from the subject's last visit in Study NEOD001-001 and at the time of the NEOD001-OLE001 Screening Visit.

- Complete physical examination - including height, weight, and examination of general appearance; head, ears, eyes, nose, and throat; neck; skin; cardiovascular system; respiratory system; abdominal system; and nervous system. The following should be assessed: macroglossia, submandibular nodes/fullness, adenopathy, ecchymoses, liver/spleen size (palpable +/-), ascites (+/-), and edema (which should be quantified on a scale of 0-4).

- Vital signs including HR, BP, RR, and body temperature (Section 6.3.2)

    - Note: subjects with uncontrolled hypotension or systolic BP <85 mmHg are not eligible for the study

- ECOG PS (Appendix 6)

- New York Heart Association (NYHA) functional status (Appendix 7)

- Peripheral Neuropathy Assessment (Section 6.3.5 and Appendix 5)

    - Note: only for subjects previously enrolled in Cohort C of Study NEOD001-001

- SF-36 Health Survey (Appendix 2)

    - Note: administer SF-36 before performing any other study assessments on the day it is administered

- 6MWT (Section 6.3.6): Two pretreatment 6MWTs are required before the first administration of study drug, with a minimum of 4 days in between the two tests. The second test must be completed 1 to 2 days before the Month 1-Day 1 Visit. Also collect HR and BP pre- and post-6MWT administration.

    - Note: NT-proBNP must be drawn before conducting 6MWT, if performed on the same calendar day

- Echocardiogram

- 12-lead ECG in triplicate (perform locally)
- Laboratory Assessments:
  - Hematology and chemistry (including amylase) per Appendix 3
  - Coagulation per Appendix 3; collect unscheduled citrated plasma samples for subjects with relevant SAEs; if defects are identified, additional analytes will be analyzed, as indicated (see Appendix 4)
  - Cardiac biomarkers per Appendix 3
  - Serum pregnancy tests (WOCBP only): Perform a serum test (central) within 28 days before Month 1-Day 1 study drug administration
  - Serum free light chain (SFLC)
  - Serum protein electrophoresis (SPEP) and 24-hour urine protein electrophoresis (UPEP)
  - Serum immunofixation (SIFE) and urine immunofixation (UIFE)
  - Urinalysis (dip stick) per Appendix 3
  - 24-hour urine protein excretion
- Other Assessments (see Laboratory Manual):
  - Serum NEOD001 concentration
  - Serum anti-NEOD001 antibodies

6.1.2 Treatment Period: Months 1 through 36, Day 1 (±5 Days)

Day 1 assessments may be conducted ±5 days from Day 1, with the exception of Month 1-Day 1 (i.e., no window is allowed at Month 1).

Subjects will receive 24 mg/kg of NEOD001 as an IV infusion every 28 (±5) days, i.e., on Day 1 of Months 1 through 36.

All laboratory tests to be done centrally, unless otherwise noted. Refer to the Central Laboratory Manual for complete instructions on collection of samples.

Although central laboratory assessments will be performed each month for study analysis, local laboratory assessments including hematology, chemistry, and urinalysis will be performed for subject management. Results will be reviewed prior to dosing at each month's Day 1 visit to confirm that continued dosing is appropriate.

Subjects who present with symptomatic orthostatic hypotension 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 the study drug withheld. If the study drug is withheld and subsequently rescheduled, central laboratory assessments required for that visit will need to be repeated if they were drawn >7 days prior to the rescheduled dosing date. However, a symptom-directed physical examination and vital signs need to be repeated prior to each dosing.

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.

Prior to Infusion:

The following assessments will be done prior to study drug administration on Day 1 of every month, unless otherwise indicated. Because questionnaires and laboratory samples should be completed prior to the 6MWT, all of the following assessments, at a minimum, should be completed 1 to 2 days prior to Day 1:

- Begin urine collection 24 hours prior to the study visit
- Concomitant medications/therapies
- Assessment of AEs
- Directed physical examination - including weight and examination of the following: general appearance; head, ears, eyes, nose, and throat; neck; skin; cardiovascular system; respiratory system; abdominal system; and nervous system. The components of the physical examination will be as clinically indicated. However, at all time points the following should be assessed: macroglossia, submandibular nodes/fullness, adenopathy, ecchymoses, liver/spleen size (palpable +/-), ascites (+/-), and edema (which should be quantified on a scale of 0-4).
- Vital signs including HR, BP, RR, and body temperature; assess in the same position for all time points (Section 6.3.2)
- ECOG PS (Appendix 6)
- NYHA functional status (Appendix 7)
- Peripheral Neuropathy Assessment (Section 6.3.5 and Appendix 5) – every 3 months
    - Note: only for subjects previously enrolled in Cohort C of Study NEOD001-001
- SF-36 Health Survey (Appendix 2) – every 6 months
    - Note: administer SF-36 before performing any other study assessments on the day it is administered

- 6MWT (Section 6.3.6) – every 6 months; also collect HR and BP pre- and post-6MWT administration
    - Notes: NT-proBNP must be drawn before conducting 6MWT, if performed on the same calendar day. The 6MWT must be performed 1-2 days prior to administration of study drug; it should not be administered on the same day as study drug administration (i.e., Day 1).
- Echocardiogram – every 12 months
    - Note: May be conducted within 10 days before the visit
- 12-lead ECG in triplicate (perform locally) – every 3 months
- Laboratory Assessments:
    - Hematology and chemistry (including amylase) per Appendix 3
    - Coagulation per Appendix 3; collect unscheduled citrated plasma samples for subjects with relevant SAEs; if defects are identified, additional analytes will be analyzed, as indicated (see Appendix 4)
    - Cardiac biomarkers per Appendix 3
    - Urine pregnancy test (WOCBP only; local laboratory) – Monthly starting with Month 2
    - SFLC – every 3 months
    - SPEP and 24-hour UPEP – every 3 months
        - Note: During the Treatment Phase, SPEP and UPEP are used to confirm the initial within-study hematologic complete response only
    - SIFE and UIFE – every 3 months
        - Note: During the Treatment Phase, SIFE and UIFE are used to confirm the initial within-study hematologic complete response only
    - Urinalysis (dip stick) per Appendix 3 – every 3 months
    - 24-hour collection for urine protein excretion – every 3 months
- Other Assessments (Laboratory Manual) – every 3 months
    - Serum NEOD001 concentration
    - Serum anti-NEOD001 antibodies

- Additional samples for anti-NEOD001 antibodies and serum NEOD001 should be collected if a significant toxicity is observed

NEOD001 Administration:

Note: Subjects who present with symptomatic orthostatic hypotension or systolic BP <85 mmHg will have the study drug held

- Month 1-Day 1:
  - Administer NEOD001 IV using the infusion duration established during Study NEOD001-001 or over 60 (±10) minutes (Section 5.3)
  - Assess vital signs including HR, BP, RR, and body temperature, halfway through the infusion (Section 6.3.2)
- All Other Months:
  - If the Month 1-Day 1 infusion was well tolerated without infusion-associated AEs, administer NEOD001 IV using the infusion duration established during Study NEOD001-001 or over 60 (±10) minutes. If needed, see Section 5.4 for dose adjustment instructions.

After Infusion:

- Monitor subjects for 90 (±10) minutes following completion of the study drug infusion. Beginning with the third infusion, the Investigator may decrease the postdose 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 (per Section 5.3). 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.
- Routine medications should not be administered in the 15 minutes after the completion of the NEOD001 infusion
- Vital signs including HR, BP, RR, and body temperature (Section 6.3.2):
  - Month 1-Day 1:
    - Immediately at end of infusion (EOI) (+5 minutes)
    - 30 (±5) minutes after EOI
    - 60 (±10) minutes after EOI
  - All Other Months:
    - Immediately at EOI (+5 minutes)

    - 60 (±10) minutes after EOI

- 12-lead ECG in triplicate (perform locally)
    - Within 15 minutes after EOI
- Serum NEOD001 concentration – every 3 months
    - EOI (record the time, but the sample can be collected at any time after the infusion on Day 1)
- Discharge subject from clinic if no immediate safety concerns and/or hypersensitivities are present after the postdose assessments and observation 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 (EOS): 30 (±5) Days After Final Dose

A final visit should be scheduled 30 (±5) days after the last administration of NEOD001. The following procedures must be conducted:

- Begin urine collection 24 hours prior to the study visit
- Concomitant medications/therapy
- Assessment of AEs
- Complete physical examination - including weight and examination of general appearance; head, ears, eyes, nose, and throat; neck; skin; cardiovascular system; respiratory system; abdominal system; and nervous system. The following should be assessed: macroglossia, submandibular nodes/fullness, adenopathy, ecchymoses, liver/spleen size (palpable +/-), ascites (+/-), and edema (which should be quantified on a scale of 0-4).
- Vital signs including HR, BP, RR, and body temperature (Section 6.3.2)
- ECOG PS (Appendix 6)
- NYHA functional status (Appendix 7)
- Peripheral Neuropathy Assessment (Section 6.3.5 and Appendix 5)
    - Note: only for subjects previously enrolled in Cohort C of Study NEOD001-001
- SF-36 Health Survey (Appendix 2)
    - Note: administer SF-36 before performing any other study assessments on the day it is administered

- 6MWT (Section 6.3.6); also collect HR and BP pre- and post-6MWT administration
    - Note: NT-proBNP must be drawn before conducting 6MWT, if performed on the same calendar day
- Echocardiogram
    - Note: repeat echocardiogram at EOS if not performed within 60 days prior to visit
- 12-lead ECG in triplicate (perform locally)
- Laboratory Assessments:
    - Hematology and chemistry (including amylase) per Appendix 3
    - Coagulation per Appendix 3; collect unscheduled citrated plasma samples for subjects with relevant SAEs; if defects are identified, additional analytes will be analyzed, as indicated (see Appendix 4)
    - Cardiac biomarkers per Appendix 3
    - Serum pregnancy test (WOCBP only; central laboratory)
    - SFLC
    - SPEP and 24-hour UPEP
    - SIFE and UIFE
    - Urinalysis (dip stick) per Appendix 3
    - 24-hour urine protein excretion
- Other Assessments (see Laboratory Manual):
    - Serum NEOD001 concentration
    - Serum anti-NEOD001 antibodies
    - Additional samples for anti-NEOD001 antibodies and serum NEOD001 should be collected if a significant toxicity is observed

6.1.4 90-day Postdose Pregnancy Test

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

6.1.5 Vital Status Telephone Call

Conduct a vital status telephone call approximately 3 months after the subject's last study visit and approximately every 3 months thereafter for up to 5 years, death, or subject withdraws consent, whichever occurs first.

6.2 ORDER OF ASSESSMENTS OF SPECIFIC TESTS

SF-36:

- Must be administered **prior** to any other visit assessments on the day it is administered

6MWT:

- Must be performed 1-2 days **prior** to administration of study drug
- Should not be administered on Day 1 (i.e., the same day as NEOD001 administration)
- Blood samples must be collected for local (if applicable) and central laboratory assessments **before** the 6MWT is administered, if being performed on the same calendar day
- Collect BP and HR **pre-** and **post-**6MWT administration

ECGs:

- When ECGs are scheduled to be performed at the same visit as PK blood collection, the ECG must be done **first**
- 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 done

Chemotherapy and Routine Medications:

- Routine medications should not be administered in the **15 minutes after** the completion of the NEOD001 infusion
- If parenteral chemotherapy is administered on the same day as NEOD001, the chemotherapy must be administered **after** the 90-minute NEOD001 observation period
- Within 3 days before the first day of a new regimen of chemotherapy, conduct an unscheduled central laboratory collection (including hematology and chemistry, PT/INR, and PTT)

6.3 METHODS OF ASSESSMENT FOR SAFETY AND EFFICACY

6.3.1 Clinical Laboratory Evaluations

A central laboratory will be used for this study for analysis of hematology, chemistry (including amylase), PT/INR, PTT, troponin T, NT-proBNP, SFLC, SPEP, SIFE, UPEP, UIFE, urinalysis, and 24-hour urine assessment. Details for the processing of laboratory specimens will be provided in the Laboratory Manual. Local hematology, chemistry, and urinalysis laboratory results will 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. Central and local pregnancy testing will be conducted as shown in Table 1 and Section 6. A positive urine pregnancy test (local laboratory) is to be confirmed with a serum pregnancy test (central laboratory). Results from local laboratory tests will not be collected in the eCRFs or the clinical database (***exception***: local laboratory pregnancy test results will be collected via an eCRF and in the clinical database).

In addition, a bioanalytical laboratory will be used for this study for the analysis of PK and anti-NEOD001 antibody samples, as well as for the storage of serum samples for future correlative testing (Section 6.4).

6.3.2 Vital Signs

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) will be measured after the subject has rested in a semi-recumbent position ≥5 minutes. Blood pressure measurements should be taken from the same arm throughout the study using an automated BP monitor that uses an oscillometric method. At Screening, BP measurements may be repeated twice. If there is a clinically important change in BP from the previous reading, measurements will be repeated immediately to confirm the change.

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

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

6.3.3 Physical Examination

Any unfavorable findings considered by the Investigator as clinically significant, especially changes occurring between Screening and EOS, will be documented in the eCRF as an AE. Physical examinations must be performed by the Investigator or a medically qualified delegate.

All physical examinations should include weight and examination of the following: general appearance; head, ears, eyes, nose, and throat; neck; skin; cardiovascular system; respiratory system; abdominal system; and nervous system. The specific components of the physical examination will be as clinically indicated. However, at all time points the following should be assessed: macroglossia, submandibular nodes/fullness, adenopathy, ecchymoses, liver/spleen size (palpable +/-), ascites (+/-), and edema (which should be quantified on a scale of 0-4). The Screening physical examination will also include a measurement of height.

6.3.4 12-Lead ECGs

Measurements will be made in triplicate, 5 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, QTcF - Fridericia's correction formula, QTcB - Bazett's correction formula, and the Investigator's overall interpretation will be recorded. When ECGs are scheduled to be performed at the same time as PK blood collection, the ECG must be done before the PK blood collection.

6.3.5 Peripheral Neuropathy Assessment

The Peripheral Neuropathy Assessment form (Appendix 5), will be used to assess reflexes, sensation, and motor strength to determine a peripheral neuropathy score in subjects previously enrolled in Cohort C of Study NEOD001-001. A peripheral neuropathy grade based on the CTCAE scale (Table 2) will be determined at each assessment.

Table 2 Common Terminology Criteria for Adverse Events Grade 1-5 for Peripheral Neuropathy

	CTCAE Grade				
	1	**2**	**3**	**4**	**5**
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

Abbreviations: ADL = activities of daily living (e.g., preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.); CTCAE = Common Terminology Criteria for Adverse Events.
a Definition: a disorder characterized by inflammation or degeneration of the peripheral sensory nerves.
Source: National Cancer Institute, 2009.

6.3.6 6-Minute Walk Test

The 6MWT will be assessed according to Table 1. As part of the 6MWT, BP and HR will be collected pre- and post-6MWT administration. The 6MWT should not be administered on the same day that study drug is administered, but may be performed 1-2 days prior to the Day 1 visit at each required assessment. The SF-36 must be administered and clinical laboratory samples (local and central) must be drawn prior to administering the 6MWT, if being performed on the same calendar day.

Details regarding the requirements for proper administration of the 6MWT are described in a separate manual.

6.4 PHARMACOKINETIC AND IMMUNOGENICITY ASSESSMENTS

All subjects enrolled in the study will undergo sparse sampling for serum NEOD001 according to Table 1. 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.

Serum anti-NEOD001 antibody levels will be measured according to Table 1. An electrochemiluminescent assay will be used to detect serum anti-NEOD001 antibodies. Any screening positives will be run at increasing dilutions to 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.

Additional samples for anti-NEOD001 antibodies and serum NEOD001 should be collected if a significant toxicity is observed (e.g., an infusion reaction in the clinic, anaphylaxis, etc.) and if possible, should be collected while the acute symptoms persist.

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 in 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 in 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. AEs will be identified and documented in the eCRF in appropriate medical terminology. The severity and the relationship to the study drug will be determined and reported in the eCRF (see Sections 7.2 and 7.3).

Note that any intermittent or as-needed ("PRN") use of medication (and specifically any newly prescribed medication) during the course of a study may indicate the occurrence of an AE that may need to be recorded on multiple eCRFs (e.g., AE and Concomitant Medication eCRFs).

7.2 ADVERSE EVENTS—SEVERITY RATING

AEs will be assessed according to CTCAE version 4.0 (National Cancer Institute, 2009). AEs 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:

- Mild (Grade 1): the AE does not interfere in a significant manner with the subject's normal functioning level—it may be an annoyance
- Moderate (Grade 2): the AE produces some impairment of functioning, but is not hazardous to health—it is uncomfortable or an embarrassment
- Severe (Grade 3): the AE produces significant impairment of functioning or incapacitation and is a definite hazard to the subject's health
- Life threatening (Grade 4): Life threatening or disabling
- Fatal (Grade 5): Causes death of the participant

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 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).

- **Related:** An Investigator should consider an AE related to the study drug if there is a reasonable possibility that the event may have been caused by the study drug.
- **Not Related:** An Investigator should consider an AE not related to the study drug if there is another reasonable explanation for the event to occur.

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 may require medical or surgical intervention to prevent on 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. Hospitalization may include social hospitalization, defined as inadequate family support/care at subject's primary residence, which results in subject being admitted to the hospital (i.e. wound care, nutrition, etc.).

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

- Emergency room visits hat 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 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 or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, 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 Unexpected AEs or Unexpected Suspected Adverse Reactions

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

7.4.1 Elective Procedures and Surgeries

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

A prescheduled elective procedure or a routinely scheduled treatment is not to be considered an SAE, even if the subject is hospitalized, provided the site stipulates that:

- The condition requiring the prescheduled elective procedure or routinely scheduled treatment was present before and did not worsen or progress between the subject's consent to participate in the clinical trial and the time of the procedure or treatment
- The prescheduled elective procedure or routinely scheduled treatment is the sole reason for admission and intervention

An untoward medical event occurring during the prescheduled elective procedure or routinely scheduled treatment should be recorded as an AE or a SAE. Any concurrent medications should also be recorded on the eCRF.

7.4.2 Other Reportable Information

In addition, and for the purposes of monitoring, the following should be reported via the SAE form, regardless of seriousness, according to the directions in Section 7.4.4:

- A new diagnosis of cancer
- Any occurrence of pregnancy (with or without AEs)

  Note: Any subject who becomes pregnant during the study must be withdrawn from treatment, and will be followed to term. A Pregnancy Follow-up Form may be used to obtain information on the outcome of the pregnancy/status of the infant.

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. When an AE resulting from disease progression meets the requirements to be considered serious, the SAE verbatim term should be reported as the sign/symptom 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, 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 Principal Investigator to report SAEs to the Sponsor or its designee within 24 hours.

All SAEs must be reported immediately (within 24 hours of discovery) 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 study-specific site and subject numbers 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.

The process for reporting an SAE, pregnancy or new cancer is as follows:

- Complete the appropriate eCRF(s)
- Complete an SAE form—this must include the subject's date of birth or age, sex, and study-specific site and subject numbers
- Complete the narrative, which should be comprehensive and include a chronological description and assessment of the event
- Complete the SAE fax cover sheet
- Call the Sponsor Medical Monitor for life-threatening or fatal events (see contact information on Team Roster in Study Manual)

- Fax the cover sheet and the SAE form (within 24 hours of discovery) to the Safety Representative number listed on the Team Roster in the Study Manual

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 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

The final analyses will be based on all subject data collected through study discontinuation.

8.1 ANALYSIS POPULATIONS

The Safety Population, which will include all subjects who receive at least one NEOD001 infusion, will be used for all analyses.

8.2 ANALYSIS OF STUDY POPULATION AND SUBJECT CHARACTERISTICS

Enrollment, major 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 summaries of AEs, changes in laboratory test results, and changes in vital signs. All subjects who receive one NEOD001 infusion will be included in the safety analysis.

All AE data will be listed by study site, subject number, and visit. Adverse events will be coded using the Medical Dictionary of Regulatory Activities (MedDRA). The incidence of TEAEs occurring on or after treatment on Study Day 1 will be tabulated by MedDRA System Organ Class and Preferred Term, and by severity and relationship to treatment. TEAEs leading to discontinuation and SAEs, including deaths, will be listed separately and summarized.

Descriptive statistics summarizing central laboratory data will be presented for all study visits. Changes from baseline to each study visit will also be summarized.

Additional safety assessments include vital signs and ECGs. Descriptive statistics of the vital sign and ECG parameters will be presented by study visit, as well as the change from baseline at each visit.

The incidence of anti-NEOD001 antibodies will be summarized.

8.4 ANALYSIS OF EFFICACY ENDPOINTS

Overall survival will be summarized using the Kaplan-Meier method. The change from baseline in the 6MWT will be summarized using the mean, standard deviation, median, and minimum and maximum value.

8.5 ANALYSIS OF OTHER ENDPOINTS

8.5.1 Pharmacokinetic

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

8.5.2 Immunogenicity

Serum anti-NEOD001 antibody titers will be listed and correlated with clinical toxicity. 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 extension study for subjects previously enrolled and treated for at least 9 months in Study NEOD001-001.

8.7 HANDLING OF DROPOUTS AND MISSING DATA

Observed data will be included in listings and summary tables. There will be no imputation of missing data.

9 DATA RECORDING, RETENTION, AND MONITORING

9.1 CASE REPORT FORMS

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

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

9.2 AVAILABILITY AND RETENTION OF RECORDS

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

Investigators are required to maintain all study documentation, including documents created or modified in electronic format, for at least 15 years following the completion of the study 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 Regulatory Authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the study (e.g., eCRFs and other pertinent data), provided that subject confidentiality is respected.

The study monitor is responsible for inspecting the eCRFs at regular intervals throughout the study to verify the following: adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The monitor should have access to subject medical records and other study-related records needed to verify the entries in 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. In the eCRFs or other documents submitted to the Sponsor or its designee, subjects must be identified by no more than their date of birth or age, sex, and study-specific site and subject numbers. Documents that are not for submission to the Sponsor (e.g., signed ICFs) should be kept in strict confidence by the Investigator in compliance with applicable regulations and ICH GCP Guidelines. The Investigator and institution must permit authorized representatives of the Sponsor, of regulatory agencies, and the IRB/IEC direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are needed for the evaluation of the study. The Investigator is obligated to inform the subject in the ICF that the above named representatives may review study-related records from subjects.

10 ETHICAL AND LEGAL ISSUES

10.1 ETHICAL CONDUCT OF THE STUDY

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

10.2 REGULATORY APPROVAL

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

10.3 ETHICS COMMITTEE APPROVAL

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

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

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

10.4 SUBJECT INFORMED CONSENT

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

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

10.5 SUBJECT COMPENSATION FOR ADVERSE EFFECTS ON HEALTH

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

10.6 PROTOCOL AMENDMENTS AND STUDY TERMINATION

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

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

10.7 FINANCE, INSURANCE AND INDEMNITY

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

10.8 PUBLICATION POLICY

All publication rights are delineated in the Clinical Study Agreement.

11 REFERENCES

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12 APPENDICES

Appendix 1 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]
- Vasectomized partner[2,3]
- Sexual abstinence[4]

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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 2 Short Form-36 Health Survey

Your Health and Well-Being

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

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

In general, would you say your health is:

Excellent
Very good
Good
Fair
Poor

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

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

The following question is about activities you might do during a typical day. Does your health now limit you in vigorous activities, such as running, lifting heavy objects, participating in strenuous sports? If so, how much? Yes, limited a lot Yes, limited a little No, not limited at all
The following question is about activities you might do during a typical day. Does your health now limit you in moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf? If so, how much? Yes, limited a lot Yes, limited a little No, not limited at all
The following question is about activities you might do during a typical day. Does your health now limit you in lifting or carrying groceries? If so, how much? Yes, limited a lot Yes, limited a little No, not limited at all
The following question is about activities you might do during a typical day. Does your health now limit you in climbing several flights of stairs? If so, how much? Yes, limited a lot Yes, limited a little No, not limited at all

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

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

During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities?

Were limited in the kind of work or other activities as a result of your physical health

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

During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities?

Had difficulty performing the work or other activities as a result of your physical health (for example, it took extra effort)

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

During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities?

Cut down on the amount of time you spent on work or other activities as a result of any emotional problems (such as feeling depressed or anxious)

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

During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities?

Accomplished less than you would like as a result of any emotional problems (such as feeling depressed or anxious)

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

During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities?

Did work or other activities less carefully than usual as a result of any emotional problems (such as feeling depressed or anxious)

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

During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all
Slightly
Moderately
Quite a bit
Extremely

How much bodily pain have you had during the past 4 weeks?

None
Very mild
Mild
Moderate
Severe
Very Severe

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

Not at all
A little bit
Moderately
Quite a bit
Extremely

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

How TRUE or FALSE is the following statement for you?

My health is excellent.

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

Appendix 3 Laboratory Tests

<table>
<tr>
<td rowspan="3">Serum Chemistry:
• ALP
• ALT (E)
• AST (E)
• Bilirubin - total (E) and direct
• GGT
• BUN
• LDH
• Creatinine (E)
• Glucose
• Cholesterol
• Triglycerides
• Calcium
• Phosphate
• Protein - total
• Albumin
• Sodium
• Potassium
• Chloride
• Bicarbonate
• Magnesium
• Amylase
• Uric acid
• Estimated glomerular filtration rate (E)
• Estimated creatinine clearance
• Creatine kinase</td>
<td>Hematology:
• Hemoglobin (E)
• Hematocrit
• RBC
• WBC
• Neutrophils (absolute, %) (E)
• Lymphocytes (absolute, %) (E)
• Monocytes (absolute, %)
• Eosinophils (absolute, %)
• Basophils (absolute, %)
• Platelet count (E)</td>
</tr>
<tr>
<td>Coagulation:
• PT
• INR
• PTT
• See also Appendix 4</td>
</tr>
<tr>
<td>Cardiac Biomarkers:
• Troponin T
• NT-proBNP</td>
</tr>
<tr>
<td rowspan="2">Urinalysis (dip stick):
• Color & clarity
• Specific gravity
• pH
• Protein
• Glucose
• Ketones
• Bilirubin
• Urobilinogen
• Blood
• Nitrite
• Leukocyte esterase
• Microscopic</td>
<td>Other:
• Serum beta hCG and urine pregnancy tests for women of childbearing potential only (E)
• Serum anti-NEOD001 antibodies
• Serum NEOD001 concentration
• Serum free light chains
• 24-hr urine protein excretion
• Serum & 24-hour urine PEP
• Serum & urine IFE</td>
</tr>
<tr>
<td>Screen for Infectious Diseases:
• HIV antibody (E)
• Hepatitis B surface antigen (HBsAg) (E)
• Hepatitis C antibody (E)</td>
</tr>
</table>

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; (E) = may be used for eligibility; GGT = gamma-glutamyl transpeptidase; hCG = human chorionic gonadotropin; HIV = human immunodeficiency virus; IFE = immunofixation electrophoresis; INR = international normalized ratio; LDH = lactate dehydrogenase; NT-proBNP = N-terminal pro B-type natriuretic peptide; PEP = protein electrophoresis; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell; WBC = white blood cell.

Appendix 4 Coagulation Indices

In addition to PT/INR and PTT, citrated plasma samples will be collected for subjects with relevant SAEs. If defects are identified, additional analytes will be analyzed; these analyses may include, but may not be limited to, the indices listed in the following table.

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

Appendix 5 Peripheral Neuropathy Assessment

prothena

Peripheral Neuropathy Assessment Form
NEOD001-OLE001

Instructions: Complete each assessment outlined below and assign a score, as described in each section. Sum up the scores at the bottom of the page for all assessments for the right side and for the left side.

Motor Assessment		
Score each assessment as: 0 - normal, 1 - 25% weakened, 2 - 50% weakened, 3 - 75% weakened or 4 - paralysis		
Assessment	*Right*	*Left*
Hip Flexion		
Hip Extension		
Knee Flexion		
Knee Extension		
Ankle Dorsiflexion		
Ankle Plantar Flexion		
Toe Extension		
Toe Flexion		
Reflex Assessment		
Score each assessment as: 0 - normal, 1 - reduced or 2 - absent		
Assessment	*Right*	*Left*
Knee		
Ankle		
Sensory (Great Toe) Assessment		
Score each assessment as: 0 - normal, 1 - reduced or 2 - absent		
Assessment	*Right*	*Left*
Touch		
Pinprick		
Vibration		
Joint proprioception		
Total Score:		

Performed by (Print Name): _____

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

Version: 4Sept2015

Appendix 6 Eastern Cooperative Oncology Group (ECOG) Performance Status

Grade	Description
0	Fully active, able to carry on all predisease 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 7 New York Heart Association (NYHA) Functional Classification

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

Source: American Heart Association, 2015.