Study Title: RAIN (Renal AL amyloid Involvement and NEOD001): A Multicenter Randomized Double-blind Phase 2b Study of NEOD001 in Previously Treated Subjects with Systemic Light-chain (AL) Amyloidosis and Persistent Renal Involvement

Protocol Number:	NEOD001-IST007 RAIN
Investigational Product:	NEOD001
US IND Number:	13383
Indication:	Light Chain (AL) Amyloidosis

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SPONSOR PROTOCOL APPROVAL PAGE

Protocol Title: RAIN (Renal AL amyloid Involvement and NEOD001): A Multicenter Randomized Double-blind Phase 2b Study of NEOD001 in Previously Treated Subjects with Systemic Light-chain (AL) Amyloidosis and Persistent Renal Involvement Protocol Number: NEOD001-201

Sponsor: Tufts Medical Center

Protocol Number: NEOD001-IST007 RAIN

Date of Original Protocol: 11 April 2017

Date of Amendment 1: 13 April 2017

Date of Amendment 2: 13 July 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 Tufts Medical Center. The following person is authorized on behalf of Tufts Medical Center to approve this protocol and the signature below documents this approval.

_____ _____

Raymond Comenzo, MD
Medical Monitor

Date

Protocol version 2.0 dated 13 July 2017

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

_____

Investigator Signature **Date**

_____

Investigator Name (Print)

Please sign, date, and return this form to your Study Monitor.

Please retain a copy for your study files.

_____

Site Name and Number

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RAIN PROTOCOL SYNOPSIS

Title	RAIN (Renal AL-amyloid Involvement and NEOD001): A Multicenter Randomized Double-blind Phase 2b Study of NEOD001 in Previously Treated Subjects with Systemic Light-chain (AL) Amyloidosis and Persistent Renal Involvement
Phase	2b
Planned Number of Study Centers	9 centers in the USA
Objective	The objective of this study is to determine if the investigational agent NEOD001, a monoclonal antibody that targets a light chain amyloid epitope, increases the frequency of confirmed renal responses (see Appendix 1) in previously treated patients with AL and renal involvement who have responded to prior treatment with a maintained complete, very good partial or partial hematologic response (CR, VGPR, PR) and do not need chemotherapy for their hematologic disease.
Study Design	This is a multicenter, Phase 2b, randomized, double-blind, placebo-controlled, two-arm, parallel-group efficacy and safety study of NEOD001 as a single agent administered intravenously in adults with AL amyloidosis who have a maintained hematologic response (Appendix 1) to their most recent treatment for AL amyloidosis (e.g., chemotherapy, autologous stem cell transplant [SCT]) and have persistent renal dysfunction. Subject screening will occur during the 28 days prior to the first administration of study drug (i.e. month 1 day 1). If screening assessments are completed and all eligibility requirements are met, the subject will be enrolled. Screening assessments are listed in Table 1. Study visits will occur every 28 days based on scheduling from month 1 day 1. A ±5-day window is allowed for visits starting after month 1. Subjects may receive up to 12 infusions of study drug. Subjects who discontinue study drug before the initial End of Study (EOS) visit should have an Early Treatment Discontinuation (ETD) Visit 30 (±5) days after their final administration of study drug. After completing 12 months of treatment and the confirmatory EOS visit, a subject may enter an open-label extension (OLE) study, during which subjects will receive active treatment with NEOD001 for 12 months and may receive concurrent chemotherapy.
Number of Subjects and Cohort Specifications	50 subjects randomized to NEOD001 and 50 subjects randomized to placebo. The randomization will be stratified (Appendix 1) according to: • Complete response/very good partial response (CR/VGPR) vs partial response (PR) to most recent line of therapy[1] • Renal stages 1 or 2 vs renal stage 3[2]
Study Drug, Dose, and Mode of Administration	Study drug consists of NEOD001 24 mg/kg (dose not to exceed 2500 mg) or placebo. Study drug will be administered once every 28 (±5) days; a minimum

	of 21 days between doses is required. Subjects may receive up to 12 infusions of study drug. Study drug will be administered in a 250 mL bag as an initial 120 (±10)-minute intravenous (IV) infusion. If, in the opinion of the Investigator, the subject tolerates the initial infusion, subsequent infusions may be administered 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. If the infusion must be extended beyond 4 hours, the study drug should be split into two 125-mL bags to ensure that the study drug will not remain at room temperature for longer than 4 hours (i.e. the second bag should remain refrigerated until ready for use). If an infusion-related reaction occurs, follow instructions in Section 5.3.2. Subjects should be closely monitored for 90 (±10) minutes following completion of the study drug infusion. The Investigator may increase this standard monitoring time if deemed appropriate or per local standards. In the event of any clinical concerns or suspicious signs or symptoms after the infusion, the subject will remain under observation for as long as the Investigator deems it appropriate
Control Group	Normal saline will be used as the placebo control.
Estimated Study and Treatment Duration	Each subject's study duration may be up to 26 months, consisting of a Screening Phase (1 month), a Treatment and Assessment Phase (13 months) that includes 12 months of treatment, the initial end-of-study (EOS) Visit 30 (±5) days after the last dose and the confirmatory EOS visit 1 month later, and the Open-label Extension (OLE) Phase during which subjects will receive active treatment with NEOD001 for 12 months and may receive concurrent chemotherapy. The 13 month Treatment and Assessment Phase is the active study period. During the OLE study, subjects will be seen monthly, and local laboratory testing for the OLE study will be obtained and collected every 3 months.
Subject Eligibility Criteria	**Inclusion Criteria** (subjects must meet ***all*** of the following criteria): 1. 18 years of age or older. 2. Biopsy-proven diagnosis of AL amyloidosis by immunohistochemistry or mass spectroscopy of a tissue biopsy excluding bone marrow. 3. Screening renal biopsy for RAIN confirming AL amyloidosis as exclusive or dominant cause of renal damage 4. Persistent renal involvement from diagnosis with proteinuria (predominantly albumin) > 500mg/day in a 24-hour urine collection 5. CKD 1 to 3 (eGFR $\geq$ 30) 6. ≥1 prior systemic hematologic therapy for a free light chain (FLC) producing hematologic malignancy underlying the initial diagnosis of AL amyloidosis with at least a partial FLC response (PR, VGPR, CR) to treatment deemed

	stable and not requiring further treatment 7. ECOG Performance Status ≤ 2 8. Clinical laboratory values: a. Absolute neutrophil count ≥ 1000/μL b. Platelet count ≥ 75,000/μL c. Total bilirubin ≤ 1.5X ULN d. Alkaline phosphatase ≤ 5X ULN e. NT-proBNP < 1800 pg/mL 9. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care. **Exclusion Criteria** (subjects must ***not meet any*** of the following criteria): 1. Amyloidosis due to mutations of the transthyretin gene or presence of other non-AL amyloidosis. 2. Female patients who are lactating, breastfeeding, or pregnant. 3. Patients who have not been treated or who have received chemotherapy within 6 months, or SCT within 12 months, for the light-chain producing hematologic disease causing AL amyloidosis, at the time of the first dose of NEOD001 (month 1 day 1). 4. Patients who at initial diagnosis or later met the International Myeloma Working Group (IMWG) definition of active multiple myeloma (Appendix 3) 5. Patients whose screening renal biopsies for RAIN show dominant causes of renal damage not related to AL amyloidosis 6. Medically documented cardiac syncope, uncompensated congestive heart failure, myocardial infarction within the previous 6 months, unstable angina pectoris, clinically significant repetitive atrial or ventricular arrhythmias despite antiarrhythmic treatment, or severe orthostatic hypotension or clinically significant uncompensated autonomic insufficiency. 7. Comorbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens. 8. Ongoing or active infection, known HIV positive, known to be hepatitis B surface antigen-positive or has known or suspected active hepatitis C infection. 9. Psychiatric illness/social situations that would limit compliance with study requirements.
Endpoints	*Primary Efficacy:* • Confirmed renal response rate after 12 months of treatment with NEOD001 or placebo (Appendix 1, Palladini 2014) *Secondary Endpoints:*

	• Measured GFR at study entry (Appendix 9)
	
	• Measured during and at the end of the active study period:
	  • Time to CKD 4 or 5
	  • Time to eGFR ≤ 15 or dialysis
	  • Time to doubling of creatinine
	  • Time to ≥ 40% reduction in eGFR
	
	• Renal response and progression in patients with maintained hematologic responses at 26 months
	
	• Safety and tolerability of NEOD001
	• All cause mortality at 26 months
	
	Ancillary (ARC):
	• Patient reported outcomes: We will obtain SF-36 surveys at study entry and at 3, 6, 9 and 12 month visits and at ETD or initial and confirmatory EOS visit (Appendix 7).
	• Renal Pathology Studies: We will score the screening renal biopsies for amyloid load and pattern of infiltration (Appendix 8).[3]
	• Renal Transcriptional Profiling Studies: We plan to use portions of the renal biopsy for later microarray and miRNA array studies (Appendix 10). Renal biopsy on study entry is a standard-of-care procedure.

Statistical Considerations and Methods	*Primary Efficacy Analysis:* This stratified randomized double-blind phase 2b study has as its primary end-point the confirmed renal response rate after 12 months of treatment with NEOD001 or placebo[2] and is designed to detect an absolute increase in the renal response rate of 30% (from 25% in those receiving placebo to 55% in those receiving NEOD001). The primary efficacy analysis of the confirmed renal response rates after 12 months of treatment with NEOD001 or placebo will be performed with the Mantel-Haenszel (MH) test at the alpha=0.05 (two-sided) level of significance. The analysis will be stratified by the randomization stratification variables. *Secondary Endpoint Analyses:* Comparisons of mGFR and eGFR at study entry will be by the Tukey mean-difference (Bland-Altman) method determining whether the measurements are sufficiently close with alpha of 0.05. Analyses of other secondary endpoints comparing patients receiving NEOD001 or placebo will depend on the endpoint. Time-to-event endpoints including time to CKD 4 or 5, to eGFR < 15 or dialysis, to doubling of creatinine, and to > 40% reduction in eGFR, will be analyzed by Kaplan-Meier (stratified log-rank) with alpha of 0.05. The comparisons of renal response and progression in patients who have had maintained hematologic responses at 26 months will be by MH test stratified by the pre-randomization stratification factors to

compare outcomes in the two groups.

Safety and tolerability

Safety and tolerability analyses will include all subjects who received any amount of study drug. Safety and tolerability will be assessed by vital signs, duration of therapy, routine laboratory assessments, frequency and severity of AEs as assessed by CTCAE grade. We will apply descriptive statistical methods to the data, supplemented by calculation of confidence intervals if indicated. We will also display the patterns of adverse events within both treatment groups.

Ancillary studies:

Ancillary studies will be performed and analyzed in a collaborative including Tufts (sponsor), the Amyloidosis Research Consortium (ARC), and for gene expression profiling and analysis the University of Michigan, home of the renal-research NEPTUNE project.

ARC

The Amyloidosis Research Consortium (ARC; www.arci.org) was founded in 2015 by Isabelle Lousada, an AL amyloidosis patient. The ARC addresses critical needs in clinical trials and related research for the underserved group of systemic amyloid diseases. We have created a collaborative research model to bring together experts in the field to address the challenges that exist in developing diagnostic tools and to carrying out innovative clinical trials. The ARC is committed to building collaborative relationships between patients, academia, industry, foundations, federal funders, and regulators to advance the best research and speed new therapies to market. The ARC is focused on increasing the amount of research and building a prioritized portfolio of translational research and clinical research. Our aim is to address the urgent, unmet medical needs in amyloidosis.

SF-36

SF-36 surveys (Appendix 7) will be scored and recorded in a central REDCap data bank (ARC). The SF-36 assesses 8 scales of health status from which a physical component summary (PCS) and a mental component summary (MCS) are derived (User's Manual for the SF-36v2 Health Survey, Second Edition). Summary scores will be standardized so a score of 50 corresponds to the average for the US population. Baseline and follow-up SF-36 scores will be compared for each patient and with population norms using 1-sample t tests. Pearson correlations, t tests, Wilcoxon 2-sample tests, and Mantel-Haenszel tests will be used to describe the associations between various component scales and scores of the SF-36 and clinical and demographic characteristics of these patients. The relationship of improvement or worsening in the PCS or MCS to 12 months of treatment with NEOD001 or placebo, and also to the presence or

	absence of confirmed renal responses, will be examined using the Mantel-Haenszel test. In order to determine whether the QOL measures reflect contributions that were independent of or equivalent to those made by treatment assignment, presence or absence of confirmed renal responses, or clinical characteristics, stepwise proportional hazards regression with the significance level for entry into and for staying in the model set at 5% will be used to identify clinical and health status factors related to changes in QOL measures from the beginning to the end of treatment. Renal Biopsy Scoring Results of renal biopsy scoring will be recorded in a central REDCap data bank (ARC). Renal biopsies will be scored by a predefined set of criteria for the degree and pattern of amyloid involvement and distribution. The renal pathology group will use established criteria and perform the scoring using a standard operating procedure and data sheet (Appendix 8).[3] Comparisons will be made between the NEOD001 and placebo groups by the CMH test stratified by the pre-randomization stratification factors at alpha of 0.05. Transcriptional Profiles Renal biopsy sections for transcriptional profiling will be processed following the standard operating procedures of The Nephrotic Syndrome Study Network ("NEPTUNE"). NEPTUNE is an integrated group of academic medical centers, patient support organizations and clinical research resources dedicated to advancing the understanding and treatment of certain kidney diseases unrelated to dysproteinemias. The tissue processing, microarray and bioinformatics work for the RAIN trial will be performed by the principal investigators of NEPTUNE at the University of Michigan in Ann Arbor (Appendix 10).
Sample Size Justification	For the primary efficacy endpoint, the assumed true rates for NEOD001 vs placebo are 55% and 25%, respectively. Based on a chi-squared statistic to evaluate the null hypothesis at the alpha=0.05 level of significance, and assuming an 18% drop-out rate for hematologic progression requiring chemotherapy, a total sample size of 82 subjects (41 in the placebo group, 41 in the NEOD001 group) will enable us to reject the null hypothesis that the response rates for subjects receiving NEOD001 and placebo are equal with probability (power) 0.8. With 50 patients receiving placebo and 50 patients receiving NEOD001, we expect to have at least 41 evaluable patients in each group.
Sponsor	Tufts Medical Center

Table 1: Table of Assessments

	Table 1. Assessments or Procedures	Screening[1]	Treatment		Initial EOS	Confirmatory EOS
		Days -28 through -1	Month 1 Day 1	Months 2 through 12 Day 1 (±5 days)[2]	EOS12/ETD[3]	EOS13
	Written Informed Consent	X				
	Eligibility Review	X				
Clinical	Medical History[4]	X				
	Historical NT-proBNP Levels	X				
	Prior/Concomitant Medications	X	X	X	X	X
	Adverse Event Assessment[5]	X	X	X	X	X
	Historical Immunohistochemical or Mass Spectrometry Typing[6]	X				
	Physical Exam[7]	X	X	X	X	X
	Vital Signs[8]	X	X	X	X	X
	ECOG PS/ NYHA Class[9]	X	X	X	X	X
Laboratory	Hematology & Chemistry (including serum creatinine, serum albumin, eGFR and amylase)[10, 16]	X	X	X	X	X
	Coagulation	X		X	X	
	Troponin T or I	X		X (Months 3, 6, 9, 12)	X	X
	NT-proBNP	X	X	X (Months 3, 6, 9, 12)	X	X
	BNP	X	X	X (Months 3, 6, 9, 12)	X	X
	EKG	X			X	
	Echocardiogram	X			X	
	Pregnancy (WOCBP)[10]	X	X	X	X	
	Serum Free Light Chains[11]	X		X (Months 3, 6, 9, 12)	X	
	Serum & Urine PEP[11, 16]	X		X (Months 3, 6, 9, 12)	X	
	Serum & Urine IFE[11]	X		X (Months 3, 6, 9, 12)	X	

	Urinalysis -Dipstick	X	X	X (Months 3, 6, 9, 12)	X	
	Archived urine sample[12]	X				X
	24-hr Urine Protein Collection for total volume, total protein, protein/creatinine ratio, and albumin)[16]	X		X (Months 3, 6, 9, 12)	X	X
	Renal biopsy[13]	X				
	Randomization		X			
	NEOD001/placebo Infusion		X	X		
	Standard-of-care follow up[14]					(X)
	RNB: Measured GFR	X				
	RNB: Inflammatory biomarkers[15]	X		X (Months 3, 6, 9, 12)	X	
	RNB: Tryptase	X				
	RNB: SF-36	X		X (Months 3, 6, 9, 12)	X	X

BNP = B-type natriuretic peptide; COG PS = Eastern Cooperative Oncology Group performance status; EOI = end of infusion; EOS = End of Study; ETD = Early Treatment Discontinuation; IFE = immunofixation electrophoresis; NT-proBNP = N-terminal pro B-type natriuretic peptide; NYHA = New York Heart Association; PEP = protein electrophoresis; PK = pharmacokinetic; RNB = Research non-billable; SF-36 = Short Form-36; WOCBP = women of childbearing potential.

[1] Rescreening is allowed once per subject. Repeat renal biopsy is not required in rescreening.

[2] Study visits will occur every 28 days based on scheduling from Month 1-Day 1. A ±5-day window is allowed for visits starting after Month 1.

[3] Conduct the EOS Visit 30 (±5) days after last administration of study drug. Subjects who discontinue study drug before the EOS Visit should have an ETD Visit 30 (±5) days after their final administration of study drug. The assessments shown for EOS/ETD should also be conducted for any unscheduled visit (i.e., a visit not specified by the protocol) as clinically indicated or if deemed necessary.

[4] Obtain comprehensive cardiac, hematologic, and oncologic medical history; additionally, for all other conditions obtain relevant medical history for the past 5 years (including all major hospitalizations and surgeries), as well as the subject's current medical status.

[5] Adverse events will be collected from the time that the informed consent form is signed until the EOS/ETD Visit or for 30 days after the last dose of study drug, whichever is later.

[6] Only for subjects who meet Inclusion Criterion #3.

[7] **Screening and EOS/ETD:** conduct a complete physical examination, including height (Screening only), weight, and examination of the following: general appearance; head, ears, eyes, nose, and throat; neck; skin; cardiovascular system; respiratory system; gastrointestinal system; and nervous system. **All other visits:** conduct a symptom- directed physical examination, including weight, and the components of the exam will be as

clinically indicated. **All visits:** assess macroglossia, submandibular nodes/fullness, adenopathy, ecchymoses, liver/spleen size (palpable +/-), ascites (+/-), and edema (which should be quantified on a scale of 0-4+).

[8] Vital signs include heart rate (HR), respiratory rate (RR), blood pressure (BP), and body temperature; assess after subject has been at rest 25 minutes; within a visit, assess in the same position for all time points. **Month 1:** Within 30 minutes before dosing, 60 (±10) minutes after the start of the infusion, at EOI (+5 minutes), and 30 (±5) minutes after EOI, and 60 (±10) minutes after EOI. **All Other Months:** Within 30 minutes before dosing, at EOI (+5 minutes), and 60 (±10) minutes after EOI.

[9] See Appendices 5 and 6.

[10] All laboratory tests to be done locally, unless otherwise noted. When laboratory tests are obtained on the same day as NEOD001 administration they should be obtained *prior to* administration of study drug Pregnancy tests for WOCBP as follows: **Screening:** serum test within 28 days before Month 1-Day 1; **Month 1:** serum test within 24 hours before Month 1-Day 1; **Months 2-12:** serum test preinfusion; **EOS/ETD:** serum test; **90 (±5) days after the last study drug administration:** serum test.

[11] Serum free light chain studies, U-PEP, U-IFE, SPEP and S-IFE will be obtained prior to administration of NEOD001 or placebo.

[12] Archive of baseline and confirmatory EOS visit urine samples, in consenting patients, from first morning urination will be maintained at Tufts. Samples should be obtained during the screening period before the renal biopsy. Samples will be shipped same-day overnight in kits provided. These samples will be banked for future unspecified testing.

[13] Renal biopsy at study entry is standard of care. Renal biopsy should be obtained after mGFR and other urine studies, including archived urine sample, have been performed. A portion of the biopsy is routinely used for frozen section and, in consenting patients, will be cryopreserved in RNA Later for future molecular testing.

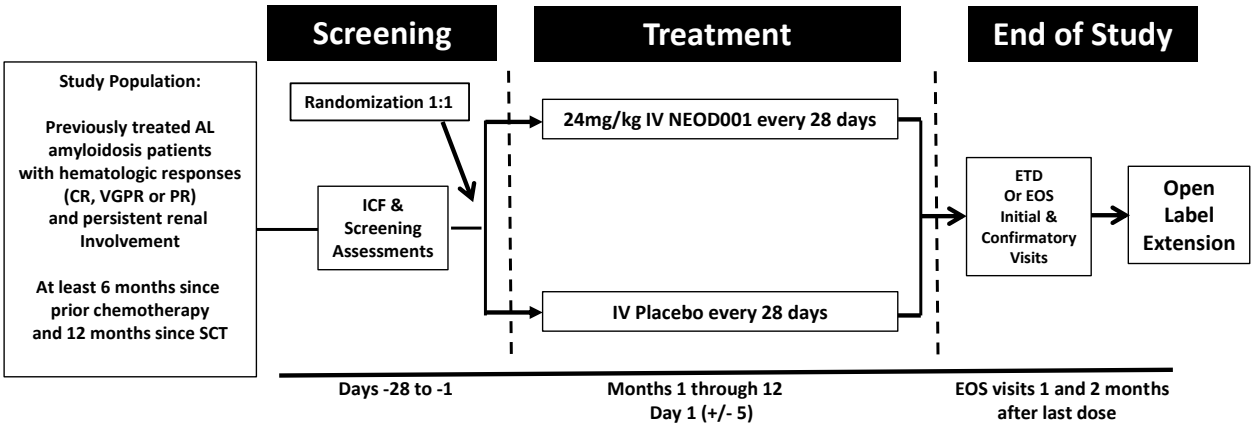
[14] Standard-of-care follow up will include local testing every 3 months of all laboratory studies included in the confirmatory visit during the OLE study.

[15] Inflammatory biomarkers include IL-6, IL-8, TNFα, C3 and C4, CRP, SAA (A-SAA), and tryptase (at screening only). Biomarkers should be repeated if clinically indicated, i.e. the subject has a hypersensitivity reaction

[16] Serum creatinine and 24 hour urine collection, including UPEP, to be sent to central lab (Covance).

Figure 1

NEOD001-RAIN Study Design



Stratification:

- Response to most recent treatment regimen: CR+VGPR vs PR
- Renal stages 1 or 2 vs Renal stage 3

Primary Endpoint:

- Confirmed renal response at 13 month visit after 12 months of treatment with NEOD001 or placebo.

CR = complete response; ETD = Early Treatment Discontinuation; EOS = End of Study; ICF = informed consent form; IV = intravenous; PR = partial response; VGPR = very good partial response.

Maximum monthly dose of NEOD001 is not to exceed 2500 mg.

GLOSSARY OF TERMS

Abbreviation/Acronym	Definition
AA	Amyloid A
ADA(s)	Anti-drug antibody(ies)
ADL	Activities of daily living
AE(s)	Adverse event(s)
AEF	Amyloid-enhancing factor
ALP	Alkaline phosphatase
AL	Amyloid light chain
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AV	Atrioventricular
BNP	B-type natriuretic peptide
BP	Blood pressure
BSA	Bovine serum albumin
BUN	Blood urea nitrogen
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMH	Cochran Mantel-Haenszel
CR	Complete response
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
D	Aspartic acid
E	Glutamic acid
ECL	Electrochemiluminescent
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EOI	End of infusion
EOS	End of Study
ETD	Early Treatment Discontinuation
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
HR	Heart rate
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Institutional Ethics Committee
IFE	Immunofixation electrophoresis
Ig	Immunoglobulin
IgG1	Immunoglobulin G1
IMWG	International Myeloma Working Group
INR	International normalized ratio
IRB	Institutional Review Board
IV	Intravenous or intravenously
LDH	Lactate dehydrogenase

MITT	Modified Intent-to-Treat
NOAEL	No-observable-adverse-effect-level
NR	No response
NT-proBNP	N-terminal pro B-type natriuretic peptide
NYHA	New York Heart Association
OLE	Open label extension
PCD	Plasma cell dyscrasia
PEP	Protein electrophoresis
PK	Pharmacokinetic(s)
PR	Partial response
PS	Performance status
PT	Prothrombin time
PTT	Partial thromboplastin time
RR	Respiratory rate
SAE	Serious adverse event
SC	Subcutaneous(ly)
SF-36	Short Form-36 Health Survey
SIFE	Serum immunofixation electrophoresis
SMC	Safety Monitoring Committee
SPEP	Serum protein electrophoresis
SCT	Stem cell transplantation
TEAE(s)	Treatment-emergent adverse event(s)
TRIAD	Transgenic Rapidly Inducible Amyloid Disease
UIFE	Urine immunofixation electrophoresis
ULN	Upper limit of normal
UPEP	Urine protein electrophoresis
US(A)	United States (of America)
USP	United States Pharmacopeial Convention
VASPI	Visual Analog Scale – Pain Intensity
VGPR	Very good partial response
WFI	Water for injection
WOCBP	Women of childbearing potential
WT	Wild-type

1 INTRODUCTION

1.1 Background

Systemic light-chain (AL) amyloidosis is a rare disease (3200 cases/year in the USA) in which unstable proteins misfold, are toxic, form fibrils and cause multiorgan dysfunction.[4] AL is due to immunoglobulin light chains (LC) produced by post-germinal center clonal plasma cells and, despite many advances in treatment, 25% of new AL patients present with rapidly fatal cardiac involvement, 25% with stage 3 chronic kidney disease (CKD), and 15% with stage 4/5 CKD.[5] Only 25% of newly diagnosed patients are eligible for high-dose melphalan and stem cell transplant with bortezomib-based consolidation, a treatment that results in about 50% of renal patients achieving renal responses at 12 months, while transplant-ineligible patients are usually treated initially with a bortezomib-containing regimen resulting in 25% of renal patients achieving renal responses.[6,7]

This is a multicenter Phase 2b randomized double-blind placebo-controlled two-arm parallel-group efficacy and safety study of NEOD001 as a single agent administered intravenously to adults with AL amyloidosis who have had a hematologic response to previous treatment for AL (e.g., chemotherapy, SCT) and have persistent renal dysfunction due to renal amyloidosis. The purpose of this trial is to determine if the experimental anti-amyloid agent NEOD001, a monoclonal antibody that targets a light chain amyloid epitope, increases the frequency of confirmed renal responses in previously treated patients with AL and renal involvement who do not need chemotherapy for the LC disease.[8] Patients will be randomized to receive NEOD001 or placebo. After completing 12 months of treatment and the confirmatory EOS visit, a subject may enter an open-label extension (OLE) study, during which subjects will receive active treatment with NEOD001 for 12 months and may receive concurrent chemotherapy.

The primary endpoint is the confirmed renal response rate at 13 months after initiating therapy (after 12 months of NEOD001 or placebo). Renal response is measured according to criteria that have been developed and validated in two large European cohorts, employing eGFR and 24-hour proteinuria.[2] A renal response is a ≥ 30% decrease in proteinuria or drop of proteinuria below 0.5 g/24h in the absence of renal progression. Renal progression is defined as ≥ 25% decrease in eGFR. A confirmed renal response is one that has been documented as present at both 12 and 13 months after initiating therapy. Secondary end-points of this trial involve comparisons of measured GFR (mGFR) compared to eGFR at study entry, and comparisons of patients who receive NEOD001 or placebo with respect to time to CKD 4 or 5 status, time to eGFR $\leq$ 15 or dialysis, time to doubling of serum creatinine, time to a $\geq$ 40% reduction in eGFR, and rates of renal response and progression at 26 months after study entry in patients with maintained hematologic responses. We will also assess safety and tolerability of NEOD001 and mortality due to all causes at 26 months.

In this multicenter trial, we plan to treat AL patients who are greater than 18 years old and have had hematologic responses to their last prior therapy and who have persistent AL renal involvement with renal stage 1, 2 or 3 disease. Patients must be chronic kidney disease stage (CKD) $\leq$ 3. Patients with NT-proBNP $\geq$ 1800 are not eligible for this trial.[9] Patients must have prior confirmed AL amyloidosis based on Congo red and immunohistochemical staining or mass spectrometry typing of a tissue biopsy (excluding bone marrow), and patients screened and found otherwise eligible must have a screening renal biopsy to confirm that amyloidosis is the cause of renal disease before being declared eligible for RAIN. Eligible patients are then stratified based on response to prior therapy (CR/VGPR vs PR) and renal stage (stages 1 or 2 vs stage 3) and randomized.[2]

Patients will receive monthly administrations of NEOD001 at 24 mg/kg (maximum 2500 mg) on day 1 of each month. The maximum planned number of infusions of NEOD001 is 12. With respect to NEOD001, there have been no hematologic side effects noted and infusion-related side effects are rare.[8] To date, NEOD001 has been safe and well tolerated and its use is designed to optimize the potential for durable functional renal improvement. We will record vital signs and patient status before and after each administration of NEOD001 or placebo. NEOD001 or placebo will be given IV monthly. NEOD001 has been shown, in a phase I/II trial, to

improve the renal status of 60% of previously treated AL patients with renal involvement.[8] There are no adjustments needed for renal function.

Hematologic and renal status will be evaluated every 3 months on study. Patients who have hematologic progression may stay on study through the 13-month active study period unless and until they begin chemotherapy for hematologic progression when they must come off study.

After completing 12 months of treatment and the confirmatory EOS visit, a subject may enter an OLE study during which subjects will receive active treatment with NEOD001 for 12 months and may receive concurrent chemotherapy.

1.2 Study Rationale

Currently, there are no approved treatments for AL amyloidosis and no existing treatments that directly neutralize the toxic soluble aggregates or remove the organ deposits of amyloid that are thought to cause organ dysfunction. Current treatment approaches are aimed at reducing or eliminating the hematologic disease that produces the free Ig light chains that are toxic and form amyloid (i.e., eliminating or reducing the cells responsible for producing light chains, thereby reducing or halting production of the toxic protein). These current treatment approaches include high-dose chemotherapy and SCT (but only for the 25% of newly diagnosed patients who can tolerate SCT) and often bortezomib- or melphalan-based or other chemotherapy for the remainder as well as clinical trials of new agents. Although complete hematologic responses can be achieved in approximately 60% of patients treated with SCT and post-SCT bortezomib-based consolidation, the rate of any organ function improvement ("organ response") after achieving a hematologic response with SCT or chemotherapy is highly variable. This is significant because a hematologic response in the absence of organ improvement provides improved survival but otherwise limited clinical benefit to patients with AL amyloidosis. The major determinant of morbidity and mortality remains end-organ damage.

1.3 Background on NEOD001

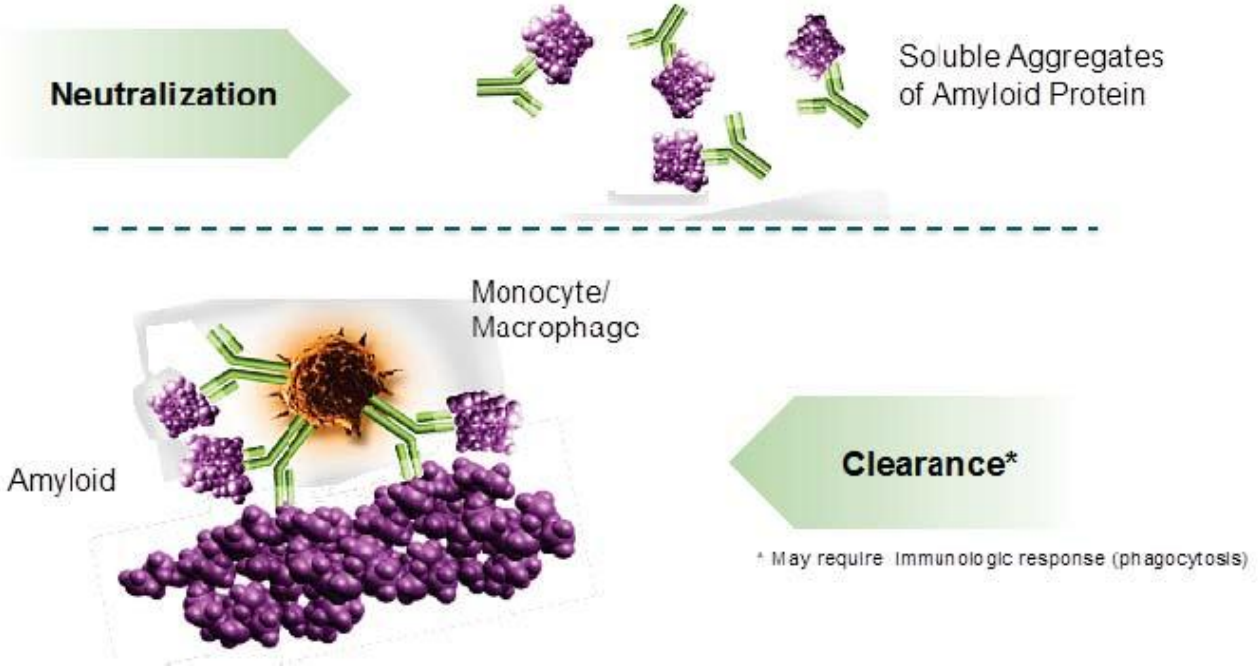
Prothena Therapeutics Limited (Prothena) is developing NEOD001, a humanized IgG1 kappa version of 2A4, the parent murine monoclonal antibody, which is directed against a cryptic epitope on amyloid fibrils. NEOD001 specifically targets misfolded light chain aggregates and amyloid deposits. In the course of specificity characterization of NEOD001, the antibody was found to react with high affinity and in a conformation-dependent manner with the misfolded light chains found in soluble aggregates and deposited light chain amyloid fibrils, however not with intact Ig or free non-amyloid light chains in circulation. NEOD001, administered by intravenous (IV) infusion, is proposed for use to target the misfolded light chains 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. NEOD001 is currently being studied in a randomized controlled Phase 3 study of NEOD001 or placebo (The VITAL Amyloidosis Study; NEOD001-CL002; NCT02312206) in newly diagnosed patients with AL amyloidosis disease also receiving bortezomib-based chemotherapy to treat an underlying PCD, and in a randomized controlled phase 2b trial (The PRONTO study; NEOD001-CL201; NCT02632786) in patients whose underlying light chain producing hematologic disease has responded to therapy and is stable but who still exhibit significant organ impairment.

Because NEOD001 and 2A4 (the parent murine monoclonal antibody for NEOD001) recognize a conserved epitope in both the AL and amyloid A (AA) proteins, nonclinical efficacy was evaluated in mouse models of both systemic AA amyloidosis (H2/hIL-6 Transgenic Rapidly Inducible Amyloid Disease [TRIAD] mouse model)

and AL amyloidosis (amyloidoma xenograft model) using 2A4.[10,11] In the AL xenograft model, treatment with ~5 mg/kg of 2A4 subcutaneously (SC), 3 times a week resulted in a statistically significant reduction in the size of the amyloidomas that were formed (by weight and volume). Efficacy studies in the TRIAD mouse model at the same dose demonstrated improvements in survival and, in some experiments, reductions in amyloid load. A single experiment using high doses of 2A4 (40 mg/kg) at either 1 week after disease induction vs 3 weeks after disease induction (when organ amyloid burden is well established) generated conflicting results; with increased organ amyloid burden in the early treatment arm, but decreased organ amyloid burden in the late treatment arm. At this time, no explanation for these differences has been found. Imaging, autoradiography, and biodistribution studies demonstrated specific binding of NEOD001 and 2A4 to their amyloid target in the TRIAD and AL xenograft models.

Figure 2 Proposed Mechanism of Action for NEOD001



1.3.1 Clinical Safety and Tolerability

The safety and tolerability of NEOD001 were investigated in a Phase 1/2 study (NEOD001-001; NCT01707264) in the US and are being investigated in both the global phase 3 study (VITAL; NEOD001-CL002) and the global phase 2b study (PRONTO; NEOD001-CL201).

Study NEOD001-001 was an open-label, dose escalation study of the IV administration of single-agent NEOD001 in subjects with AL amyloidosis. It enrolled 27 subjects in the Escalation Phase in 7 dose-level cohorts (evaluating dose levels from 0.5 mg/kg to 24.0 mg/kg) and an additional 42 subjects in the Expansion Phase. Data from all patients (N=69) in the Phase 1/2 study demonstrated that monthly infusions (every 28 days) of NEOD001 were safe and well tolerated. An interim analysis as of May 9, 2016 showed that a total of 69 patients received 913 infusions of up to 24 mg/kg, with a mean treatment duration of 13.2 months. The Phase 1/2 study (N=69) consists of previously-treated patients with AL amyloidosis and persistent organ dysfunction who received a mean of 2.5 prior lines of plasma cell directed therapy. No hypersensitivity reactions or drug-related serious adverse events were reported and no anti-NEOD001 antibodies were detected. The most commonly reported treatment-emergent adverse events, regardless of relationship to study drug were fatigue, upper respiratory tract infection, nausea, diarrhea, edema, anemia, and dizziness (Table 2). No dose limiting toxicities have been observed and no patient discontinued treatment due to drug-related adverse events.

Table 2 Treatment-Emergent Adverse Events (≥10%) Regardless of Relationship to NEOD001

	All Subjects (N=69)	
Preferred Term	**Total TEAEs n (%)**	**TEAEs ≥ Grade 3 n (%)**
Fatigue	23 (33.3)	1 (1.4)
Upper respiratory tract infection	18 (26.1)	0
Nausea	17 (24.6)	0
Diarrhea	16 (23.2)	0
Edema	13 (18.8)	1 (1.4)
Anemia	12 (17.4)	0
Dizziness	12 (17.4)	0
Increased blood creatinine	10 (14.5)	0
Cough	10 (14.5)	0
Constipation	9 (13)	0
Headache	9 (13)	0
Dyspnea	8 (11.6)	0
Rash	8 (11.6)	0
Vomiting	8 (11.6)	0
Peripheral Edema	7 (10.1)	0
Pain in extremety	7 (10.1)	0

As of the May 9, 2016 date, best response rates from total cardiac- (n=36) and renal- (n=35) evaluable patients were 53% and 63%, respectively, consistent with an earlier interim analysis from the dose-escalation phase (Gertz 2016). In the first exploratory analysis of this kind, NEOD001 demonstrated improvement of peripheral neuropathy, evidenced by a mean 35% decrease in the Neuropathy Impairment Score of the Lower Limb (NIS-LL) in the expansion cohort (n=11), leading to an 82% response rate. Two patients in this cohort demonstrated complete resolution of their peripheral neuropathy, as measured by NIS-LL.

2 OBJECTIVES

The primary objective of this study is to determine if the experimental anti-amyloid agent NEOD001, a monoclonal antibody that targets a light chain amyloid epitope, increases the frequency of confirmed renal responses in previously treated patients with AL and renal involvement who do not need chemotherapy for the LC producing disease. Patients will be randomized to receive NEOD001 or placebo. Renal response is defined as per Palladini 2014 (Appendix 4) and a confirmed response is one that is documented after completion of 12 months of treatment by testing on two occasions one month apart.

The secondary objectives are to compare measured GFR and eGFR at study entry, and to compare the two groups (NEOD001, placebo) with respect to a number of variables including time to CKD 4 or 5, time to eGFR ≤ 15 or dialysis, time to doubling of creatinine, time to ≥ 40% reduction in eGFR, and renal responses and progression in patients with maintained hematologic responses at 26 months. We will also assess the safety and tolerability of NEOD001 and all cause mortality at 26 months,

3 STUDY PLAN

3.1 Study Design

This is a multicenter Phase 2b, randomized, double-blind, placebo-controlled, two-arm, parallel-group efficacy study of NEOD001 as a single agent administered intravenously in adults with AL amyloidosis who had a hematologic response (Appendix 1) to previous treatment for their AL amyloidosis and have persistent renal dysfunction due to AL amyloidosis.

Subject screening will occur during the 28 days prior to the first administration of study drug (i.e., month 1 day 1). If all other eligibility requirements are met, the subject will undergo renal biopsy and, if AL amyloid is confirmed as the cause of renal disease, all screening assessments will be completed and the patient will be enrolled in RAIN. Screening assessments are listed in Table 1. Patients will have a renal biopsy to confirm that the basis of renal dysfunction is amyloidosis and may have renal function studies measuring urinary clearance of Iothalamate (Conray® - iothalamate meglumine injection U.S.P 60%; Mallinckrodt Inc., St. Louis, MO) from the blood. The renal function studies require 1 day and will be performed prior to the renal biopsy. Month 1 day 1 start of therapy will occur at least 2 days after the renal biopsy.

Study visits will occur every 28 days based on scheduling from month 1 day 1. A ±5-day window is allowed for visits starting after month 1. Subjects may receive up to 12 infusions of study drug. Subjects who discontinue study drug before the initial EOS visit should have an Early Treatment Discontinuation (ETD) visit 30 (±5) days after their final administration of study drug. After completing 12 months of treatment and the initial EOS visit, each patient will return one month later for a confirmatory EOS visit in order to confirm the results of renal testing obtained at the initial EOS visit.

After completing 12 months of treatment with NEOD001 or placebo and the confirmatory EOS visit, a subject may enter an open-label extension (OLE) study, during which subjects will receive active treatment with NEOD001 for 12 months and may receive concurrent chemotherapy.

3.2 Endpoints

3.2.1 Primary Efficacy

- Confirmed renal response rate after 12 months of treatment with NEOD001 or placebo (Appendix 1, Palladini 2014)

3.2.2 Secondary Endpoints

- Measured GFR at study entry (Appendix 9)
- Measured during and at the end of the active study period:
    - Time to CKD 4 or 5
    - Time to eGFR < 15 or dialysis
    - Time to doubling of creatinine
    - Time to > 40% reduction in eGFR
- Renal response and progression in patients with maintained hematologic responses at 26 months
- Safety and tolerability of NEOD001
- All cause mortality at 26 months

3.2.3 Ancillary Studies

Ancillary studies for this trial are being performed in collaboration with the Amyloidosis Research Consortium (ARC; described in synopsis). ARC will maintain ancillary study data in a REDCap database that the Tufts Neely Center for Clinical Cancer Research will create and oversee. The ancillary studies are being performed by a collaborative of Tufts, the ARC and for the gene expression work the University of Michigan. This work is being conducted under CDA and with IP agreements and carve-outs currently being negotiated. Patients will be assigned alphanumeric characters (absent all personal identifying information) that are linked to the Case

Report Forms maintained in REDCap by the participating centers and the Tufts Neely Center for Clinical Cancer Research.

The ancillary studies are designed in order to determine if there are differences among patients who receive NEOD001 and those who do not, and to define and identify differences among patients who have renal responses and those who do not, and renal progression or not, whether or not those patients receive NEOD001.

- Patient reported outcomes: Patients who receive NEOD001 or have renal responses or renal progression may experience changes in their quality of life. Patient reporting of outcomes is very important to in order to answer whether changes in renal disease status are associated with changes in quality of life. We will obtain SF-36 surveys at study entry and at 3, 6, 9 and 12 month visits and at ETD or initial and confirmatory EOS visit (Appendix 7). Scores will be computed and comparisons made by norm-based scoring (User's Manual for the SF-36v2 Health Survey, Second Edition).

- Renal Pathology Studies: We hypothesize that the findings related to amyloid and to renal injury in entry renal biopsies will correlate with risk of progression of renal disease and possibly with likelihood of responding to NEOD001. Renal biopsies containing amyloid as the critical factor in renal dysfunction will also contain some pattern of intrinsic renal injury with findings related to glomerulosclerosis, tubular atrophy and interstitial fibrosis. We will score the screening renal biopsies for amyloid load and pattern of infiltration as well as for these intrinsic renal injury patterns. (Appendix 8).[3] Results of renal biopsy scoring will be recorded by ARC. The renal pathology group will use established criteria and perform the scoring using a standard operating procedure and data sheet.[3] Comparisons will be made between the various groups, and among confirmed renal responses in the NEOD001 and placebo groups, by the CMH test stratified by the pre-randomization stratification factors at alpha of 0.05.

- Renal Transcriptional Profiling Studies: In these optional studies we ask whether or not there are transcriptional signatures that track with renal response, response to NEOD001, and renal progression Renal biopsy specimens will be obtained from consenting patients for transcriptional profiling following the standard operating procedures of The Nephrotic Syndrome Study Network ("NEPTUNE"). NEPTUNE is an integrated group of academic medical centers, patient support organizations and clinical research resources dedicated to advancing the understanding and treatment of certain kidney diseases unrelated to dysproteinemias. The tissue processing, microarray and bioinformatics work for the RAIN trial will be performed by the principal investigators of NEPTUNE at the University of Michigan in Ann Arbor (Appendix 10). Two of the participating RAIN centers (Mayo Rochester and the University of Pennsylvania) are also part of NEPTUNE. The ARC is seeking grant support to perform these studies; patient renal biopsy tissue will be processed and kept in RAIN centers until ARC funding is secured. Once the transcriptional profiles have been completed, at the end of study, RAIN investigators in the ARC, Tufts biostatistical personnel and the NEPTUNE investigators at the University of Michigan will analyze the data for publication. The intent of the ARC is also to make the completely de-identified but annotated transcriptional database freely available to qualified investigators.

3.3 Number of Sites and Subjects

This is a multicenter study in 9 centers. At least 100 subjects will be enrolled and randomized (1:1) with 50 subjects randomized to NEOD001 and 50 subjects randomized to placebo.

3.4 Randomization and Blinding

3.4.1 Randomization

A subject number will be assigned via a web-based registration for each subject who has signed an informed consent form (ICF). If a subject has completed all screening requirements and meets all of the eligibility

criteria, a Subject Registration Form will be submitted to the medical monitor for eligibility review and approval. If approved, randomization will be implemented via the Internet connection. At least 100 subjects will be randomized in a 1:1 ratio into one of two arms, NEOD001 24 mg/kg (50 subjects) or placebo (50 subjects). The randomization will be stratified by two factors:

- Hematologic response: Complete response/very good partial response (CR/VGPR) vs partial response (PR) to therapy (Appendix 1)
- Renal stage: Stage 1 and 2 vs stage 3 (Appendix 1, Palladini 2014)

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

3.4.2 Emergency Unblinding

The Investigator has the ability to break the blind for a specific subject in the event of an immediate medical emergency wherein knowledge of the subject's treatment (NEOD001 or placebo) must be known in order to provide adequate medical treatment. In these situations, the breaking of the blind must be reported to the Sponsor (Tufts) or its designee within 24 hours. Subjects may continue to receive study treatment with the approval of the medical monitor.

One or two Unblinded Pharmacists or an appropriate designee (henceforth collectively referred to as the Unblinded Pharmacist) will be identified at each site who will be responsible for preparing the study drug; all other study team members must remain blinded to study drug assignment. The Unblinded Pharmacist will obtain the randomization number and treatment assignment information from the IWRS, and will then prepare and reconstitute the study drug, providing it to the Investigator for administration. The Unblinded Pharmacist will maintain the records for drug accountability for audits or inspections.

Any other requests to reveal a subject's treatment must be requested of, and approved in writing by, the Sponsor (Tufts).

In addition, in the event of any safety concern, the Data Safety Monitoring Committee (DSMC) will have the option to unblind the treatment of any subject. In this situation, only the SMC will have access to the unblinded data.

3.5 Medical Monitor

The medical monitor (Raymond Comenzo, MD) will participate in central approval of sites for study initiation, confirming that all local approvals, documentation and training requirements have been met; will review and confirm subject eligibility, and documentation of screening results, thereby triggering enrolment and randomization of consenting subjects; will answer queries from investigators regarding specific cases and clinical situations; and will monitor changes in eGFR when the levels go below 30. All of these activities will be documented.

3.6 Estimated Study Duration

Each subject's study duration may be up to 26 months, consisting of a Screening Phase (1 month), a Treatment and Assessment Phase (1 months) that includes 12 months of treatment, the initial end-of-study (EOS) Visit 30 (±5) days after the last dose and the confirmatory EOS visit 1 month later, and the Open-label

Extension (OLE) Phase during which subjects will receive active treatment with NEOD001 for 12 months and may receive concurrent chemotherapy.

The 13-month Treatment and Assessment Phase is the active study period.

During the OLE study, subjects will be seen monthly, and local and central laboratory testing for the OLE study will be obtained and collected every 3 months. The OLE study will continue until the last subject enrolled on study completes study participation.

3.7 Definition of End of Study

The study will end when the last subject treated with NEOD001 or placebo completes either the ETD visit or the active study period and, if eligible, the 12 months on the OLE study after the confirmatory EOS visit.

4.0 SELECTION, DISCONTINUATION, AND WITHDRAWAL OF SUBJECTS

4.1 Inclusion Criteria

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

1. 18 years of age or older

2. Biopsy-proven diagnosis of AL amyloidosis by immunohistochemistry or mass spectroscopy of a tissue biopsy excluding bone marrow

3. Screening renal biopsy for RAIN confirming AL amyloidosis as exclusive or dominant cause of renal damage

4. Persistent renal involvement with proteinuria (predominantly albumin) > 500mg/day in a 24-hour urine collection

5. CKD 1, 2 or 3

6. ≥1 prior systemic hematologic therapy for free light chain (FLC) producing hematologic malignancy underlying the initial diagnosis of AL amyloidosis with a FLC response to treatment (PR, VGPR, CR) that is deemed stable and not requiring further treatment

7. ECOG Performance Status ≤ 2

8. Clinical laboratory values:
   - Absolute neutrophil count > 1000/μL
   - Platelet count > 75,000/μL
   - Total bilirubin ≤ 1.5X ULN
   - Alkaline phosphatase ≤ 5X ULN
   - ALT or AST ≤3X ULN
   - NT-proBNP < 1800 pg/mL

9. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.

4.2 Exclusion Criteria

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

1. Amyloidosis due to mutations of the transthyretin gene or presence of other non-AL amyloidosis

2. Female patients who are lactating, breastfeeding, or pregnant. Men and women of childbearing potential need to use birth control while participating in the study.

3. Patients who have received chemotherapy within 6 months, or SCT within 12 months, for the light-chain producing hematologic disease causing AL amyloidosis, at the time of the first dose of NEOD001 (month 1 day 1)

5. Patients who at initial diagnosis or later met the International Myeloma Working Group (IMWG) definition of active multiple myeloma (Appendix 3)

6. Medically documented cardiac syncope, uncompensated congestive heart failure, myocardial infarction within the previous 6 months, unstable angina pectoris, clinically significant repetitive atrial or ventricular arrhythmias despite antiarrhythmic treatment, or severe orthostatic hypotension or clinically significant uncompensated autonomic insufficiency.

7. Comorbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens.

8. Ongoing or active infection, known HIV positive, known to be hepatitis B surface antigen-positive or has known or suspected active hepatitis C infection.

9. Psychiatric illness/social situations that would limit compliance with study requirements. This will not be assessed for the study. Patients in active care that limits their ability to come to the center for therapy or patients with family situations that limit their ability to come to the center for therapy will not be eligible because they will not be able to comply with study requirements.

4.3 Early Treatment Discontinuation

If the subject discontinues study drug prior to the initial EOS visit, the subject should return for an ETD Visit 30 (±5) days after their final administration of study drug as per Section 6.2. 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 letter will be submitted to the IRB for review prior to use. This information will be recorded in the study records.

If the subject discontinues study drug prior to initial EOS visit, but is willing to continue to participate in study visits, continue to collect data through the ETD Visit (i.e., 30 [±5] days after their final administration of study drug). Following the ETD Visit, subsequent clinic evaluations will be standard-of-care visits with testing as clinically warranted, usually at a minimum of every 3 months. Testing in this circumstance can be performed at a distance. Every effort should be made for the subject to return to the clinic at the month 12 time point for completion of all of the initial EOS visit assessments.

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

• Hematologic progression requiring immediate initiation of chemotherapy; the chemotherapy regimen should be documented on the appropriate case report form.

• Need for organ transplant or major surgery.

• 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 (Raymond Comenzo, MD) should be notified as soon as possible of any discontinuation of study drug due to an AE.

• Suspected or confirmed pregnancy or nursing during study treatment period. Female subjects whose pregnancy test is positive at the ETD visit must be followed to term or until termination of the pregnancy.

4.4 Early Termination from the Study

Early termination occurs if the subject fails to complete the entire study, through the confirmatory EOS visit and 12-month period after the confirmatory 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 (Tufts) or its designee should be notified in a timely manner of all subject discontinuations. When possible, the tests and evaluations listed for the ETD Visit should be carried out.

Early termination from the study may occur if:

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

• Subject withdraws consent

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

• Subject is lost to follow-up

The Sponsor, (Tufts Medical Center) and the Prothena Therapeutics Limited who is funding the study reserve the right to discontinue the study at any time for any reason, including but not limited to, clinical or administrative reasons, or to discontinue participation of an individual Investigator or site for any reason, including but not limited to, poor enrollment or noncompliance. At any point in the study, if the subject is unwilling to return to the clinic for further visits but is willing to discuss their health status by phone, follow-up phone calls should be made to the subject or their caregiver every 3 months.

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, at completion of the last subject's participation in the OLE, survival status will be collected within legal and ethical boundaries for all randomized subjects who withdrew participation from the main or OLE study. If vital status is determined, the subject will not be considered lost to follow-up.

4.5 Replacement of Subjects

Randomized subjects who do not begin month 1 day 1 treatment with NEOD001 or placebo may be replaced. Randomized subjects who have received treatment and drop out of the study for any reason will not be replaced.

4.6 Termination of the Clinical Study

If the Investigator, the Sponsor (Tufts) or the Medical Monitor becomes aware of conditions or events that suggest a possible hazard to subjects if the clinical study continues, then the clinical study may be terminated. The clinical study may also be terminated at the Sponsor's discretion in the absence of such a finding, at any time and for any reason.

Conditions that may warrant termination of the clinical study include, but are not limited to:

- The discovery of an unexpected, relevant, or unacceptable risk to the subjects enrolled in the clinical study
- A decision by the Sponsor (Tufts) to suspend the study, or to suspend administration of the study drug, for any reason

4.7 Local Recruitment Methods

All other sites will follow their own recruitment methods per their SOPs. Tufts Medical Center will follow the following methods:

1. Who will identify potential study subjects: The Principal Investigator, Co-Investigators, and Study Nurse Coordinator will work together to identify potential study subjects
2. Describe how subjects will be identified (e.g., medical record screening, approached in clinic): Study subjects will be identified through new patient intake forms, during tumor board reviews, at clinic visits, by patient self-referral, (e.g. as contacting the study coordinator directly from the contact information on a website) and by physician referrals. If a patient (potential study participant) contacts the study nurse/coordinator by calling the telephone number or responding to other contact information on a website posting / advertisement for a particular study, the following information will be obtained from the potential study participant: name, telephone number, diagnosis, and medical history (medical history includes a brief description of the treatment he/she has received to date). The study nurse/coordinator will provide information about the study (limited to the information in the ICF and website posting) and the potential study participant will be advised to schedule an appointment with the PI or a Co-I (study doctor) to evaluate eligibility. Upon request, the study nurse can provide the consent form via mail or e-mail. Potential study participants will be advised to call the study nurse/coordinator with any questions they have about the consent form.
3. Who will approach subjects or their legally authorized representative about participation: The Principal Investigator, Co-Investigator or study nurse, at the request of the PI or Co-I, will approach subjects about participation.
4. When will subjects or their legally authorized representative be approached about participation: Potential subjects will be approached during their clinic visits.
5. How will subjects or their legally authorized representative be approached about participation: During the course of a clinic visit, the patient will be given all the various options for the treatment for their disease. All standard treatment options will be discussed along with any clinical trials that the patient may be eligible for. The risks and possible benefits will be presented and discussed with the patient by the study investigator or by their physician. If the patient demonstrates an interest in participating in a particular clinical trial, the specific study procedures will be more thoroughly reviewed with the patient and he/she will be given a copy of the Informed Consent Form to take home and to read about. For further detail about the consent process, see Section I.

5. TREATMENT OF SUBJECTS

5.1 Study Drug

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/vial NEOD001. After reconstitution with 9.6 mL of sterile water for injection (WFI), the vial will contain 50 mg/mL of NEOD001, 17.5 mM L-Histidine, 7.5 mM L-Histidine Hydrochloride monohydrate, 230 mM Trehalose dehydrate, 0.02% Polysorbate 20.

At a minimum, the label for each vial shipped to a clinical site will provide the following information: batch number/lot number, required storage conditions, directions for use, and any region-specific caution statements, e.g., “New Drug -Limited by United States Federal Law to Investigational Use.” 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 (i.e., supply arrived at room temperature or was not placed in refrigerator upon receipt), the Sponsor or its designee must be contacted immediately. 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 Sponsor or its designee provides further direction.

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 5.2 and the Pharmacy Manual for further details about shipping, storage and handling of NEOD001.

5.1.2 Accountability and Return of Study Supplies

The study drug will be dispensed at the discretion of the Investigator under the direction of the Unblinded Pharmacist, in accordance with the conditions specified in this protocol. It is the Unblinded Pharmacist’s responsibility to ensure that accurate records of study drug disposition and destruction are maintained.

5.2 Dosage, Preparation, and Administration

Study drug consists of NEOD001 or placebo. 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 will be calculated based on the current weight at that visit. A change of ±10% from the weight being used for dosing should trigger recalculation of the dose based on the new weight.

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. A separate placebo will not be provided for this study. Subjects who receive placebo will be administered a

250 mL IV bag of 0.9% saline, which will look identical to the NEOD001 infusion bag. Refer to the Pharmacy Manual for complete information on preparing and administering the study drug.

One or two Unblinded Pharmacists or an appropriate designee (henceforth collectively referred to as the Unblinded Pharmacist) will be identified at each site who will be responsible for preparing the study drug; all other study team members must remain blinded to study drug assignment. The Unblinded Pharmacist will obtain the randomization number and treatment assignment information from the IVRS/IWRS, and will then prepare and reconstitute the study drug, providing it to the Investigator for administration. The Unblinded Pharmacist will maintain the records for drug accountability for audits or inspections.

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.

Study drug will be administered as an initial 120 (±10)-minute IV infusion on Month 1-Day 1. If, in the opinion of the Investigator, the subject tolerates the initial administration, subsequent infusions may be administered over 60 (±10) minutes once every 28 (±5) days; a minimum of 21 days between doses is required. Subjects may receive up to 12 infusions of study drug.

If there is concern about infusing 250 mL over 60 (±10) minutes in any specific subject, the length of the infusion may be extended over a longer period of time as clinically indicated. If the infusion must be extended beyond 4 hours, the study drug should be split into two 125-mL bags to ensure that the study drug will not remain at room temperature for longer than 4 hours (i.e., the second bag 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.

All subjects will be closely monitored for approximately 90 (±10) minutes after completion of the study drug infusion. The Investigator may increase this standard monitoring time if deemed appropriate or per local standards. In the event of any clinical concerns or suspicious signs or symptoms after the infusion, the subject will remain under observation for as long as the Investigator deems it appropriate.

5.3 Dosage Adjustments

5.3.1 Withholding of Study Drug

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

5.3.2 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 per institutional practice, which may include, but is not limited to, epinephrine, IV fluids, corticosteroids, vasopressors, oxygen, bronchodilators, antihistamines, or acetaminophen/paracetamol. Subjects should be evaluated and carefully monitored until there is complete resolution of the AE or hypersensitivity signs and symptoms.

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 (i.e., if the initial infusion is administered over 120 minutes, the new rate should be based on administering 250 mL over at least 180 minutes). If the subject is to receive additional infusions in

subsequent weeks, the rate of these infusions should be discussed with and agreed upon prospectively by the Investigator and the Medical Monitor. In addition, for all subsequent infusions, maximal premedication must be administered according to institutional practice and should include an H1 blocker, an H2 blocker, an antipyretic such as acetaminophen/paracetamol and a steroid (e.g., 25-50 mg hydrocortisone IV).

If a subject experiences a Grade 3 infusion-related and/or hypersensitivity AE, the infusion should not be restarted. The decision to continue dosing this subject at their next scheduled administration should be discussed with the Medical Monitor. If the decision is made to proceed with subsequent dosing, **both** the dose and infusion rate will be reduced by 50% from the original dose and infusion rate. In addition, maximal premedication must be administered according to institutional practice and should include an H1 blocker, an H2 blocker, an antipyretic such as acetaminophen/paracetamol and a steroid (e.g., 25-50 mg hydrocortisone IV). Subjects who have an infusion-related and/or hypersensitivity AE at the subsequent scheduled study drug administration must have study drug permanently discontinued.

Subjects who experience a Grade 4 infusion-related and/or hypersensitivity AE must have study drug permanently discontinued.

5.3.3 Dose Reductions

Dose reductions may be allowed in the event that AEs are observed that 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.

5.4 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.

5.5 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 ETD/EOS visits, and any changes to concomitant medications during the study will be recorded on the appropriate eCRF.

5.5.1 Allowed (Concomitant)

• Calcium channel blockers (if on stable dose)

• Steroids (***exception:*** not allowed for treatment of AL amyloidosis)

5.5.2 Prohibited (Concomitant)

• Chemotherapy

• Other investigational agents

• Myeloablative chemotherapy with ASCT

• Organ transplant

• Doxycycline

• Minocycline

• Diflunisal

• Histone deacetylase (HDAC) inhibitors

6 STUDY PROCEDURES

6.1 Evaluations by Visit

6.1.1 Screening

With the exception of the assessments to be considered standard of care (e.g., blood and tissue samples), 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.

The following will be performed within the 28 days prior to the month 1 day 1 visit:

• Signed ICF

• Review inclusion and exclusion criteria to assess eligibility

• Medical History - Obtain comprehensive cardiac, hematologic, and oncologic medical history; additionally, for all other conditions obtain relevant medical history for the past 5 years (including all major hospitalizations and surgeries), as well as the subject's current medical status

• Prior and concomitant medications/therapy

• Confirmation of diagnosis by prior immunohistochemical or mass spectrometry tissue typing of amyloid

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

• Vital signs – heart rate (HR), BP, respiratory rate (RR), and body temperature after the subject has been at rest for 25 minutes

• ECOG PS

• NYHA Class

• Hematology and chemistry (including amylase)

• Coagulation

• Troponin T or I

• NT-proBNP

• BNP

• Serum pregnancy test for WOCBP within 28 days before month 1 day 1 study drug administration. Note:

Women with tubal ligations are considered to be of childbearing potential but women who are surgically sterile (hysterectomy) or postmenopausal 22 years are not considered to be of childbearing potential

• Serum free light chains

• Serum protein electrophoresis (SPEP) and 24-hour urine protein electrophoresis (UPEP)

• Serum immunofixation electrophoresis (SIFE) and urine immunofixation electrophoresis (UIFE)

• Urinalysis - dipstick

• 24-hour urine protein and creatinine excretion

• Echocardiogram

• Electrocardiogram

• Archived urine sample

• Renal function studies

• Renal biopsy

• Inflammatory biomarkers

• Tryptase

• SF-36

6.1.2 Treatment Visits
Study visits will occur every 28 days based on scheduling from month 1 day 1. A ±5-day window is allowed for visits starting after month 1. Subjects may receive up to 12 infusions of study drug; a minimum of 21 days between doses is required.

The predose assessments for each visit may be performed within the 2 days before the visit (with the exception of pregnancy tests, which must be performed within 24 hours of study drug administration). Local laboratory assessments will be performed.

Subjects who present with symptomatic orthostatic hypotension and/or systolic BP <85 mm Hg, which in the medical judgment of the Investigator would interfere with the subject's ability to safely receive treatment, will have study drug withheld. If study drug is withheld and subsequently rescheduled, 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 exam and vital signs need to be repeated prior to each dosing.

6.1.2.1 Month 1 day 1
Prior to Study Drug Infusion:

The following assessments will be done prior to dosing on month 1 day 1:

• 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; gastrointestinal system; and nervous system. The components of the physical exam will be as clinically indicated; however, 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 within 30 minutes before dosing, after subject has been at rest 25 minutes; assess in same position for all time points
• ECOG PS
• NYHA Class
• Hematology and chemistry laboratory testing (including amylase)
• NT-proBNP
• BNP
• Serum pregnancy test within 24 hours before study drug administration
• Urinalysis - dipstick
• Randomization – After the subject is randomized, study drug treatment may be initiated

Study Drug Administration:

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

• Administer study drug IV over 120 (±10) minutes

• Vital signs including HR, BP, RR, and body temperature – assess 60 (±10) minutes after the start of the infusion; assess in same position for all time points

Assessments After Infusion:

• Monitor subjects for 90 (±10) minutes following completion of the study drug infusion. The Investigator may increase this standard monitoring time if deemed appropriate or per local standards. In the event of any clinical concerns or suspicious signs or symptoms after the infusion, the subject will remain under observation for as long as the Investigator deems it appropriate.

• Vital signs including HR, BP, RR, and body temperature after subject has been at rest 25 minutes; assess in same position for all time points:

• At the end of infusion (EOI) (+5 minutes)

• 30 (±5) minutes after EOI

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

6.1.2.2 Months 2 through 12 – day 1 (±5 Days)

Prior to Study Drug Infusion:

The following assessments will be done prior to dosing on Day 1:

• 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; gastrointestinal system; and nervous system. The components of the physical exam will be as clinically indicated; however, 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 within 30 minutes before dosing, after subject has been at rest 25 minutes; assess in same position for all time points
• ECOG PS/NYHA Class
• Hematology and chemistry laboratory testing (including amylase)
• Coagulation
• Troponin T or I – Months 3, 6, 9, 12
• NT-proBNP
• BNP
• Serum pregnancy test (WOCBP)
• Serum free light chains – Months 3, 6, 9, 12
• SPEP and 24-hour UPEP – Months 3, 6, 9, 12
• SIFE and UIFE – Months 3, 6, 9, 12
• Urinalysis - dipstick – Months 3, 6, 9, 12
• 24-hour collection for urine protein excretion – Months 3, 6, 9, 12
• Inflammatory biomarkers – Months 3, 6, 9, 12
• SF36 – Months 3, 6, 9, 12

Study Drug Administration:

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

• Administer study drug IV over 60 (±10) minutes if the month 1 day 1 infusion was well tolerated.

Assessments After Infusion:

• Monitor subjects for 90 (±10) minutes following completion of the study drug infusion. The Investigator may increase this standard monitoring time if deemed appropriate or per local standards. In the event of any clinical concerns or suspicious signs or symptoms after the infusion, the subject will remain under observation for as long as the Investigator deems it appropriate.

• Vital signs including HR, BP, RR, and body temperature – after subject has been at rest 25 minutes; assess in same position for all time points:

• 60 (±10) minutes after EOI

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

6.2 Early Treatment Discontinuation (ETD) or Initial EOS visit: 30 (±5) days AFTER Final Dose

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

• Concomitant medications/therapy

• Assessment of AEs

• Complete physical examination -including weight and examination of general appearance; head, ears, eyes,

nose, and throat; neck; skin; cardiovascular system; respiratory system; gastrointestinal 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 - after subject has been at rest 25 minutes

• ECOG PS

• NYHA Class

• Hematology and chemistry laboratory testing (including amylase)

• Coagulation

• Troponin T or I

• NT-proBNP

• BNP

• Serum pregnancy test (WOCBP only)

• Serum free light chains

• SPEP and 24-hour UPEP

• SIFE and UIFE

• Urinalysis -dipstick

• 24-hour urine protein excretion

• Inflammatory biomarkers

• SF36

6.2.1 Confirmatory EOS visit: 30 (+/- 5) days after the initial EOS visit

A confirmatory EOS visit should occur 30 (±5) days after the initial EOS visit. final administration of study drug. The assessments include.

• 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; gastrointestinal 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 - after subject has been at rest 25 minutes

• ECOG PS

• NYHA Class

• Hematology and chemistry laboratory testing (including amylase)

- Coagulation
- Troponin T or I
- NT-proBNP
- BNP
- Serum pregnancy test (WOCBP only)
- Urinalysis -dipstick
- 24-hour urine protein excretion
- SF36

6.3 90-day Post-dose Pregnancy Test

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

6.4 Vital Status Follow-Up Phone Call

Conduct vital status telephone call approximately 4 weeks after ETD visit or confirmatory EOS visit and approximately every 3 months thereafter until 24 months after study entry if the subject does not comply with standard-of-care visits or testing.

6.5 METHODS OF ASSESSMENT

6.5.1 Safety

6.5.1.1 Clinical Laboratory Evaluations

Local laboratories in the 9 centers will be used for this study for analysis of hematology, chemistry (including amylase), pregnancy testing, coagulation, cardiac biomarkers, serum free light chains, SPEP, 24-hour UPEP, SIFE, UIFE, urinalyses, and 24-hour urine protein excretion.

Hematology and chemistry results will be reviewed prior to dosing at each month's day 1 visit to confirm that continued dosing is appropriate.

6.5.1.2 Vital Signs

Predose vital signs should be assessed within 30 minutes before dosing. Vital signs should be measured after the subject has been at rest 25 minutes. Within a single visit, assess in the same position for all time points.

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

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

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

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

6.5.1.3 Physical Examination

Any unfavorable changes in physical examination findings considered by the Investigator as clinically significant will be documented in the eCRF as an AE. Physical examinations must be performed by the Investigator or a medically qualified delegate.

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

6.5.2 Efficacy

6.5.2.1 Primary: Renal Response

See Appendix 4.

6.5.2.2 Secondary

Comparisons of mGFR and eGFR at study entry.

Time to CKD 4 or 5

Time to eGFR < 15 or dialysis

Time to doubling of creatinine

Time to > 40% reduction in eGFR

Renal response and progression in patients who have had maintained hematologic responses at 26 months

Safety and tolerability of NEOD001

All cause mortality at 26 months

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

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

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

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 more than one eCRF.

7.2 Adverse Events—Severity Rating

Adverse events will be assessed according to NCI CTCAE version 4.0. Adverse events that do not have a corresponding CTCAE term will be assessed according to their impact on the participant's ability to perform daily activities as listed below. The severity of each AE should be characterized and then classified into one of five clearly defined categories as follows:

• **Grade 1 (mild):** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

• **Grade 2 (moderate):** Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activity of daily living (e.g., preparing meals, shopping for groceries or clothes, using the telephone, managing money).

• **Grade 3 (severe):** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (e.g., bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).

• **Grade 4 (life threatening):** Life-threatening consequences; urgent intervention indicated.

• **Grade 5 (fatal):** Death related to AE.

These five categories are based on the Investigator's clinical judgment, which in turn depends on consideration

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

7.3 Adverse Events—Causality Rating

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

Guidelines for "Related" Events

• There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.

• There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.

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

Guidelines for "Not related" Events

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

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

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

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

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

Consider the Following When Assessing Causality

• Temporal associations between the agent and the event

• Cessation or rechallenge

• Compatibility with known class effect

• Known effects of concomitant medications

• Preexisting risk factors

• A plausible mechanism

• Concurrent illnesses

7.4 Serious Adverse Events and Unexpected Adverse events

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

• Is fatal

• Is life-threatening

• Is persistent or significantly incapacitating or causes substantial disruption of the ability to conduct normal life functions

• Requires inpatient hospitalization

• Prolongs existing hospitalization

• Is a congenital anomaly or birth defect

• Is an important medical event that may jeopardize the subject and/or may require medical or surgical intervention to prevent one of the outcomes listed above

Definition of Life-threatening

An adverse event 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 adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Definition of Hospitalization

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

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

• Emergency room visits (that do not result in a full hospital admission)

• Outpatient surgery

• Preplanned or elective procedures

• Protocol procedures

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

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

Definition of Disability

Disability is defined as a persistent and substantial disruption in a person's ability to conduct normal life functions.

Definition of Medically Significant

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

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

Definition of Suspected Adverse Reactions

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

Definition of Unexpected

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the Investigator Brochure or is not listed at the specificity or severity that has been observed. "Unexpected," as used in this definition, also refers to adverse events 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, any occurrence of exposure through lactation and any

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

7.4.3 Disease Progression and Death

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

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

7.4.4 Serious Adverse Events—Reporting

It is the responsibility of the Investigator to report SAEs to the Sponsor (Tufts) within 24 hours of awareness of the event or safety information, whether initial or follow-up, and of the Sponsor to fulfill all SAE reporting requirements to the FDA and to the manufacturer of NEOD001 (Prothena).

1) For expedited reporting of SUSARs, Tufts Medical Center will send the SAE report to Prothena and Novella at the following email addresses:

a. drugsafety@prothena.com

b. Safety-Inbox@novellaclinical.com

2.) For annual and ad hoc safety reporting, Tufts Medical Center will send SAE reports only to Prothena

a. drugsafety@prothena.com

All SAEs must be reported immediately (within 24 hours of awareness) to the Sponsor (Tufts Medical Center). 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 as a follow-up to the initial report. SAEs will be reported using the SAE forms provided as part of the study. Please remember to give details of the subject identification number or other appropriate terminology and ensure the narrative is comprehensive and includes a chronology and assessment of the event.

Reporting of SAEs to the Institutional Review Board/Institutional Ethics Committee (IRB/IEC) will be done in compliance with the standard operating procedures and policies of the IRB/IEC of record 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 Investigator is encouraged to discuss any AEs with the Sponsor Medical Monitor for which the issue of seriousness is unclear or questioned. The Medical Monitor for this study is Dr. Raymond Comenzo and you may contact him by phone at 617-636-6454 and by e-mail at rcomenzo@tuftsmedicalcenter.org.

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

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

7.4.5 Data Safety and Monitoring Committee

An independent Data Safety Monitoring Committee (DSMC), consisting of at least 2 clinicians and a biostatistician not directly involved with the conduct of the trial, will meet to review specified blinded subject data during the conduct of the study. The purpose of these independent data reviews is to assess the totality of the safety data and provide recommendations for protocol modifications. Tufts Cancer Center Data Safety and Monitoring Board (DSMB) operates as an independent oversight committee and will be used to monitor the trial for the safety of the participants. The DSMB meets quarterly. The sponsor, Tufts Medical Center, will be responsible for providing DSMB committee members with a summary of the study data and all other requested information at least 7 days before the scheduled meeting.

An ad-hoc meeting may be called by the principal investigator, Medical Monitor or by the DSMB chairperson. In the event of an SAE or an emergent safety concern, the principal investigator or his designee will report the event to the IRB and to the DSMB chairperson. The DSMB will meet within 7 days (via conference call or e-mail discussion) following the notification of an unanticipated problem. The structure of the ad hoc meetings will follow that of regular meetings. The DSMB members will vote on recommendations for continuing, modifying, or stopping enrollment in the trial. The chairperson will provide the sponsor with a written report summarizing the recommendations. In addition, the study will be placed on the agenda for the next regular DSMB meeting to review the follow-up actions and reassess risk.

8 STATISTICAL METHODS AND CONSIDERATIONS

8.1 Analysis Populations

Primary efficacy analysis is based on patients who are randomized and receive treatment for 12 months with NEOD001 or placebo.

Analysis of secondary time-to-event and also safety endpoints will be based on intention-to-treat. All patients randomized and treated with NEOD001 or placebo will be included.

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

1. The Intent-to-Treat Population will include all randomized subjects who receive any amount of study drug (NEOD001 or placebo). Treatment assignment will be based on the randomized treatment.
2. The Safety Population will include all subjects who received any amount of study drug (NEOD001 or placebo). The Safety Population will be the primary population used for safety analyses. Treatment assignment will be based on the treatment actually received. For example, in the event of randomization, dispensing, or treatment errors, subjects will be included in the treatment group based on the treatment that was received.

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, disease characteristics and markers of organ function at Screening will be summarized using means, standard deviations, medians, ranges for continuous variables, and proportions for categorical variables.

8.3 Analysis of Efficacy Endpoints

8.3.1 Primary Efficacy Analysis

This stratified randomized double-blind phase 2b study has as its primary efficacy endpoint confirmed renal response at the confirmatory EOS visit to evaluate 12 months of study treatment. The primary efficacy analysis will test the following hypotheses:

- H_0: The confirmed renal response rate after 12 months of treatment is equal between placebo and NEOD001.
- H_1: The confirmed renal response rate after 12 months of treatment is different between placebo and NEOD001.

The primary efficacy analysis of the confirmed renal response rates after 12 months of treatment with NEOD001 or placebo will be performed with the Mantel-Haenszel (MH) test at the alpha=0.05 (two-sided) level of significance. The analysis will be stratified by the randomization stratification variables. The number and percentage, with associated 95% exact confidence intervals (CI) of subjects in each category of response will be presented by treatment group. The proportional treatment difference with associated exact 95% CI will be presented.

8.3.2 Secondary Endpoint Analyses

Comparisons of mGFR and eGFR at study entry will be by the Tukey mean-difference (Bland-Altman) method determining whether the measurements are sufficiently close at alpha level of 0.05.

Analyses of time-to-event secondary endpoints comparing the NEOD001 and placebo groups will be performed by Kaplan-Meier (stratified log-rank) at an alpha level of 0.05. These endpoints include time to CKD 4 or 5, time to eGFR $\leq$ 15 or dialysis, time to doubling of serum creatinine, and time to $\geq$ 40% reduction in eGFR.

The comparisons of renal response and progression in patients with maintained hematologic responses at 26 months who received NEOD001 or placebo will be analyzed using a standard t-test and also using a Cochran Mantel-Haenszel (CMH) test stratified by the pre-randomization stratification factors. The number and percentage, with associated 95% exact confidence intervals (CI), of subjects in each category of response will be presented by treatment group. The proportional treatment difference with associated exact 95% CI will be presented.

8.3.3 Ancillary Studies Analyses

The ancillary studies analyses will be performed by the Amyloidosis Research Consortium (ARC) in collaboration with Tufts Medical Center and the other RAIN study centers. Original forms will be faxed or reported electronically to the ARC data manager for entry into the RAIN ancillary studies database. The ancillary studies database will be maintained by ARC personnel and be accessed by Tufts and ARC data managers. This database is part of the secure REDCap database that is used for this trial.

SF-36 surveys (Appendix 7) will be scored and recorded in a central REDCap data bank. The SF-36 assesses 8 scales of health status from which a physical component summary (PCS) and a mental component summary (MCS) are derived (User's Manual for the SF-36v2 Health Survey, Second Edition). Summary scores will be standardized so a score of 50 corresponds to the average for the US population. Baseline and follow-up SF-36 scores will be compared for each patient and with population norms using 1-sample t tests. Pearson correlations, t tests, Wilcoxon 2-sample tests, and Mantel-Haenszel tests will be used to describe the associations between various component scales and scores of the SF-36 and clinical and demographic characteristics of these patients. The relationship of improvement or worsening in the PCS or MCS to 12 months of treatment with NEOD001 or placebo, and also to the presence or absence of confirmed renal responses, will be examined using the Mantel-Haenszel test. In order to determine whether the QOL measures reflect contributions that were independent of or equivalent to those made by treatment assignment, presence or absence of confirmed renal responses, or clinical characteristics, stepwise proportional hazards regression with the significance level for entry into and for staying in the model set at 5% will be used to identify clinical and health status factors related to changes in QOL measures from the beginning to the end of treatment.

Renal biopsies will be scored by a predefined set of criteria for the degree and pattern of amyloid involvement and distribution (Appendix 8). The renal pathology group will use established criteria, perform the scoring using a standard operating procedure and record results in a central data bank.[3] Comparisons will be made between the NEOD001 and placebo groups by the CMH test stratified by the pre-randomization stratification factors at alpha of 0.05.

The ARC will seek additional funding to perform microarray and miRNA array profiling of renal biopsy specimens from RAIN patients and to conduct biostatistical analyses of the results in collaboration with the University of Michigan investigators, Tufts Medical Center and the other RAIN study centers.

8.4 Analysis of Safety Endpoints

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 number of infusions per patient, the total dose of NEOD001 received per patient, and the number of patients whose infusions were interrupted for infusion reactions.

Safety and tolerability of NEOD001 will be assessed by vital signs, duration of therapy, routine laboratory assessments, frequency and severity of AEs as assessed by CTCAE grade. We will apply descriptive statistical methods to the data, supplemented by calculation of confidence intervals if indicated. We will also display the grades and patterns of adverse events within both treatment groups.

8.5. Determination of Sample Size

This stratified randomized double-blind phase 2b study has as its primary efficacy end-point the confirmed renal response rate at 13 months after initiating therapy and is designed to detect an absolute increase in the renal response rate of 30% (from 25% in those receiving placebo to 55% in those receiving NEOD001). For the primary efficacy endpoint, the assumed true rates for NEOD001 vs placebo are 55% and 25%, respectively. Based on a chi-squared statistic to evaluate the null hypothesis at the alpha=0.05 level of significance, and assuming an 18% drop-out rate for hematologic progression requiring chemotherapy, a total sample size of 82 subjects (41 in the placebo group, 41 in the NEOD001 group) will enable us to reject the null hypothesis that the response rates for subjects receiving NEOD001 and placebo are equal with probability (power) 0.8. With 50 patients receiving placebo and 50 patients receiving NEOD001, we expect to have at least 41 evaluable patients in each group.

Of note, we are estimating the renal response rate over time in the arm not receiving NEOD001. In the relapsed setting, patients receiving lenalidomide and dexamethasone had an 18% renal response rate at 6 and 12 months; an additional 18% responded by 18 months.[12] In relapsed patients receiving cyclophosphamide, lenalidomide and dexamethasone, 19% had renal responses, while in a phase 1/2 trial in relapsed patients (N=70) treated with bortezomib, 29% had a renal response.[13,14] In the initial therapy setting, patients with renal involvement who received cyclophosphamide, bortezomib and dexamethasone (CyBorD) had a 25% renal response rate.[7] Post-ASCT with bortezomib-based consolidation, while 50% of renal patients respond by the end of the first year, an additional 20% of renal patients respond in the second year post-ASCT.[6] While we do not know the mix of patients who will be screened and enrolled in this trial, it is reasonable to assume that one third will be post-SCT, one third post initial and one third post second-line therapy. Allowing for a 6 month interval after chemotherapy and a 12 month interval after SCT, the weighted average of the renal response rates in these groups is 22.3%. We have chosen a higher estimate (25%) as the confirmed renal response rate in this study in patients receiving placebo.

8.6 Handling of Dropouts and Missing Data

Subjects who discontinue during the study period with ETD visits will be included in intent-to-treat but not the primary endpoint analyses. The number of such subjects will be noted in the summary table of outcomes. Analyses excluding these subjects will also be performed and described. 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 (Tufts) is responsible for maintaining a record of all system users. The participants of the study will not be identified by name on any study documents to be collected by the Sponsor.

All clinical information requested in this protocol will be recorded on the eCRFs provided by the Sponsor (or via other data collection methods, e.g., electronic laboratory data transfer). The Investigator is responsible for reviewing all eCRFs, verifying them for accuracy, and approving them via an electronic signature. 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 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. ICFs and adequate records for the receipt and disposition of all study medications must be retained for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated, or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA and other applicable Regulatory Authorities are notified, unless a longer

period is required by applicable law or regulation. 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 the Investigator for the purpose of inspecting the various records of the study (e.g., eCRFs and other pertinent data), provided that subject confidentiality is respected.

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

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

9.4 Subject Confidentiality

The Investigator must ensure that each subject's anonymity is maintained as described below. On the eCRFs or other documents submitted to the Sponsor or its designee, subjects must be identified by no more than their date of birth or age, sex, and study-specific site and subject numbers. Documents that are not for submission to the Sponsor (e.g., signed ICFs) should be kept in strict confidence by the Investigator in compliance with applicable regulations and ICH GCP Guidelines. The Investigator and institution must permit authorized representatives of the Sponsor, 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.
Study results will not be shared with subjects or the subject's primary care or treating doctor.

10.0 Potential Risks associated with NEOD001

Hypersensitivity and Immunogenicity
NEOD001 is a monoclonal antibody. These antibodies (proteins) attach to the amyloid and may make the body "recognize" the amyloid as foreign bodies in order to get an immune response to remove the amyloid. There is the possibility of a reaction to the NEOD001 as it is being infused (given) through the vein; these are called infusion reactions. Symptoms can include fever, chills, rash, and/or hives, changes in blood pressure (decrease or increase), temperature and heart rate (decrease or increase). If infusion reactions are severe, they can be potentially life-threatening or even fatal. Temperature, breathing rate, heart rate, and blood pressure will be measured at each visit. Participants will be watched closely during the infusion and after the completion of the infusion. If they do have a reaction to the study drug, the study doctor may need to give the

study drug at a slower rate (over a longer period of time), give participants a lower dose, and/or give additional medications to prevent the reaction, or may have to stop participants from taking study drug. Also, if participants have a reaction, the study doctor may give some medications within 30 minutes before the start of the infusions for the rest of the cycles to try to prevent participants from getting infusion reactions.

NEOD001 is currently being tested in other clinical studies to check how effective the study drug is. It was also tested in a Phase 1/2 clinical study that was designed to test different dose levels to find the highest dose that could be given safely. The highest dose of NEOD001 tested was 24 mg/kg which was considered to be safe, and that dose being used in this study.

The most common side effects that were seen with NEOD001 (those that were experienced by at least 1 in 10 people in the Phase 1/2 study) based on information that was collected as of September 2016, were as follows:

The most common side effects seen in ≥ 20% of the NEOD001-001 (Phase 1/2) subjects include:

- Fatigue
- Nausea
- Common cold (upper respiratory tract infection)
- Swelling of the hands or feet (Peripheral Edema)
- Increase in frequency of loose or water stools (Diarrhea)
- Decrease in red blood cell count (Anemia)

The most common side effects seen in ≥ 10% of the NEOD001-001 (Phase 1/2) subjects include:

- Increased creatinine in blood
- Dizziness
- Cough
- Constipation
- Headache
- Vomiting
- Difficulty breathing (Dyspnea)
- Pain in hands and legs (pain in extremity)
- Back pain
- Muscle spasms
- Rash
- Urinary tract infection

Twenty three subjects were enrolled in the Phase 2 study and 129 subjects were enrolled in the Phase 3 study and received 24 mg/kg NEOD001 or placebo; the patients did not know what they were receiving. In the Phase 2 study, one subject experienced vasovagal syncope (fainting) but recovered from it.

Sixty-eight (52.7%) subjects had at least 1 serious side effect in the Phase 3 study. The serious side effects investigators thought were related to study drug in this blinded study, include the following: anemia and acquired factor VIII deficiency (a rare but potentially life-threatening bleeding disorder);both events resolved. Sinus Tachycardia (increased heart rate), [resolved and the subject remained in the study]. Increased Liver Enzymes event (GGT increased, 3 alkaline phosphatase, and AST increased) was resolved and the syncope (fainting), the subject who experienced fainting remains in the study.

There is always a chance that an unexpected side effect, including death, may happen to people who take this study drug or any drug. Participants vital status including organ function and immune function will be monitored by the study doctor/staff at least monthly during the study. Participants should tell the study

doctor or medical team about any side effects they are having. The study doctor may be able to give medications to help treat the side effects and prevent them from becoming worse. The study doctor may also choose to stop NEOD001 for a short time or reduce its dose to allow the participant to recover from any side effects.

Amyloid can deposit in vital organs, such as your heart, kidney, liver, spleen. The amyloid in organs can cause them to not function as well as they should. Though NEOD001 is being investigated for its potential to stop or even reverse your organ dysfunction, it is possible that it could cause worsening of organ function when the drug targets the amyloid already deposited in organs. Participants organ function will be monitored closely with blood and urine tests and physical examinations throughout the study.

Each month before participants receive study drug, the study doctor will review lab results and participants physical condition before giving the study drug. If their organ function has worsened, or the study doctor believes that study drug is making the condition worse, participants may not be able to receive the study drug. If participants are going to receive the study drug, the study doctor will follow them closely for side effects. Many side effects go away shortly after the study drug is stopped, but in some instances the side effects can be serious, long lasting, or permanent. Participants may also experience side effects that were not seen in other subjects in the ongoing studies.

Participants will be asked about all prescription and non-prescription drugs, herbal preparations and nutritional supplements that they are taking or planning to take. Since the effect of the study drug taken with other medications is not known, it is important that they tell the study doctor or nurse about new symptoms they may experience.

Interference with other drugs
Some investigational agents, chemotherapies and contrast agents may interfere with the way the body processes NEOD001. This interference could increase or decrease amount of NEOD001 in the body. It is very important that participants do not use other investigational agents, and should tell the study doctor about all medications, supplements, or herbal medicine that they are taking during the study. Participants should notify the study doctor immediately about any side effects to avoid possible harm.

10.1 Reproductive Risks

The effect of study drug used on a fetus (an unborn child) or a nursing infant is unknown. Therefore, women who are pregnant or nursing are not allowed to be in this study. Nobody knows what these risks are right now. Some drugs cause women to have their babies prematurely (early) or to have babies with birth defects.

Women: If female participants are able to have children, they must use a highly effective method of birth control and a barrier method while taking study treatment, as agreed with the study doctor. Participants must use the birth control method they and the study doctor agree upon from the time they begin Screening through at least 90 days after participant's last dose of study drug to prevent pregnancy.

A "highly effective method of birth control" is defined as a method that has a low failure rate when used consistently and correctly. It includes implants, injectables, birth control pills, some intrauterine devices (IUDs), sexual abstinence (which is defined as refraining from all aspects of sexual activity) or a sterilized partner (tubes tied in women or a vasectomy in men).

Men: Male participants must use a barrier method while on treatment with NEOD001 from the time of

screening through at least 90 days after their last dose of the study drug to prevent pregnancy of their partner.

Some birth control pills may not work when participants are taking certain drugs.

Participants must be aware that they can still become pregnant even if they use a highly effective method of birth control.

Women: If female participants become pregnant while they are on study treatment or within 90 days of their last dose NEOD001 they must notify the study staff. If participants become pregnant on the study, they must immediately stop taking the study treatment. The Sponsor will continue to collect information about their pregnancy and the birth of the baby even after study treatment is stopped.

Men: If a male participant's partner becomes pregnant while they are on study treatment, or within 90 days of their last dose of NEOD001, they must notify the study doctor. The study doctor will discuss this with them further. Male participants should not donate sperm while they are taking the study drug and for 90 days after they stop taking the study drug.

10.2 Risks from Taking Diphenhydramine or Acetaminophen

If participants have a reaction or side effects to the study drug they may be given diphenhydramine, also known as Benadryl, and acetaminophen, also known as Tylenol, to help decrease the chance of having subsequent reactions or side effects before future infusions, or to prevent reactions.

The known risks of taking diphenhydramine include marked drowsiness or excitability. Alcohol, sedatives and tranquilizers may increase drowsiness. Participants should avoid alcoholic drinks and should be careful when driving a motor vehicle or operating machinery.

The known risks of taking acetaminophen include severe liver damage if an adult takes more than 4,000 mg in 24 hours (participants will only be given 650 mg), if it is taken with other drugs that contain acetaminophen, or if they have 3 or more alcoholic drinks every day while using acetaminophen. The study doctor will ask participants to tell him/her about all of the other medications that they are taking.

10.3 Venipuncture Risk (Risk of taking blood)

Drawing blood from participants arm may cause pain, bruising, lightheadedness, and, on rare occasions, infection.

10.4 Intravenous (IV) Risk

An IV (a hollow needle/plastic tube) will be placed in participants arm to give the study drug. When the needle goes into a vein, it may hurt for a short time. Also, there may be minor discomfort of having the needle/plastic tube taped to the arm. In about 1 in 10 cases, a small amount of bleeding under the skin will produce a bruise. The risk of a blood clot forming in the vein is about 1 in 100. The risk of infection or significant blood loss is about 1 in 1,000.

10.5 Biopsy Risk

The risks of kidney biopsy will be reviewed in detail with the participant by the doctor who performs the biopsy and they will be asked to sign a specific consent form for that procedure. For some subjects a historical biopsy confirming the type of amyloid they have may not be available. In those instances, a sample of the participants tissue from a biopsy may need to be sent to a lab for a special test to confirm that they have AL amyloidosis. People who are at high risk of having another possible type of amyloidosis, that is those who are black or African American, over 75 years of age, or those who have a history of familial amyloidosis may need to have this tissue typing performed. Mass spectrometry is the name of a procedure that will help to do this. If this is

the case, the study doctor will need to obtain tissue that has been stored from the biopsy, or if this is not available, the study doctor may request an additional biopsy for amyloid typing which is standard of care.

The risks of providing a biopsy to obtain a tissue sample are:
- Bleeding at the time the samples are removed
- Infection at the time the samples are removed
- Pain at the time the samples are removed

10.6 Risk of Electrocardiogram (ECG) Procedure

Skin irritation is rare but this could occur during an ECG from the electrodes that are used.

10.7 Risk of Echocardiogram Procedure

There are no risks involved in a standard transthoracic echocardiogram. Participants may feel some discomfort similar to pulling off an adhesive bandage when the technician removes the electrodes placed on their chest during the procedure.

Loss of confidentiality is also a possible risk of study participation.

11 BENEFITS

The knowledge gained from this study may help other people with AL amyloidosis in the future. Participants may not personally benefit from this study.

12 ETHICAL AND LEGAL ISSUES

12.1 Ethical Conduct of the Study

The study will conform to ICH GCP Guidelines and all appropriate FDA, Health Canada, and European regulations.

12.2 Regulatory Approval

The study will start once the required regulatory approvals have been obtained in the appropriate jurisdictions and will open in individual centers as approvals are documented.

12.3 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 Investigator is 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

Copies of approval letters and notices from the IRB/IEC to the site investigators must be promptly forwarded to the Sponsor.

12.4 Communication Among Sites

- *When and how sites will be provided with the current version of the protocol, informed consent form, and other study documents.*
    - *Once the Tufts Medical Center IRB has approved the current version of the protocol, consent form(s) and other study documents, the Clinical Trials Specialist will email the approved documents to all the additional sites.*
- *That all required approvals will be obtained at each site (including approval by the site's IRB of record).*
    - *Tufts Medical Center will work with sites to receive IRB approvals from each site prior to activating them to enrollment.*
- *How all modifications will be communicated to sites, and will be reviewed and approved (including approval by the site's IRB of record) before the modification is implemented.*
    - *All communications will be made via email to each site. Tufts Medical Center will have to review and approve all changes to consent form and other documents prior to submitting to the local IRB.*
- *All participating sites will safeguard data as required by local information security policies.*
- *All local site investigators will conduct the study appropriately per protocol and any protocol deviations will be reported to the local IRB per their institutional standards.*
- *All non-compliance with the study protocol or other reportable new information will be reported in accordance with local policy of each site.*
- Describe the method for communicating the following information to participating sites:
    - *Problems*
    - *Interim results*
    - *Study closure*
    - *Amendments*
    - *Research related communications*

  All the above information will be communicated to each site via email in a timely fashion.
- *Tufts Medical Center is the Data Coordinating Center.*
- *Specify if Tufts' data will be shared outside of Tufts (e.g., with other investigators, sponsor, etc.) and how data will be shared.*
    - *All data will be captured in Redcap Cloud and sites will only have access to their specific data. Only Tufts Medical Center will have access to all sites data for data analyses. Interim safety reports will be de-identified and coded when presented at each site.*
- *Describe any collaborations not described above, such as:*
    - Tufts Medical Center is the sponsor of the study .All additional sites are sub-contracted with Tufts and will receive funds from the sponsor.

12.5 Subject Informed Consent

An IRB/IEC-approved copy of the ICF and all amendments from the Sponsor (Tufts Medical Center) will be forwarded to all sites.

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 consent interview will take place in a private room.

Potentially eligible subjects will be identified by one of the investigators at the time of an initial or follow-up clinic visit. In a discussion with a potential subject regarding all treatment, this clinical trial and all non-trial therapeutic options will be presented to a patient, along with potential risks and benefits. Subjects will be offered a copy of the ICF and will be afforded ample time to read it and discuss options with their family, as well as the investigators. Questions will be addressed, the study consent form will be further reviewed and the study procedures further discussed if the patient is interested in participating in the study. The study coordinator may be introduced at this point or at an earlier time and he/she will review the informed consent form to assess that all the appropriate issues have been covered. Once all questions are answered and the patient agrees to participate, the informed consent will be signed by the study subject and investigator. The informed consent process will be then documented in the subject's medical record. A copy of the Informed Consent Form will be placed in the medical record, and a copy will be given to the subject. The original is then placed in the research binder.

The PI or a Co-I will obtain written consent; the study coordinator will assist with this process.

The subject will be given the Informed Consent Form to take home after it is carefully reviewed with the subject by the study Investigator to enable the subject to make an informed decision.

Informed Consent Process will be conducted over the course of days and/or weeks, depending on the nature of the patient's condition and the complexity of the study. The patient and family members will be given detailed information about the study protocol by members of the research team including the Study Investigators and Study Coordinator. The information will be repeated and reinforced. The patient and family members will be encouraged to ask questions throughout this process and will be given many opportunities to discuss every aspect of their care and management. At various times, patients will be queried to assess their level of understanding and information will be provided based on those assessments.

Alternative and standard of care treatments will be discussed with the subject so they are aware of all their options. Consent discussions will take place in a private setting and every effort will be made to ensure confidentiality; however, confidentiality cannot be absolutely guaranteed due to the possibility of unforeseen circumstances.

It is anticipated that non-English speakers will be enrolled in this research study. At Tufts Medical Center, the Short Form is allowed to consent these patients. The short-form consent procedure will be followed according to IRB policy. The PI or Co-Is will employ a translator to assist in conducting the consent interview. Translated short form documents will be provided in the appropriate language.

The additional sites will have to ensure that they are also following their local IRB policy for consenting non-English speaking patients.

12.6 Resources Available

1. Members of the study team, as well as staff nurses, fellows and other clinic staff may be present during study procedures.
2. The PI, the Co-I or the study coordinator will give the subjects information about when they will receive the study drug(s), as well as ensure the study drug is ordered. The PI, the Co-I or the study coordinator/research nurse will give the subjects information about how to take the study drug (s).

   Any procedures that are commonly performed by phlebotomists, technicians, and nurses as part of standard clinical practice will be done by these clinical staff, regardless of whether the tests are being done

solely for research purposes. Assessments such as physical exams will only be done by study investigators. Any questionnaires or other patient materials that may be generated will be given and explained to the subject by study staff.

3. Research procedures will take place within the hospital. Crash carts and other emergency interventions will be immediately available. Tufts Medical Center's emergency department (located within the same building complex as the location where study procedures occur) is verified by the American College of Surgeons and designated by the Massachusetts Department of Public Health as a Level I Adult and Pediatric Trauma Center.

12.7 Subject Compensation for Participating in the Study

Subject and their caregivers will be provided with travel services on a case by case basis by a company called ClinEdge. ClinEdge will also arrange for the reimbursement for reasonable out of pocket costs for mileage (up to $.55 per mile for personal vehicle travel cost. The total amount reimbursed will be equal to the total mileage traveled), meals (up to $37per day for the subject and $37per day for a caregiver), and other incidentals (like parking or taxi fares to and from the hospital) that they spend for each study visit. The study coordinator will provide subjects with an information packet containing the necessary forms, guidelines and instructions for using this travel service. Subject will need to bring all the receipts for any of these expenses in order to reimbursed for them. In order to provide this travel service for subjects, ClinEdge must have access to personal information of travelers, including name and address, however, this personal information will be used by ClinEdge only as needed to make these travel arrangements.

There are no plans to provide financial compensation to subjects for any knowledge or understanding of AL amyloidosis that is gained from testing or analysis of their bodily fluids and tissue samples collected during the study.

12.8 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.

12.9 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 and approve all protocol amendments. The Investigator must send a copy of the approval letter from the IRB/IEC to the 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.

12.10 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.

12.11 Publication Policy

All publication rights are delineated in the Clinical Study Agreement.

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14 APPENDICES

Appendix 1 For Stratification

Hematologic Response and Progression Criteria

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

Abbreviations: dFLC = difference between involved and uninvolved free light chains. *Only applicable for subjects with dFLC > 50 mg/L (5 mg/dL) at study entry.

Stratification for Renal Staging

Test	Value	Score
Proteinuria	≤5 g/24 hours	0
	>5g/24 hours	1
eGFR	≥50 mL/min/1.73 m^2	0
	<50 mL/min/1.73 m^2	1
	Total Score	0 = Renal Stage 1 1 = Renal Stage 2 2 = Renal Stage 3

eGFR = estimated glomerular filtration rate.

Appendix 2 Examples of Highly Effective Contraception Methods

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

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

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

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

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

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

Source: Clinical Trial Facilitation Group, 2014.

Appendix 3 Revised International Myeloma Working Group (IMWG) Diagnostic Criteria for Multiple Myeloma

Definition of Multiple Myeloma

Clonal bone marrow plasma cells > 10% or biopsy-proven bone or extramedullary plasmacytoma* and any one or more of the following myeloma defining events:

Myeloma defining events:

• Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:

• Hypercalcaemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal (ULN) or >2.75 mmol/L (>11 mg/dL)

• Renal insufficiency: creatinine clearance <40 mL per min† or serum creatinine >177 jmol/L (>2 mg/dL) in the absence of amyloidosis

• Anemia: hemoglobin value of >20 g/L below the lower limit of normal, or a hemoglobin value <100 g/L

• Bone lesions: one or more osteolytic lesions on skeletal radiography, computerized tomography (CT), or PET-CT‡

• Any one or more of the following biomarkers of malignancy:

• Clonal bone marrow plasma cell percentage > 60%

• Involved:uninvolved serum free light chain ratio§ > 100

• >1 focal lesions > 5mm in size on magnetic resonance imaging (MRI) studies

PET-CT= ^{18}F-fuorodeoxyglucose positron emission tomography with computed tomography.
*Clonality should be established by showing kappa/lambda light-chain restriction on fow cytometry, immunohistochemistry, or immunofuorescence. Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and core biopsy, the highest value should be used.

†Measured or estimated by validated equations.

‡If bone marrow has less than 10% clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement.

§These values are based on the serum Freelite assay (The Binding Site Group, Birmingham, UK). The involved free light chain must be > 100 mg/L.

Appendix 4 Modified Organ Response and Progression Criteria

Organ	Response	Progression
Heart	NT-proBNP response (>30% and >300 ng/L decrease in subjects with baseline NT-proBNP 2650 ng/L) or NYHA class response (2 class decrease in subjects with baseline NYHA class 3 or 4)	NT-proBNP progression (>30% and >300 ng/L increase)
Renal	>30% decrease in proteinuria or drop of proteinuria below 0.5 g/24 hours in the absence of renal progression	>25% decrease in eGFR

Abbreviations: eGFR = estimated glomerular filtration rate; NT-proBNP = N-terminal pro B-type natriuretic peptide; NYHA = New York Heart Association.

Appendix 5 ECOG Performance Status

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

Appendix 6 NYHA Functional Classification

NYHA Class	Symptom
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.

Appendix 7 SF-36

(SF-36v2® Health Survey Standard, United States (English))

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 mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

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
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

		Yes, limited a lot	Yes, limited a little	No, not limited at all
a	<u>Vigorous activities</u>, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b	<u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c	Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d	Climbing <u>several</u> flights of stairs	☐ 1	☐ 2	☐ 3
e	Climbing <u>one</u> flight of stairs	☐ 1	☐ 2	☐ 3
f	Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g	Walking <u>more than a mile</u>	☐ 1	☐ 2	☐ 3
h	Walking <u>several hundred yards</u>	☐ 1	☐ 2	☐ 3
i	Walking <u>one hundred yards</u>	☐ 1	☐ 2	☐ 3
j	Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

4. During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health</u>?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the <u>amount of time</u> you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b <u>Accomplished less</u> than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Were limited in the <u>kind</u> of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Had <u>difficulty</u> performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of any emotional problems</u> (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
a Cut down on the <u>amount of time</u> you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b <u>Accomplished less</u> than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities <u>less carefully than usual</u>	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?

None	Very mild	Mild	Moderate	Severe	Very severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

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

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

9. These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the <u>past 4 weeks</u>…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the <u>past 4 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> 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
.	.	.	.	.
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
	.	.	.	.	.
a I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

Appendix 8 Renal Scoring

Approach to scoring amyloid and chronic lesions in kidney biopsies

Renal biopsy reports and renal biopsy slides are reviewed from patients with diagnosis of AL amyloid, based on Congo red positive, clonal staining of deposits with, where electron microscopy is available, classic randomly arranged fibrillary deposits.

For scoring of severity, a minimum of 5 glomeruli must be present. Scoring is performed on light microscopic slides. PAS and/or Jones silver stain is preferable for scoring.

Amyloid type, determined by immunofluorescence staining for kappa and lambda (or in some cases also by mass spectrometry) is noted.

Scoring of biopsy adequacy and sclerosis/fibrosis lesions:

The number of glomeruli available by light microscopy is recorded and the distribution of the biopsy, whether including cortex and/or medulla, is noted.

The percent of acute tubular injury is estimated from assessing each high-power field, giving a percentage of overall cortex involved with flattening, blebbing and/or vacuolization of tubules.

The presence of inflammation in scarred or non-scarred areas is noted.

Percent global sclerosis and segmental sclerosis is assessed.

Tubulointerstitial fibrosis is estimated, estimating degree in each high-power cortical field, to the nearest 10% with >0% and < 5% estimated as 5%, and average tubulointerstitital fibrosis calculated from all cortical fields, rounding to nearest 10%.

The sum of the percentage of global glomerulosclerosis and percentage of tubulointerstitial fibrosis generate a Composite Scarring Injury Score (CSIS) for each patient.

Amyloid Scoring

The distribution of amyloid is noted, and the extent of deposition is scored on a scale of 0 to 3+ (zero, absent; 1+, minimal, 2+, moderate, and 3+, severe) for each anatomical compartment, with a single overall score based on overall involvement.

Involvement of glomeruli:

Mesangial area:

0 no glomerular amyloid

1+ up to 25% expansion of mesangial area due to amyloid deposits.

2+ involves 25-50% of the glomerular tuft.

3+ involves >50% of the glomerular tuft.

Capillary wall:

0 no capillary wall amyloid

1+ up to 25% involvement of capillary wall due to amyloid deposits.

2+ involves 25-50% of capillary wall.

3+ involves >50% of capillary wall.

Involvement of interstitium:

0 no amyloid in interstitium

1+ <25% of interstitial area involved with amyloid

2+ 25-50% of interstitial area involved with amyloid

3+ >50% of interstitial area involved with amyloid

Involvement of arterioles/arteries

Vascular lesions are scored based on overall assessment as a single score.

0 no amyloid in vessels

1+ wall thickness increased by amyloid but to a degree less than the diameter of the lumen

2+ wall thickness increased by amyloid to equal or slightly greater than the diameter of the lumen

3+ wall thickness increased by amyloid to far exceed the diameter of the lumen with extreme luminal narrowing or occlusion

The sum of mesangial, capillary, interstitial, vascular amyloid involvement generated an amyloid score (AS) for each patient.

Other

Additional lesions are noted. These may include other lesions related to the monoclonal protein, or other additional disease processes, such as e.g. diabetic nephropathy.

Amyloid Renal Biopsy Scoring **Scorer:** **Date:**

Biopsy Number	
Patient Identifier	
Date of Biopsy	

Number of glomeruli		
% Global sclerosis		
% Segmental sclerosis		
Sample: Cortex	Y	N
Medulla	Y	N
% ATI (to nearest 10%)		
% Tubulointerstitial fibrosis (to nearest 10%, with fibrosis present but <5% scored as 5%)		

Amyloid distribution	**Distribution**		**0-3+**
	Mesangial		
	Capillary Wall		
	Vascular		
	Interstitial		
	Other		

Amyloid Type (specify by IF/IHC/Mass spec)	Kappa	Lambda

Other Lesions:

LCCN	Y	N	Suspicious
LC Proximal tubulopathy	Y	N	Suspicious
Other:	Specify:		

Inflammation:

In scar	Y	N
In nonscar	Y	N

Score based on:

Report	
Slides	
Both	

Appendix 9 Measuring GFR by Lesley Inker, MD

STUDY RATIONALE:

Measured GFR is the gold standard for assessing kidney function[15,16]. However, measuring GFR is costly and complicated both for routine clinical use and research studies. Currently, kidney function is estimated in routine clinical practice and most research settings using estimating equations based on serum creatinine[17]. Although serum creatinine is inexpensive, convenient, it has several limitations as it varies with age, gender and especially muscle mass and diet. Since muscle mass and diet can change with illness and its recovery, estimated GFR from serum creatinine is not very accurate or sensitive at detecting change in populations with acute or chronic illness. Novel filtration markers such as low molecular weight proteins (serum cystatin C, β-trace protein and β-2-microglobulin) and novel metabolites (accuGFR) are emerging[18,19] and since they are not based on muscle mass may provide more accurate estimates especially in patients with illness. However, explicit testing is required since these markers might be influenced by inflammation and disease, as well as the treatment itself.

There is great need to accurately measure GFR for both clinical care and research studies involving new treatments. To date, there is no published data on the concordance of measured GFR and estimated GFR in patients with AL amyloidosis. The aim of this study is to assess the performance of CKD-EPI creatinine, to those using novel filtration markers in comparison to iothalamate clearance measured in AL amyloidosis patients.

<u>GFR measurement protocol</u>

Non-diabetic subjects will be fasting from midnight onward on the night prior to the study visit and will be asked to avoid changes in medications that influence GFR (e.g. anti-inflammatory agents, renin angiotension blocking agents). Participants with diabetes will be asked to eat normal breakfast. All participants will be asked to drink water two to three glasses of non-caffeinated beverages at home and an additional 10 to 15 mL/kg body weight upon arrival at clinical research center).

On the day of the GFR visit, one intravenous line may be inserted. This is used for blood draws and the participant or the study nurse could elect to do repeated venipuncture to obtain the repeated blood samples. A total of 0.5 ml of Iothalamate (Conray® - iothalamate meglumine injection U.S.P 60%; Mallinckrodt Inc., St. Louis, MO) will be mixed with 0.5 ml of sterile water in a syringe given subcutaneously. If an IV line is inserted, normal saline will be administered through the IV line after each blood draw to maintain patency and to assist with urine flow. Before each blood draw, a small sample of blood will be drawn and discarded before sample collection. The participant will be instructed to drink sufficient water to ensure a urine flow rate of approximately 3 mL/min to a maximum value of 10 mL/min to avoid water retention.

Table 3 and the figure below shows the timing of the urine and blood samples to be taken. The subject will be asked to void immediately prior to the iothalamate injection. The urine will be collected and this collection will be referred to as the U0 specimen. The subject will be asked to void again at approximately 1 hour after iothalamate injection. This collected urine will be referred to as Urinary Equilibrium specimen (UE). The first blood sample (P1) should be collected within 5 minutes after the void. The urinary clearance periods will begin following the P1 blood collection will consist of two timed urinary clearance periods of approximately 45 minutes (See Table 3 and Figure). For the first urine collection period, all urine voided between 60 and 105 minutes will be collected. At approximately 105 minutes, the subject will be asked to empty their bladder again. All of the urine collected between the UE and this time will be referred as the U1 sample. A second blood sample (P2) will be taken within 5 minutes after void and the second urine collection period will then begin. For the second urine collection period, all urine voided between the P2 sample (approximately 105-110 minutes) and 150 minutes will be collected. At approximately 150 minutes, the subject will be asked to empty

their bladder again. All of the urine collected between the P2 and this time will be referred as the U2 sample. Collect blood sample (P3) within 5 minutes of the void. The urine for each period (U1 and U2) will be kept in a separate container. However, all voids within a urine period can be placed in the same container (see Figure). All blood samples should be collected from the opposite arm from that which was used for the injection of iothalamate. The volume of the urine collection will be determined to the nearest mL.

Table 3 Urine and Blood Samples for mGFR

Minutes	**-5**	**0**	**60**	**105**	**150**	**TOTAL (mL)**
Sub-Q Injection		**Iothal**				
Urine samples (10mL)	**U0[1,2]**		**UE[1,2]**	**U1[1,2]**	**U2[1,2]**	**40**
Plasma samples- (4mL).			**P1[3,4]**	**P2[3,4]**	**P3[3,4]**	**12**
Serum sample -SST tiger top tube (10 mL)[5]	**2X**					**20**
Snack			**X**			
Water	**Encourage water intake**					

Iothal=iothalamate

[1] U1 will be collected between 60 and approximately 105 minutes. U2 will be collected between 105 and approximately 150 minutes. Urine samples will be sent to Mayo Clinic, Rochester.

[2] Prior to aliquot, the volume of the collection will be determined

[3] Plasma blood samples will be collected within 5 minutes of void.

[3] Plasma samples to be sent to Mayo Clinic, Rochester.

[5] Serum samples for assay of creatinine, urea and cystatin and optional stored samples, to be sent to University of Minnesota.

Figure: Schematic of timing of blood and urine collections

U0 ***-5 minutes***	**Baseline** ***Time 0***	**Equilibrium (UE)** ***60 min***	**Plasma 1 (P1)**	**Urine period 1 (U1)** ***~45 min***	**Plasma 2 (P2)**	**Urine period 2 *(U2)*** ***~45 min***	**Plasma 3 (P3)**
• Patient to void and collected in U0 container • Record exact time	• Serum Blood Collection. Two 10ml tubes. • Iothalomate to be injected SC	• All urine to be collected in UE container • Record exact time	Collect 0-5 minutes after UE	• All urine to be collected in U1 container • Record exact time	Collect 0-5 minutes after U1	• All urine to be collected in U2 container • Record exact time	Collect 0-5 minutes after U2
Subjects be fed a meal and are free to move around during the GFR test. The subject will be instructed to drink sufficient water to ensure a urine flow rate of approximately 3 mL/min to a maximum value of 10 mL/min.							
Darker shading refers to the two urine collection periods with plasma samples before and after All urine collections to have accurate volume determinations							

Participants will be fed a meal and are free to move around during the GFR test. The study nurse will assess study subjects following administration of the iothalamate for any adverse events (AE). After the final blood sample, the IV line will be removed if inserted; participants will be observed for approximately 15-30 minutes before they return home.

Laboratory analyses

All laboratory tests for samples obtained on the day of GFR measurement will be performed at Mayo Clinic

Rochester or University of Minnesota. Quantification of iothalamate in urine and plasma will be performed using a tandem mass spectrometric method, in the GFR laboratory of Dr John Lieske[20,21]. Serum filtration markers will be measured at University of Minnesota. Serum creatinine will be measured using the Roche enzymatic method (Roche-Hitachi P-Module instrument with Roche Creatininase Plus assay, Hoffman-La Roche, Ltd., Basel, Switzerland), traceable to the National Institute of Standards and Technology (NIST) creatinine standard reference material 967 (CV 1.71%)[22]. Serum cystatin C will be assayed using the Gentian reagents on the Roche Cobas instrument, which has been shown to be traceable to the International Federation of Clinical Chemistry (IFCC) Working Group for the Standardization of Serum Cystatin C and the Institute for Reference Materials and Measurements (IRMM) certified reference materials[23-25.] BTP will be measured on the Siemens Dade Behring Nephelometer (CV 5.36%). B2M will be measured on the Roche Modular P (CV 3.2%). Optional blood samples will be aliquoted and stored for future tests including AccuGFR.

INCLUSION AND EXCLUSION CRITERIA for GFR study

Inclusion Criteria
1. Consenting participants in RAIN

Exclusion Criteria
The subject must not meet any of the following:
1. Excluded from RAIN
2. Persons with known allergic reaction to iohexol, iodine, iothalamate or shellfish
3. Inability to cease taking medications that affect creatinine levels (e.g. trimethoprim or trimethoprimsulfamethoxazole and cimetidine) for two days prior to the study visit
4. Inability to maintain a stable regimen of anti-inflammatory agents and angiotensin converting enzyme inhibitors for one week prior to study visit
5. Current treatment with amiodarone or metformin. Metformin can be stopped the day prior.
6. Acute exacerbation of asthma or chronic obstructive lung disease in the past three months requiring hospitalization or oral steroid therapy
7. Hypercalcemia, defined as a calcium of > 11 g/dL
8. Weight loss >10% over 2 months prior to Day 1 of this study
9. Had a major surgical procedure within 4 weeks prior to mGFR testing
10. **Recent documented acute kidney injury without documentation of recovery to stable baseline**

STUDY DURATION: 1 day

STATISTICAL AND ANALYSIS PLAN

Calculation of clearance Urinary clearances for each period will be calculated using the equation:

Urinary Clearance = $U_{i1}V_1/\exp[(\ln P_{i0} + \ln P_{i1})/2]$
where U and P are defined as urine and plasma concentrations of iothalamate, respectively, V is the urine flow rate, and subscripts 0 and 1 denote the samples obtained at the beginning and end of collection period i. Values will be normalized to body surface area.

Performance metrics Bias will be assessed as the median difference between mGFR and eGFR, and precision as the interquartile range for the differences[26]. Accuracy will be assessed as root mean squared error and as the percentage of estimates that are greater than 30% from mGFR (1- P_{30}). Confidence intervals will be calculated by bootstrap methods (2,000 bootstraps)[27]. The significance of the differences among equations will be determined using McNemar test for 1 -P_{30} and comparing the eGFR estimates for their ability to predict mGFR thresholds of 60, 45, and 30 mL/min/1.73 m^2.

POTENTIAL RISKS AND DISCOMFORTS
Adverse reactions associated with iothalamate include:

Very Common (10% or higher)
- Hot flashes
- Pain
- Feeling of body warmth

Common (1-10%):
- Nausea and vomiting
- Hives
- Inflammation of your nose

Uncommon (0.1-1%)
- Facial flush
- Rash
- Cough

Rare (0.01-0.1%)
- Diarrhea
- Dry mouth
- Injection side reaction
- A reaction that resembles anaphylaxis, e.g., by hives, laryngeal edema, or shock, but does not involve IgE antibodies or allergens and therefore it has no allergic basis

Very Rare (less than 0.01%)
- Renal failure- kidneys stop working normally

Serious events may include severe cardiovascular responses include rare cases of hypotensive shock (not enough blood and oxygen flow to the body's major organs, including the brain, which can cause dizziness, blurry vision, confusion, weakness, fatigue, and nausea), coronary insufficiency (insufficient blood flow through one or more coronary arteries), cardiac arrhythmia or fibrillation (irregular heartbeat), and cardiac arrest (heart attack).

Intravenous (IV) Risk
An IV (a hollow needle/plastic tube) will be placed in participants arm to give the study drug. When the needle goes into a vein, it may hurt for a short time. Also, there may be minor discomfort of having the needle/plastic tube taped to the arm. In about 1 in 10 cases, a small amount of bleeding under the skin will produce a bruise. The risk of a blood clot forming in the vein is about 1 in 100. The risk of infection or significant blood loss is about 1 in 1,000.

Risk of Loss of Confidentiality
When participating in research studies, like this one, there is always a risk that records, samples, or personal / medical information will not be kept completely private. The research team is aware that any loss of confidentiality could have a negative impact on the participant. Each member of the study team will try to maintain the highest level of confidentiality possible in recording, storing, and transmitting information about the participants.

BENEFITS
Participants may not personally benefit from this sub-study but this testing may help patients in the future.

Table 4 Schedule of Procedures for mGFR

Study Procedures	Screening[a] to be done as part of RAIN screening	Day 1 GFR measured
Informed Consent	X	
Inclusion/Exclusion Criteria	X	
Medical History	X	
Physical Examination	X	
Concomitant Medications	X	
Review Study restrictions/prohibited medications/assess for AKI	X	X
Vital Signs, Height, and Weight		X
ECOG Performance Status	X	
Creatinine to estimate the GFR	X	X
Other filtration marker and stored serum		X
Urine Pregnancy Test[b]		X
Urinalysis	X	
Measured GFR uring urinary clearance of iothalamate		X

[b]Females of child-bearing potential only.

Appendix 10 Renal Gene Expression Profiling

The following abstract describes the systems biology approach of the NEPTUNE project. The RAIN study is NOT using all of the research elements that are used in the NEPTUNE project.

Gadegbeku CA1, Gipson DS, Holzman LB, Ojo AO, Song PX, Barisoni L, Sampson MG, Kopp JB, Lemley KV, Nelson PJ, Lienczewski CC, Adler SG, Appel GB, Cattran DC, Choi MJ, Contreras G, Dell KM, Fervenza FC, Gibson KL, Greenbaum LA, Hernandez JD, Hewitt SM, Hingorani SR, Hladunewich M, Hogan MC, Hogan SL, Kaskel FJ, Lieske JC, Meyers KE, Nachman PH, Nast CC, Neu AM, Reich HN, Sedor JR, Sethna CB, Trachtman H, Tuttle KR, Zhdanova O, Zilleruelo GE, Kretzler M.

Design of the Nephrotic Syndrome Study Network (NEPTUNE) to evaluate primary glomerular nephropathy by a multidisciplinary approach.

Kidney Int. 2013 Apr;83(4):749-56. doi: 10.1038/ki.2012.428. Epub 2013 Jan 16.

Abstract

The Nephrotic Syndrome Study Network (NEPTUNE) is a North American multicenter collaborative consortium established to develop a translational research infrastructure for nephrotic syndrome. This includes a longitudinal observational cohort study, a pilot and ancillary study program, a training program, and a patient contact registry. NEPTUNE will enroll 450 adults and children with minimal change disease, focal segmental glomerulosclerosis, and membranous nephropathy for detailed clinical, histopathological, and molecular phenotyping at the time of clinically indicated renal biopsy. Initial visits will include an extensive clinical history, physical examination, collection of urine, blood and renal tissue samples, and assessments of quality of life and patient-reported outcomes. Follow-up history, physical measures, urine and blood samples, and questionnaires will be obtained every 4 months in the first year and biannually, thereafter. Molecular profiles and gene expression data will be linked to phenotypic, genetic, and digitalized histological data for comprehensive analyses using systems biology approaches. Analytical strategies were designed to transform descriptive information to mechanistic disease classification for nephrotic syndrome and to identify clinical, histological, and genomic disease predictors. Thus, understanding the complexity of the disease pathogenesis will guide further investigation for targeted therapeutic strategies.

<u>RAIN study: renal biopsy specimens</u>

Patients on RAIN will be given the opportunity to consent to having a portion of their renal biopsy tissue used for gene expression analysis. Gene expression analysis involves extracting RNA from the cryopreserved tissue, making complementary DNA from RNA, and analyzing the level of expression by use of The GeneChip™ Human Genome U133 Plus 2.0 Assay (Affymetrix, Santa Clara, CA, soon to be a Thermofisher company). The data that is generated will be analyzed by the computational biologists of the NEPTUNE project in collaboration with biostatisticians from the collaborators (Tufts and ARC; personnel to be identified).
The renal biopsy samples (a minimum of $1mm^3$) obtained for transcriptional profiling from consenting patients on RAIN will be placed in cryovials with RNA Later and stored at -80^o C in the RAIN centers. The procedures used are identical to the NEPTUNE standard operating procedures which Dr. Kretzler has shared with the medical monitor (Dr. Comenzo) and the sponsor (Tufts).

<u>ARC, RAIN and NEPTUNE</u>

The ARC is seeking grant support for the ancillary studies of RAIN, including the transcriptional profiling of renal biopsy specimens. The investigators at the University of Michigan, led by Dr Kretzler, will receive the specimens for transcriptional profiling from the RAIN centers when funding is secured. Philanthropic support will also be provided for the studies by the ARC; in the event that funding for the transcriptional profiling is not

forthcoming, renal biopsy specimens will be sent to and stored at Tufts in LN_2 storage in Dr. Comenzo' s laboratory.

Appendix 11 Open Label Extension Study

The purpose of the study is to evaluate the long-term safety and effects of NEOD001 in subjects with AL amyloidosis who were previously enrolled and treated for at least 12 months in the main study. In the absence of unacceptable treatment-related toxicity or withdrawal of consent, subjects may receive NEOD001 at the discretion of the Investigator for up to 12 infusions.

Estimated Study and Treatment Duration

A subject may receive up to 12 infusions of NEOD001 at the discretion of the Investigator. A subject's study duration may be up to 13 months, consisting of a Screening and Treatment Phase (12 months), and the End of Treatment (EOT) Visit 30 (±5) days after the last dose.

Definition of End of Study

The study will end when the last subject completes 12 months of study treatment and the EOT Visit.

Table 5: OLE Table of Assessments

		Treatment		EOS Visit
		Screening/ Month 1 Day 1	**Months 2 through 12 Day 1 (±5 days)**	
	Informed Consent			
	Eligibility Review			
	Prior/Concomitant Medications	X	X	X
	Adverse Event Assessment		X	X
	Physical Exam	X	X	X
	Vital Signs	X	X	X
	ECOG PS/ NYHA Class	X	X	X
Laboratory	Hematology & Chemistry (including serum creatinine, eGFR and amylase)[1]	X	X	X[1]
	Coagulation	X	X	X
	Troponin T or I	X		X
	NT-proBNP	X	X (Months 3, 6, 9, 12)	X
	BNP	X	X (Months 3, 6, 9, 12)	X
	Pregnancy (WOCBP)	X	X	X
	Serum Free Light Chains	X	X (Months 3, 6, 9, 12)	X
	Serum & Urine PEP[2]	X	X (Months 3, 6, 9, 12)	X

Serum & Urine IFE	X	X (Months 3, 6, 9, 12)	X
Urinalysis -Dipstick	X	X (Months 3, 6, 9, 12)	X
24-hr Urine Protein Collection for total volume, total protein, creatinine clearance, protein/creatinine ratio, and albumin)[2]	X	X (Months 6)[2]	X[2]
NEOD001 infusion	X	X	
RNB: SF-36	X	X (Months 3, 6, 9, 12)	X

[1] Serum creatinine to be sent to central lab (Covance) at EOS visit for subjects who have maintained an hematologic response from baseline.
[2] 24 hour urine, including UPEP, to be sent to central lab (Covance) at month 6 and at EOS visit.

OLE Checklist for Eligibility
Inclusion:

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

1. 18 years of age or older

2. Completed entire active study period (12 months) on RAIN with no unacceptable treatment-related toxicity.

3. CKD 1, 2 or 3

4. ECOG Performance Status ≤ 2

5. Clinical laboratory values:
   - Absolute neutrophil count > 1000/μL
   - Platelet count > 75,000/μL
   - Total bilirubin ≤ 1.5X ULN
   - Alkaline phosphatase ≤ 5X ULN
   - ALT or AST ≤3X ULN

6. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.

Exclusion:

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

1. Female patients who are lactating, breastfeeding, or pregnant. Men and women of childbearing potential need to use birth control while participating in the study.

2. Patients who did NOT complete the entire active study period of RAIN

3. Patients who are CKD 4 or 5 or on dialysis (eGFR < 30)

4. Medically documented cardiac syncope, uncompensated congestive heart failure, myocardial infarction within the previous 6 months, unstable angina pectoris, clinically significant repetitive atrial or ventricular arrhythmias despite antiarrhythmic treatment, or severe orthostatic hypotension or clinically significant uncompensated autonomic insufficiency.

5. Comorbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens.

6. Ongoing or active infection, known HIV positive, known to be hepatitis B surface antigen-positive or has known or suspected active hepatitis C infection.

7. Psychiatric illness/social situations that would limit compliance with study requirements

STUDY PROCEDURES

EVALUATIONS BY VISIT
Screening Period:

- Informed Consent: Participants will read, confirm understanding, and sign this informed consent before they can participate in this study.
- Medical History: The study doctor and/or nurse will ask participants questions about their past and current health, prior surgeries, prior treatment for their amyloidosis, prior laboratory results and other prescription and over-the-counter drug use.
- Vital signs: Measurements of blood pressure, heart rate, temperature and breathing rate.
    - Measurements done in different positions, i.e., sitting and standing.
- Physical Examination and Weight: The study doctor will perform a physical examination including evaluation of the heart and participants ability to perform everyday tasks.
- ECOG Performance Status Scale (ECOG PS): An evaluation of the level of activity.
- New York Heart Association (NYHA) Functional Classification: study doctor will evaluate the heart and participants ability to perform everyday tasks
- Blood Sample Collection: Blood will be taken from a vein in the arm using a needle.
    - The blood (approximately 30 mL or 2 tablespoons) will be used to check participants general health, to check the level of certain markers that might be able to tell the status of the amyloidosis, organ function, as well as to test for levels of NEOD001 and antibodies to NEOD001. Also a pregnancy test will be conducted if participants are females who are able to get pregnant, to make sure that they are not pregnant.
- Urine Sample Collection: a urine sample will be used to test the general health and health of participants kidneys.
- 24-hour Urine Sample Collection: Participants will be given a container to collect the urine samples for 24 hours. This will measure if they have any abnormal protein present in the urine and how well their kidneys are working.

Treatment Period: Month X-Day 1 (±5 Days)
Month X-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 (or their standard dose from the initial RAIN study should they have had a dose reduction) as an IV infusion every 28 (±5) days, i.e., on Month X-Day 1.

All laboratory tests to be done centrally. 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.

Month 1-Day 1 Onward (± 5 days):

- Vital signs will be assessed before, during and three times after the study drug infusion
- Physical Examination and Weight
- ECOG Performance Status Scale (ECOG PS)
- New York Heart Association (NYHA)
- Routine blood tests to check general health (about 2 teaspoons) - can be done up to three days before study infusion.
- A blood sample for a pregnancy test will be collected if female participant who is able to get pregnant, to make sure that they are not pregnant starting with Month 2.
- Urine Sample Collection: a urine sample will be used to test general health and health of participants kidneys.
- 24-hour Urine Sample Collection: Participants will be given a container to collect the urine samples for 24 hours. This will measure if they have any abnormal protein present in the urine and how well their kidneys are working.

NEOD001 Administration:

Month 1-Day 1:

- Administer NEOD001 IV dosed as described above using the infusion duration established over 120 (±10) minutes and pre-medications if indicated by the patient's history
- Assess vital signs and body temperature, halfway through the infusion (i.e., approximately 60 minutes after the start of the infusion)

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 the main study or over 60 (±10) minutes.

After Infusion:

- Monitor subjects for 90 (±10) minutes following completion of the study drug infusion. The Investigator may increase this standard monitoring time if deemed appropriate or per local standards. In the event of any clinical concerns or suspicious signs or symptoms after the infusion, the subject will remain under observation for as long as the Investigator deems it appropriate.

End of Treatment/Early Treatment Discontinuation (EOT/ETD): 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:

- Physical examination, including weight
- ECOG PS
- NYHA class
- Vital signs
- Blood samples – (approximately 28 mL, less than 2 tablespoons) will be collected for lab tests
- Urine Sample

- 24-hour Urine Sample Collection – Participants will be asked to bring in their 24-hour urine sample to the clinic, if applicable
- The study doctor or nurse will ask questions to determine if they are having any side effects and changes in their medications will be reviewed

Potential Risks associated with NEOD001

Hypersensitivity and Immunogenicity

NEOD001 is a monoclonal antibody. These antibodies (proteins) attach to the amyloid and may make the body "recognize" the amyloid as foreign bodies in order to get an immune response to remove the amyloid. There is the possibility of a reaction to the NEOD001 as it is being infused (given) through the vein; these are called infusion reactions. Symptoms can include fever, chills, rash, and/or hives, changes in blood pressure (decrease or increase), temperature and heart rate (decrease or increase). If infusion reactions are severe, they can be potentially life-threatening or even fatal. Temperature, breathing rate, heart rate, and blood pressure will be measured at each visit. Participants will be watched closely during the infusion and after the completion of the infusion. If they do have a reaction to the study drug, the study doctor may need to give the study drug at a slower rate (over a longer period of time), give participants a lower dose, and/or give additional medications to prevent the reaction, or may have to stop participants from taking study drug. Also, if participants have a reaction, the study doctor may give some medications within 30 minutes before the start of the infusions for the rest of the cycles to try to prevent participants from getting infusion reactions.

NEOD001 is currently being tested in other clinical studies to check how effective the study drug is. It was also tested in a Phase 1/2 clinical study that was designed to test different dose levels to find the highest dose that could be given safely. The highest dose of NEOD001 tested was 24 mg/kg which was considered to be safe, and that dose being used in this study.

The most common side effects that were seen with NEOD001 (those that were experienced by at least 1 in 10 people in the Phase 1/2 study) based on information that was collected as of September 2016, were as follows:

The most common side effects seen in ≥ 20% of the NEOD001-001 (Phase 1/2) subjects include:

- Fatigue
- Nausea
- Common cold (upper respiratory tract infection)
- Swelling of the hands or feet (Peripheral Edema)
- Increase in frequency of loose or water stools (Diarrhea)
- Decrease in red blood cell count (Anemia)

The most common side effects seen in ≥ 10% of the NEOD001-001 (Phase 1/2) subjects include:

- Increased creatinine in blood
- Dizziness
- Cough
- Constipation
- Headache
- Vomiting
- Difficulty breathing (Dyspnea)
- Pain in hands and legs (pain in extremity)
- Back pain

- Muscle spasms
- Rash
- Urinary tract infection

Twenty three subjects were enrolled in the Phase 2 study and 129 subjects were enrolled in the Phase 3 study and received 24 mg/kg NEOD001 or placebo; the patients did not know what they were receiving. In the Phase 2 study, one subject experienced vasovagal syncope (fainting) but recovered from it.

Sixty-eight (52.7%) subjects had at least 1 serious side effect in the Phase 3 study. The serious side effects investigators thought were related to study drug in this blinded study, include the following: anemia and acquired factor VIII deficiency (a rare but potentially life-threatening bleeding disorder);both events resolved. Sinus Tachycardia (increased heart rate), [resolved and the subject remained in the study]. Increased Liver Enzymes event (GGT increased, 3 alkaline phosphatase, and AST increased) was resolved and the syncope (fainting), the subject who experienced fainting remains in the study.

There is always a chance that an unexpected side effect, including death, may happen to people who take this study drug or any drug. Participants vital status including organ function and immune function will be monitored by the study doctor/staff at least monthly during the study. Participants should tell the study doctor or medical team about any side effects they are having. The study doctor may be able to give medications to help treat the side effects and prevent them from becoming worse. The study doctor may also choose to stop NEOD001 for a short time or reduce its dose to allow the participant to recover from any side effects.

Amyloid can deposit in vital organs, such as your heart, kidney, liver, spleen. The amyloid in organs can cause them to not function as well as they should. Though NEOD001 is being investigated for its potential to stop or even reverse your organ dysfunction, it is possible that it could cause worsening of organ function when the drug targets the amyloid already deposited in organs. Participants organ function will be monitored closely with blood and urine tests and physical examinations throughout the study.

Each month before participants receive study drug, the study doctor will review lab results and participants physical condition before giving the study drug. If their organ function has worsened, or the study doctor believes that study drug is making the condition worse, participants may not be able to receive the study drug. If participants are going to receive the study drug, the study doctor will follow them closely for side effects. Many side effects go away shortly after the study drug is stopped, but in some instances the side effects can be serious, long lasting, or permanent. Participants may also experience side effects that were not seen in other subjects in the ongoing studies.

Participants will be asked about all prescription and non-prescription drugs, herbal preparations and nutritional supplements that they are taking or planning to take. Since the effect of the study drug taken with other medications is not known, it is important that they tell the study doctor or nurse about new symptoms they may experience.

Interference with other drugs
Some investigational agents, chemotherapies and contrast agents may interfere with the way the body processes NEOD001. This interference could increase or decrease amount of NEOD001 in the body. It is very important that participants do not use other investigational agents, and should tell the study doctor about all medications, supplements, or herbal medicine that they are taking during the study. Participants should notify the study doctor immediately about any side effects to avoid possible harm.

Reproductive Risks
The effect of study drug used on a fetus (an unborn child) or a nursing infant is unknown. Therefore, women who are pregnant or nursing are not allowed to be in this study. Nobody knows what these risks are right now. Some drugs cause women to have their babies prematurely (early) or to have babies with birth defects.

Women: If female participants are able to have children, they must use a highly effective method of birth control and a barrier method while taking study treatment, as agreed with the study doctor. Participants must use the birth control method they and the study doctor agree upon from the time they begin Screening through at least 90 days after participant's last dose of study drug to prevent pregnancy.

A "highly effective method of birth control" is defined as a method that has a low failure rate when used consistently and correctly. It includes implants, injectables, birth control pills, some intrauterine devices (IUDs), sexual abstinence (which is defined as refraining from all aspects of sexual activity) or a sterilized partner (tubes tied in women or a vasectomy in men).

Men: Male participants must use a barrier method while on treatment with NEOD001 from the time of screening through at least 90 days after their last dose of the study drug to prevent pregnancy of their partner.

Some birth control pills may not work when participants are taking certain drugs.

Participants must be aware that they can still become pregnant even if they use a highly effective method of birth control.

Women: If female participants become pregnant while they are on study treatment or within 90 days of their last dose NEOD001 they must notify the study staff. If participants become pregnant on the study, they must immediately stop taking the study treatment. The Sponsor will continue to collect information about their pregnancy and the birth of the baby even after study treatment is stopped.

Men: If a male participant's partner becomes pregnant while they are on study treatment, or within 90 days of their last dose of NEOD001, they must notify the study doctor. The study doctor will discuss this with them further. Male participants should not donate sperm while they are taking the study drug and for 90 days after they stop taking the study drug.

Risks from Taking Diphenhydramine or Acetaminophen
If participants have a reaction or side effects to the study drug they may be given diphenhydramine, also known as Benadryl, and acetaminophen, also known as Tylenol, to help decrease the chance of having subsequent reactions or side effects before future infusions, or to prevent reactions.

The known risks of taking diphenhydramine include marked drowsiness or excitability. Alcohol, sedatives and tranquilizers may increase drowsiness. Participants should avoid alcoholic drinks and should be careful when driving a motor vehicle or operating machinery.

The known risks of taking acetaminophen include severe liver damage if an adult takes more than 4,000 mg in 24 hours (participants will only be given 650 mg), if it is taken with other drugs that contain acetaminophen, or if they have 3 or more alcoholic drinks every day while using acetaminophen. The study doctor will ask participants to tell him/her about all of the other medications that they are taking.

Venipuncture Risk (Risk of taking blood)
Drawing blood from participants arm may cause pain, bruising, lightheadedness, and, on rare occasions, infection.

Intravenous (IV) Risk
An IV (a hollow needle/plastic tube) will be placed in participants arm to give the study drug. When the needle goes into a vein, it may hurt for a short time. Also, there may be minor discomfort of having the needle/plastic tube taped to the arm. In about 1 in 10 cases, a small amount of bleeding under the skin will produce a bruise. The risk of a blood clot forming in the vein is about 1 in 100. The risk of infection or significant blood loss is about 1 in 1,000.

Biopsy Risk
The risks of kidney biopsy will be reviewed in detail with the participant by the doctor who performs the biopsy and they will be asked to sign a specific consent form for that procedure. For some subjects a historical biopsy confirming the type of amyloid they have may not be available. In those instances, a sample of the participants tissue from a biopsy may need to be sent to a lab for a special test to confirm that they have AL amyloidosis. People who are at high risk of having another possible type of amyloidosis, that is those who are black or African American, over 75 years of age, or those who have a history of familial amyloidosis may need to have this tissue typing performed. Mass spectrometry is the name of a procedure that will help to do this. If this is the case, the study doctor will need to obtain tissue that has been stored from the biopsy, or if this is not available, the study doctor may request an additional biopsy for amyloid typing which is standard of care.

The risks of providing a biopsy to obtain a tissue sample are:
- Bleeding at the time the samples are removed
- Infection at the time the samples are removed
- Pain at the time the samples are removed

Electrocardiogram (ECG) Procedure

Skin irritation is rare but this could occur during an ECG from the electrodes that are used.

Echocardiogram Procedure

There are no risks involved in a standard transthoracic echocardiogram. Participants may feel some discomfort similar to pulling off an adhesive bandage when the technician removes the electrodes placed on their chest during the procedure.

Loss of confidentiality is also a possible risk of study participation.

BENEFITS
The knowledge gained from this study may help other people with AL amyloidosis in the future. Participants may not personally benefit from this study.