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Statistical Analysis Plan for Protocol NEOD001-OLE001

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

Investigational Product:	NEOD001
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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation	Term
IQR	interquartile range
IV	intravenous
kg	kilogram
L	liter
lb	pounds
m	meter
m^2	meters squared
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mg/dL	milligrams per deciliter
min	minimum
mL	milliliters
mmHg	millimeters of mercury
msec	milliseconds
NCS	not clinically significant
ng	nanogram
ng/L	nanograms per liter
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
PE	physical examination
PEP	protein electrophoresis
PK	pharmacokinetic
pg/mL	picogram per milliliter
PN	peripheral neuropathy
PS	performance status
PT	preferred term
PT/INR	prothrombin time/international normalized ratio
PTT	partial thromboplastin time
QT	measure of time between start of Q wave and end of T wave
QTcB	QT formula corrected by Bazett's formula

Abbreviation	Term
QTcF	QT interval corrected by Fridericia's formula
RR	respiratory rate or time between 2 consecutive R waves
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SF-36v2	Short Form-36 version 2 Health Survey
sFLC	serum free light chains
SI	Système International unit
SOC	system organ class
TEAE	treatment-emergent adverse event
temp	temperature
ULN	upper limit of normal
vs	versus
WHO	World Health Organization
WOCBP	women of childbearing potential

1. INTRODUCTION

This document outlines the statistical methods to be implemented during the analyses of Study NEOD001-OLE001 (Open-label Extension [OLE] Study to Evaluate the Long-term Safety and Tolerability of NEOD001 in Subjects with Light Chain [AL] Amyloidosis). The purpose of this plan is to provide specific guidelines from which the analyses will proceed. Any deviations from this statistical analysis plan (SAP) will be documented in the clinical study report (CSR).

2. INFORMATION FROM THE STUDY PROTOCOL

2.1. Study Objective

2.1.1. Primary Objective

The primary objective of this study is to evaluate the long-term safety and tolerability of NEOD001.

2.1.2. Secondary Objectives

The secondary objectives of this study are:

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

2.1.3. Exploratory Objectives

The exploratory objectives of this study are:

- To evaluate overall survival
- To evaluate general health-related quality of life using the Short Form-36 version 2 (SF-36v2) health survey
- To evaluate change in 6-minute walk test (6MWT)
- To evaluate cardiac, renal, peripheral neuropathy, and hepatic response
- To evaluate time to organ response and progression

2.2. Study Design

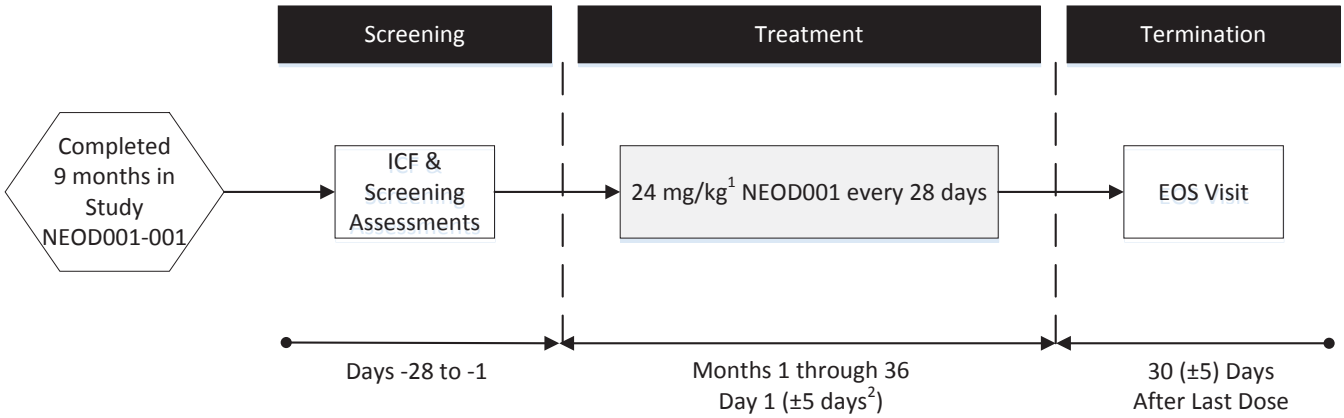
2.2.1. Overall Study Design

This is a multicenter, Phase 2, open-label extension (OLE) study. The purpose of the study is to evaluate the long-term safety and tolerability of NEOD001 in up to approximately 70 subjects with AL amyloidosis who were previously enrolled and treated for at least 9 months in Study NEOD001-001.

A subject's participation in this extension study may be up to 38 months or until the study is terminated, whichever occurs first. The extension study consists of a Screening Phase (1 month), Treatment Phase (36 months), and an End of Study (EOS) Visit 30 (±5) days after the last dose. NEOD001 will be administered once every 28 (±5) days using the infusion duration that subject has been established in Study NEOD001-001 or over 60 (±10) minutes. Vital status telephone calls are to occur approximately 3 months after the subject's last study visit and approximately every 3 months thereafter for up to 5 years, death, or until the subject withdraws consent, whichever occurs first.

Study visits will include collection of adverse events (AEs), vital signs, 12-lead electrocardiograms (ECGs), routine laboratory assessments, immunogenicity testing, 6-minute walk (6MWT) distance, and the SF-36 health-related quality of life survey results.

Figure 1 NEOD001-OLE001 Study Design



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

2.2.2. Study Drug

Study drug consists of NEOD001. The NEOD001 dose is 24 mg/kg (not to exceed 2500 mg) and will be administered once every 28 (±5) days using the infusion duration established in Study NEOD001-001 or over 60 (±10) minutes. The length of the infusion may be extended over a longer period of time when it is clinically indicated. Each vial of 500 mg of NEOD001 will be reconstituted with 9.6 mL sterile water for injection to a concentration of 50 mg/mL, resulting in a buffered, isotonic, preservative-free solution with a total extractable volume of 10 mL. Study drug will be prepared in a 250 mL intravenous (IV) bag of 0.9% saline. The equivalent volume of reconstituted NEOD001 will be withdrawn from the IV bag prior to transferring the drug solution into the IV bag, such that the total IV bag volume will be 250 mL.

Please refer to the protocol for complete product details.

2.2.3. Study Procedures

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

Table 1: Schedule of Study Procedures

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

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

1. Rescreening is allowed once per subject. Only repeat tests that did not meet eligibility requirements.

2. Day 1 assessments may be conducted ±5 days from Day 1, with the exception of Month 1-Day 1 (i.e., no window is allowed at Month 1).
3. Conduct the EOS Visit 30 (±5) days after last administration of study drug. Two additional evaluations are to be conducted beyond this time point, see Footnotes 18 and 23.
4. Obtain medical history since subject's last visit in Study NEOD001-001 (including all major hospitalizations and surgeries), as well as the subject's current medical status and prior therapies for AL amyloidosis. Adverse events that resolved prior to the subject's last visit in Study NEOD001-001 and prior to signing the ICF for this study should be assessed as possible medical history in this study.
5. Record all prior therapies for AL amyloidosis taken prior to signing ICF for this study and since last visit in Study NEOD001-001. Record all prior/concomitant medications taken or received by a subject within the 28 days prior to the Month 1-Day 1 Visit through the EOS Visit, and any changes to concomitant medications during the study. See Study Manual for more information.
6. Adverse events will be collected from the time that the informed consent form is signed through 30 days after the last dose of study drug or last study visit, whichever is later. Record any adverse events that were ongoing from the subject's last visit in Study NEOD001-001 and at the time of the NEOD001-OLE001 Screening Visit.
7. Physical examination will include weight, height (Screening only), and examination of the following: general appearance; head, ears, eyes, nose, and throat; neck; skin; cardiovascular system; respiratory system; abdominal system; and nervous system. A complete physical examination will be done at Screening and EOS; at all other visits, the components of the physical examination will be as clinically indicated. However, at all time points the following should be assessed: macroglossia, submandibular nodes/fullness, adenopathy, ecchymoses, liver/spleen size (palpable +/-), ascites (+/-), and edema (which should be quantified on a scale of 0-4).
8. Vital signs include heart rate (HR), blood pressure (BP), respiratory rate (RR), and body temperature; assess per protocol Section 6.3.2. **Month 1-Day 1:** Predose, halfway through infusion, immediately at EOI (+5 minutes), and 30 (±5) minutes and 60 (±10) minutes after EOI. **All Other Months-Day 1:** Predose, EOI (+5 minutes), and 60 (±10) minutes after EOI.
9. Peripheral neuropathy assessment: only for subjects previously enrolled in Cohort C of Study NEOD001-001.
10. Perform every 3 months (Months 3, 6, 9, 12, etc.).
11. Administer SF-36 before performing any other study assessments on the day it is administered (see protocol Appendix 2).
12. Perform every 6 months (Months 6, 12, 18, etc.).
13. NT-proBNP must be drawn before conducting 6MWT, if performed on the same calendar day. Collect blood pressure and heart rate pre- and post-6MWT administration.
14. Two pretreatment 6MWTs are required before the first administration of study drug, with a minimum of 4 days in between the two tests. The second test must be completed 1 to 2 days before the Month 1-Day 1 Visit.
15. Echocardiogram to be conducted every 12 months and may be conducted within 10 days before the visit.
16. Repeat echocardiogram at EOS if not performed within 60 days prior to visit.
17. For all post-Screening visits, ECGs are to be performed predose and within 15 minutes after the EOI.
18. Conduct telephone call approximately 3 months after subject's last study visit and approximately every 3 months thereafter for up to 5 years, death, or subject withdraws consent, whichever occurs first.
19. Hematology and chemistry per Appendix 3. At Screening, include Screen for Infectious Diseases per Appendix 3. Within 3 days before the first day of a new regimen of chemotherapy, conduct an unscheduled central laboratory collection (including hematology, chemistry, PT/INR, and PTT).
20. Coagulation per Appendix 3. Collect unscheduled citrated plasma samples for subjects with relevant serious adverse event(s); if defects are identified, additional analytes will be analyzed, as indicated (see Appendix 4).
21. All laboratory tests to be done centrally, unless otherwise noted.
22. Perform pregnancy tests for WOCBP as follows: **Screening:** serum test (central) within 28 days before Month 1-Day 1; **Monthly starting with Month 2**: urine test (local) predose; **EOS:** serum test (central). A positive urine pregnancy test (local laboratory) is to be confirmed with a serum pregnancy test (central laboratory).
23. Perform serum pregnancy test (local; WOCBP only) 90 (±5) days after the last study drug administration.
24. Begin urine collections 24 hours prior to the study visit.
25. After Baseline, use to confirm initial within-study hematologic complete response only.
26. Urinalysis per Appendix 3.
27. NEOD001 serum samples (for population PK analysis): collect predose, at EOI (record the time, but the sample can be collected at any time after the infusion on Day 1), and at other times as clinically indicated, such as when significant toxicity occurs.
28. Anti-NEOD001 antibody samples: collect predose and at other times as clinically indicated, such as when significant toxicity occurs.
29. NEOD001 will be administered every 28 (±5) days. Subjects should be closely monitored for 90 (±10) minutes following completion of the study drug infusion. Beginning with the third infusion, the Investigator may decrease the postdose monitoring time to no less than 60 minutes, if no infusion-related reactions were observed in the previous infusions and allowed per the IRB/IEC. The Investigator may increase the monitoring time if deemed appropriate or per local standards. In the event of any clinical concerns or suspicious signs or symptoms after the infusion, the subject will remain under observation for as long as the Investigator deems it appropriate. If parenteral chemotherapy is administered on the same day as NEOD001, the chemotherapy must be administered **after** the observation period.

2.2.4. Definition of Baseline

2.2.4.1. NEOD001 Baseline

The NEOD001 Baseline will be derived using one of the two following methods:

1. Last assessment prior to first infusion in the original parent study (NEOD001-001) if the time from last dose in the original parent study (NEOD001-001) to first dose in the OLE (NEOD001-OLE001) is *less than or equal to 60 days*.
2. Last assessment prior to first infusion in the OLE if the time from last dose in the original parent study (NEOD001-001) to first dose in the OLE is *greater than 60 days*. The initial OLE visit can be included as a baseline evaluation.

2.2.4.2. OLE Baseline

The OLE Baseline for the 6MWT distance (meters) will be defined as the longest distance walked prior to the first infusion in the OLE. Otherwise, OLE Baseline is defined as the last assessment prior to first infusion in the OLE.

2.3. Study Endpoints

2.3.1. Primary Endpoints

The primary study endpoints are the frequency and severity of AEs, changes in laboratory assessments from OLE baseline, and change in vital signs and 12-lead ECGs from NEOD001 baseline and OLE baseline.

2.3.2. Secondary Endpoints

2.3.2.1. Immunogenicity

Immunogenicity of NEOD001 will be assessed by anti-NEOD001 antibody levels. Serum anti-NEOD001 antibody levels and change from the OLE Baseline will be listed. Serum anti-NEOD001 antibody levels may be correlated with serum NEOD001 concentrations and select safety endpoints, if sufficient data exist.

2.3.2.2. Pharmacokinetics (PK)

Data on serum NEOD001 concentrations from this study will be provided in a by-subject line listing.

2.3.3. Exploratory Efficacy Endpoints

The following are the exploratory efficacy endpoints.

2.3.3.1. Time to Event Endpoints

- Time to all-cause mortality from first infusion of study drug in the original parent study (NEOD001-001)
- Cardiac progression-free survival from first infusion of study drug in the original parent study (NEOD001-001)

- Time to derived organ progression from first infusion of study drug in the original parent study (NEOD001-001), and from first OLE NEOD001 infusion of study drug
- Time to first organ response from first infusion of study drug in the original parent study (NEOD001-001), and from first OLE NEOD001 infusion of study drug
- Duration of organ response from first derived organ response

2.3.3.2. Quality of Life Endpoints: Change from OLE Baseline in SF-36v2 Scores

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

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

Responses to items allow for direct calculation of subscales for each of the 8 dimensions, while PCS and MCS scores are computed from weighted subscale scores (Maruish, 2011). The lower the score the more disability, the higher the score the less disability. A score of 50 is the mean in the US General Population. The standard deviation is 10 for all scales and both summary measures. The SF-36v2 will be scored using the algorithm provided by Optum with the instrument license (Health Outcomes™ Scoring Software 4.5). Algorithms that allow for the evaluation of summary component scores in the presence of missing data have been developed using Item Response Theory (IRT) and regression methods. Scores for respondents with incomplete answers can be derived using the maximum data recovery approach for the missing data estimation for all scales except the PF scale. For the PF scale, an estimated score based on an IRT model is utilized as long as at least one of its items has valid data, otherwise the scale score will be missing. Both the PCS score and the MCS score can be calculated if (1) at least seven scale scores are available, (2) the PF scale is not missing when evaluating the PCS, and (3) the MH scale is not missing when calculating the MCS. The scoring algorithm to apply to the calculation of the summary scores depends upon which particular scale score is missing from the 8-scale profile.

2.3.3.3. Functional Endpoint: Change from OLE Baseline in the 6-Minute Walk Test (6MWT) Distance (meters)

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

2.3.3.4. Cardiac Endpoints

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

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

Response	Stable Disease	Progression
Decrease in NT-proBNP from baseline of >30% and >300 ng/L or decrease in NYHA class of ≥2 in subjects with baseline NYHA class III or IV	Assessment was neither Response nor Progression	Increase in NT-proBNP from baseline of >30% and >300 ng/L

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

- Cardiac response from NEOD001 and OLE baselines (see Section 2.2.4), as assessed by NT-proBNP response criteria, at each visit
- Cardiac best response from NEOD001 and OLE baselines (see Section 2.2.4), as assessed by NT-proBNP response criteria. Best response will be over the course of the study.
- Change and percent change from NEOD001 and OLE baselines (see Section 2.2.4) to each visit in NT-proBNP

2.3.3.5. Renal Endpoints

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

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

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

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

- Renal response from NEOD001 and OLE baselines (see Section 2.2.4) at each visit
- Renal best response from NEOD001 and OLE baselines (see Section 2.2.4). Best response will be evaluated over the course of the study.
- Change and percent change from NEOD001 and OLE baselines (see Section 2.2.4) to each visit in creatinine, proteinuria, and estimated glomerular filtration rate (eGFR)
- Time to eGFR ≤15 mL/min/1.73 m^2 (Chronic Kidney Stage 5) from NEOD001 and OLE baselines (see Section 2.2.4)

2.3.3.6. Peripheral Neuropathy Endpoints

The following endpoints will be evaluated in the Peripheral Neuropathy Evaluable Population (see Section 5). Peripheral neuropathy response and progression as defined in Coelho, 2012, are those with an increase from baseline in Neuropathy Impairment Score in the Lower Limbs (NIS-LL) total score of <2 points and those with an increase from baseline in NIS-LL of ≥2 points, respectively.

- Change and percent change from NEOD001 and OLE baselines (see Section 2.2.4) to each visit in the NIS-LL total score to each visit
- Peripheral neuropathy response from NEOD001 and OLE baselines (see Section 2.2.4) at each visit
- Change and percent change from NEOD001 and OLE baselines (see Section 2.2.4)in the 3 NIS-LL component scores (sensory function, reflexes, muscle strength) to each visit

3. SAMPLE SIZE JUSTIFICATION

Not applicable as this is an extension study for subjects previously enrolled and treated for at least 9 months in Study NEOD001-001.

4. GENERAL STATISTICAL METHODS

4.1. Reporting Conventions

Individual subject data obtained from electronic case report forms (eCRFs), central laboratories, external sources, and any derived data will be presented in data listings by subject. The primary data source will be used for all analyses. All data listings that contain an evaluation date will contain a relative study day. Pre-treatment and on-treatment study days are numbered relative to the day of the first dose of study drug in the OLE which is designated as Day 1. The preceding day is Day -1, the day before that is Day -2, etc.

All output will be incorporated into Microsoft Word rich text format (.rtf) files, sorted and labeled according to the International Council for Harmonisation (ICH) recommendations, and formatted to the appropriate page size(s).

For categorical variables, summary tabulations of the number and percentage of subjects within each category (with a category for missing data) of the parameter will be presented. Percentage calculations will be based on non-missing data, unless otherwise specified. Percentages are rounded to 1 decimal place, unless otherwise specified.

For frequency counts of categorical variables, categories whose counts are zero will be displayed for the sake of completeness. For example, if none of the subjects discontinue due to "lost to follow-up," this reason will be included in the table with a count of 0. Percentages based on frequency counts will be presented to one decimal place, and values less than 1% will be presented as "<1%." Values less than 100% but greater than 99% will be presented as ">99%."

For continuous variables, the number of subjects, mean, standard deviation (SD), median, 25th quartile (Q1), 75th quartile (Q3), minimum, and maximum values will be presented. The precision of summary statistics, unless otherwise, specified will be as follows: mean and median to 1 more decimal place than the raw data, and SD to 2 decimal places more than the raw data. In general, the number of decimal places should not exceed 3 decimal places unless appropriate. Confidence intervals (CIs) will be provided and will be rounded to 1 decimal place, unless otherwise specified, in the table and listing shell.

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

4.2. Computing Environment

All descriptive statistical analyses will be performed using SAS statistical software Version 9.4 or higher, unless otherwise noted. Medical history and AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 19.0. Concomitant medications will be coded using World Health Organization (WHO) Drug Dictionary, B2 Enhanced September 2015.

4.3. Partial Dates and Unknown Times

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

- Death Date
  - The last date that each subject was known to be alive will be identified as the greatest date associated with the subject's completed assessments, including telephone contacts at which the subject was confirmed to be alive.
  - For missing day only – Day will be imputed as the first day of the month (i.e., 1) with the following exception: if the partial date falls in the same month as the last known alive date, then the partial date will be imputed to equal the last known alive date.
  - For missing day and month – Day and month will be imputed as the first day of the year (i.e., 1 January) with the following exception: if the partial date falls in the same year as the last known alive date, then the partial date will be imputed to equal the last known alive date.
- Start Dates (e.g., event date, AE onset date, start date of medication, or hospitalization admission date)
  - For missing start day only – Day will be imputed as the first day of the month (i.e., 1) with the following exception: if the partial date falls in the same month and year as the date being used in the calculation (e.g., first infusion date, informed consent date), then the partial date will be imputed to equal the date being used for the calculation.
  - For missing start day and month – Day and month will be imputed as the first day of the year (i.e., 1 January) with the following exception: if the partial date falls in the same year as the date being used in the calculation (e.g., first infusion date, informed consent date), then the partial date will be imputed to equal the date being used for the calculation.
  - When applicable, imputed start dates must be prior to the stop date.
- Stop Dates (e.g., AE resolution date or stop date of medication)
  - For missing stop day only – Day will be imputed as the last day of the month (i.e., 28, 29, 30, or 31).
  - For missing stop day and month – Day and month will be imputed as the last day of the year (i.e., 31 December).
  - Imputed stop dates must be on or after the start date.

If a time required for calculation related to exposure is missing, the following standards will be applied:

- If start time is missing for an infusion where the volume recorded on the eCRF is greater than 0 mL then start time will be imputed as the pre-dose time of vital signs at the same

visit + 1 minute. This should only be done for the first dose time within a given visit should there be more than one record.

- If stop time is missing for an infusion where the volume is greater than 0 mL then stop time will be imputed as the 'immediately after infusion' time of the vital signs at the same visit - 1 minute. This will only be done for the last dose time within a given visit should there be more than one record.
- If vital sign assessment times are not available, infusion start date/time is missing, and infusion stop date/time is non-missing then the start date/time will be imputed as stop date/time - 2 hours at the Month 1 Day 1 visit or as the stop date/time - 1 hour for all other visits.
- If vital sign assessment times are not available, infusion stop date/time is missing, and infusion start date/time is non-missing then the stop date/time will be imputed as start date/time + 2 hours at the Month 1 Day 1 visit or as the start date/time + 1 hour for all other visits.

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

4.4. Data Conventions

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

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

4.5. Standard Calculations

Variables requiring calculation will be derived using the following formulas:

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

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

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

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

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

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

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

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

  height (cm) = height (in) × 2.54

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

  weight (kg) = weight (lb) / 2.2046

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

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

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

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

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

  Change = post baseline value – baseline value

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

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

4.6. Analysis Visit Windows

Each visit will be denoted by its "month" and "day" such that the first dose day is denoted as Month 1-Day 1; subsequent months will use sequential numbers (e.g., the second dose is administered on Month 2-Day 1). Each infusion is scheduled to be 28 days from the previous infusion (±2 days for Months 2 and 3; ±5 days for Months 4 and beyond).

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

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

4.6.1. NEOD001 Therapy Visit Windows

Table 2 defines the visit windows for assessments taken at 1-month intervals to be established with respect to relative day from the start of NEOD001 therapy.

Table 2: NEOD001 Therapy 1-Month Interval Visit Windows (Days)

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

[a] Study day will be calculated from first dose date according to Section 2.2.4.1.
[b] NEOD001 Baseline is defined in Section 2.2.4.1.

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

Table 3: NEOD001 Therapy 3-Month Interval Visit Windows (Days)

Months	Target Study Day[a]	Analysis Window Study Day[a]	
		Low	High
NEOD001 Baseline[b]	1	Closest visit to Day 1, prior to first NEOD001 dose	
NEOD001 Month 3	84	2	126 [= 84 + 84/2]
NEOD001 Month 6	168	127 [= (84 + 84/2) +1]	210 [= (168 +84/2)]
NEOD001 Month x	28*x	(x-3)*28 + 84/2 + 1	x*28 + 84/2

[a] Study day will be calculated from first dose date according to Section 2.2.4.1.
[b] NEOD001 Baseline is defined in Section 2.2.4.1.

The duration of 60 days between the time from last dose in the original parent study (NEOD001-001) to first dose in the OLE was chosen based on PK experience of elimination of study drug.

Note that the assessment used in the analyses is chosen step by step as follows in cases when multiple records exist within the same analysis window:

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

4.6.2. OLE Therapy Visit Windows

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

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

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

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

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

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

Months	Target Study Day[a]	Analysis Window Study Day[a]	
		Low	High
OLE Baseline[b]	1	Closest visit to Day 1, prior to first OLE NEOD001 dose	
OLE Month 3	84	2	126 [= 84 + 84/2]
OLE Month 6	168	127 [= (84 + 84/ 2) +1]	210 [= (168 + 84/2)]
OLE Month x	28*x	(x-3)*28 + 84/2 + 1	x*28 + 84/2

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

Note that same scheme will be applied as described Section 4.6.1 when multiple records exist within the same analysis window.

5. ANALYSIS POPULATIONS

The NEOD001 Safety Population will include all subjects who received any amount of NEOD001 in the original parent study (NEOD001-001).

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

The Cardiac Evaluable Population will include subjects who had cardiac involvement in the original parent study (NEOD001-001), defined as subjects who had an NT-proBNP ≥ 650 ng/L at Screening and at least one post-baseline assessment of NT-proBNP.

The Renal Evaluable Population will include subjects who had renal involvement in the original parent study (NEOD001-001), defined as proteinuria >0.5g/day in a 24-hour urine collection (the value reported as Total Protein on the Disease Specific Urine Laboratory Tests CRF) at Screening and at least one post-baseline assessment of proteinuria.

The Peripheral Neuropathy Evaluable Population will include subjects who had peripheral nerve involvement in the original parent study (NEOD001-001), defined as subjects who were marked as having had peripheral nerve involvement at baseline per the Amyloidosis Baseline Disease Assessment AND had a Screening peripheral neuropathy assessment score of 2 or greater from the Peripheral Neuropathy Assessment CRF and at least one post-baseline peripheral neuropathy assessment from the Peripheral Neuropathy Assessment CRF.

6. EXAMINATION OF SUBGROUPS

No prespecified evaluation of subgroups will be performed.

7. STUDY POPULATION

7.1. Subject Disposition

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

- the number of subjects dosed in the original parent study (NEOD001-001; NEOD001 Safety Population)
- the number of subjects screened in the OLE
- the number screened but not enrolled in the OLE
- the number enrolled in the OLE (OLE Safety Population)
- the number in each analysis organ evaluable population
- the number who discontinued treatment early in the OLE and reason(s) for discontinuation of treatment as recorded on the OLE eCRF
- the number who withdraw from OLE study prior to completing the study and reason(s) for withdrawal as recorded on the OLE eCRF

Time on study will be calculated as last known date of contact minus date of first infusion in NEOD001-OLE001 plus one.

By-subject data listings of all the above study disposition data including study completion and any reasons for premature treatment and/or study withdrawal will be presented.

7.2. Demographics and Baseline Characteristics

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

Demographic variables will include the following:

- Age at informed consent including the subgroups <65 vs ≥65 years and <75 vs ≥75 years
- Sex
- Race
- Ethnicity

Other baseline characteristics will include the following:

- Weight (kg)
- Height (cm)
- BMI (kg/m^2) including frequency of the following subgroups: <20, ≥20 to <30, ≥30 kg/m^2

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

No inferential statistical comparisons will be performed.

All demographic and baseline characteristics data will be presented in by-subject data listings.

7.3. Baseline AL Amyloidosis Disease Characteristics

The following disease histories from the original parent study (NEOD001-001) will be summarized for the OLE Safety Population:

- Age (years) at AL amyloidosis diagnosis
- Duration (months) since AL amyloidosis diagnosis
- Number of derived involved organs (1, 2, 3, or 4 organs: cardiac, renal, peripheral neuropathy, and hepatic) based on the organ evaluable populations defined in Section 5
- Number of physician assessed involved organs (gastrointestinal, autonomic nervous system, lung, soft tissue/lymphatic, or other) as recorded on the eCRF
- Total number of involved organs (derived plus physician assessed; range 1-9)
- Screening NT-proBNP: <1800 ng/L, ≥1800 ng/L
- NYHA Class: I, II, III, IV
- Baseline FLC Ratio: Low (<0.26), Normal (0.26 – 1.65), High (>1.65)

In addition, from the OLE Baseline 6MWT distance (meters) will be summarized including frequency of the subgroups: <300 meters vs. ≥300 meters.

No inferential statistical comparisons will be performed.

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

7.4. General Medical History

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

Medical history collected during NEOD001-OLE001 will be summarized by SOC and PT using the OLE Safety Population. Summaries will be ordered by descending order of NEOD001-OLE001 24 mg/kg incidence of SOC and PT within each SOC.

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

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

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

Pretreatment medications, recorded on the Concomitant Medications eCRF, are those medications with start and stop dates prior to the first infusion of study drug in the OLE. Prior concomitant medications are those medications started prior and continued after the first infusion of study drug in the OLE. New concomitant medications are those medications that were started

on or after the first infusion of study drug in OLE. Concomitant chemotherapy is described in Section 7.7. If it cannot be determined whether the medication was a new concomitant medication due to a partial start or stop date or if the medication is taken on the same date as the first infusion of study drug, then it will be counted as a new concomitant medication.

Pretreatment medications will be listed only. Prior and new concomitant medications will be summarized by WHO ATC level 3, WHO ATC level 4, and preferred name using the OLE Safety Population. Prior and new concomitant medications will also be summarized separately as well. These summaries will present the number and percentage of subjects using each medication. Subjects may have more than one medication per ATC level and preferred name. At each level of subject summarization, a subject is counted once if he/she reported one or more medications at that level. Each summary will be ordered by descending order of NEOD001 incidence of ATC level and preferred name within each ATC level.

7.6. Premedication

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

7.7. Chemotherapy

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

7.8. Concurrent Procedures

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

8. EFFICACY ANALYSES

All recorded efficacy endpoint data will be presented in by-subject data listings for the OLE Safety Population. No summary tables or figures will be produced for the efficacy endpoints.

8.1. Adjustments for Covariates

Not applicable.

8.2. Handling of Dropouts or Missing Data

For the SF-36v2, missing data conventions for partially completed questionnaires are specified in Section 2.3.3.2.

No imputations will be performed on missing data.

8.3. Interim Analyses and Data Monitoring

Not applicable.

8.4. Multicenter Studies

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

8.5. Multiple Comparisons/Multiplicity

No adjustments for multiplicity will be made.

9. SAFETY ANALYSES

Safety analyses will be conducted using the NEOD001 and OLE Safety Populations as specified below.

No inferential comparison of safety endpoints will be performed, unless otherwise specified.

9.1. Extent of Exposure

Study drug exposure during the OLE and separately for the original parent study (NEOD001-001) and OLE combined will be summarized including:

- Total Number of Infusions received will be determined for each subject by number of times the start time of drug infused is reported. If multiple infusion start times are reported on a single day, then only 1 infusion will be counted for that day. If the start time of drug infused is missing but total volume infused is greater than 0 mL, 1 infusion will be counted for that day.
- Total Number of Dose Interruptions will be determined for each subject by the number of times the IV was not completed in OLE, or segment outcome of the infusion was interrupted in parent study.
- Dose Strength (mg/kg) will be calculated for each subject at each OLE visit and each visit in parent study separately as follows:
  - For each OLE visit, dose (mg) recorded on the Study Drug Exposure CRF will be divided by the weight (kg) at that visit (Vital Signs CRF). If the dose (mg) is missing but the total duration of infusion is at least 50 minutes which is the lower limit of the protocol specified time (i.e. 60 min – 10 min), and IV completed is marked "Yes" then dose strength will be imputed to be equal to the planned dose strength (described below).
  - For each visit in parent study, the total dose (mg) reported will be divided by the weight used to calculate dose strength for that visit. If Current Visit is marked for Weight Used to determine dose and no corresponding weight is available from the vital sign page then the screening/baseline weight will be assigned as the weight used to calculate total dose. Dose strength will only be calculated where both the total dose and weight used are available.

Once visit/individual specific dose strengths are determined, subjects will be assigned a single average dose strength value across all visits to be used for summary statistics in the table.

- Percent of Planned Dose Strength will be determined by dividing the average dose strength per visit by the average planned dose strength per visit for each subject. Calculation of average dose strength is described above. Planned dose strength will be assigned by visit based on NEOD001 dose level. The average of planned dose strength will be the average of the individual planned dose strength calculated at each visit.

Once visit/individual specific percent of planned dose strength are determined, subjects will be assigned a single average percent of planned dose strength value across all visits to be used for summary statistics in the table.

- Total Number of Dose Reductions will be determined for each subject by the number of times the percent of planned dose was less than 100.

In addition, duration of exposure (months) will be calculated including treatment delays and interruptions as: (last dose date – first dose date+1)/30.4375. Duration will be calculated from the first infusion in the original parent study (NEOD001-001) and separately from the first infusion in the OLE. Each duration of exposure will be summarized using descriptive statistics. The number and percentage of subjects with duration of exposure in the following categories will be summarized:

- <3 months
- ≥3 and <6 months
- ≥6 and <9 months
- ≥9 and <12 months
- ≥12 and <15 months
- ≥15 months and <18 months
- ≥18 months and <21 months
- ≥21 months and <24 months
- ≥24 months

Additional 3-month intervals may be added based on the available data. The number of total infusions will be summarized with similar categories, replacing months with infusions.

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

9.2. Adverse Events

Verbatim terms on the OLE Adverse Event eCRFs will be mapped to PT and SOC using MedDRA version 19.0. AEs will be reported and severity will be categorized using the Common Terminology Criteria for Adverse Events (CTCAE, Version 4.03).

AE summaries will use the OLE Safety Population.

All AE summaries will be restricted to treatment-emergent adverse events (TEAEs), which are defined as any AE that newly appears, increases in frequency, or worsens in severity following initiation of study drug and up to 30 days after date of last dose or last study visit, whichever is later. If it cannot be determined whether the AE is treatment emergent due to a partial onset date, then it will be counted as such.

Each AE summary will be displayed by treatment group. Summaries that are displayed by SOC and PT will be ordered by descending order of NEOD001-OLE001 24 mg/kg incidence of SOC and PT within each SOC.

The following listings will be presented by subject, with non-TEAEs flagged:

- All AEs
- Serious adverse events (SAEs) (this is a subset of the AEs where serious is marked as "Yes")
- CTCAE Grade 3 or higher AEs (this is a subset of AEs where severity is missing or marked as CTCAE Grade 3, 4, or 5)
- Related AEs (this is a subset of the AEs where relationship marked as "Related" or relationship is missing)
- AEs leading to Study Drug Withdrawal (this is a subset of the AEs where Action Taken with Study Treatment is checked as "Drug Discontinued")
- Fatal AEs (this is a subset of the AEs where outcome is indicated as "Fatal" or the CTCAE grade is 5)
- AEs resulting in any dose change (i.e., interruption, reduction, held, or prolongation)
- AEs assessed by the investigator as infusion-associated (this is a subset of the AEs where infusion-associated AE was reported as "Yes.")
- AEs within one day of any infusion (this is a subset of the AEs where AE onset date was the same day as the date of any infusion)

9.2.1. Types of Incidence Rates

9.2.1.1. Crude Incidence Rates

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

To assess the long-term treatment effects overall and relative to shorter term treatment, the crude incidence of TEAEs will be summarized by combined study from the original parent study and OLE study (NEOD001-001), followed by the OLE only (NEOD001-OLE001). TEAEs that started in the original parent study will be summarized for subjects who initiated at 24 mg/kg, subjects who ever took 24 mg/kg, and subjects who took any dose of NEOD001. TEAEs that start on or after the first dose of OLE NEOD001 (i.e., OLE TEAEs) will be summarized using the OLE dose 24 mg/kg. The treatment group schema is shown in Table 6 using the NEOD001 Safety Population.

Table 6: Treatment Group Schema

NEOD001-001 + NEOD001-OLE001			**NEOD001-OLE001**
Initiated at 24 mg/kg (N=xx)	All 24 mg/kg (N=xx)	Any Dose (N=xx)	24 mg/kg (N=xx)

9.2.1.2. Cumulative Incidence Rates

The cumulative incidence rate is the probability that a particular AE occurs by a specified time. To compute the cumulative rate using the life table method, exposure time intervals from the first NEOD001 dose of the original parent study (NEOD001-001) (i.e., ≤1 month, >1 month to ≤3 months, >3 month to ≤6 months, >6 months to ≤1 year, >1 to ≤1.5 years, >1.5 to ≤2 years, >2 to ≤3 years, …, and > maximum years) are specified, and the number of subjects at risk of experiencing an AE in each time interval is determined by taking the average number of subjects at risk at the start and end of each time interval. As subjects leave the study over time, the number of subjects at risk of experiencing the AE in each time interval decreases. The cumulative incidence rate over each time intervals is as follows:

$$1 - \{[1 - P(t_1)][1 - P(t_2)] \ldots [1 - P(t_k)]\}$$

where $P(t_i)$ is the number of subjects with the AE divided by the number of subjects at risk in time interval t_i and where i ranges from 1 to k.

To illustrate the difference between crude and cumulative incidence rates and how these are computed, an example is provided (O'Neill, 1988). Suppose that 3000 subjects are initially exposed to a drug and followed for up to 1 year with varying durations of exposure (see Table 7). Assume further that 30 subjects experience SAEs, most of which occur later in the study as duration of exposure increases. The crude rate is 30/3000 = 0.01 and the 12-month cumulative rate is 0.055. When AEs occur later in time as fewer subjects are at risk due to discontinuations or tolerability, the crude rate underestimates the longer-term risk and overestimates the shorter-term risk.

Using the example in Table 7, the number of subjects at the start of a time interval is the number of subjects at the start of the previous time interval minus the number of subjects lost to follow-up or who dropped out minus the number of subjects with SAEs. For instance, the number of subjects at the start of the 3rd time interval is equal to

$$[1800 - 399 - 1] = 1400$$

The proportion of subjects with SAEs at each time interval $P(t_i)$ is computed by dividing the number of subjects with SAEs by the number of subjects at risk in the time interval. For example, the number of subjects at risk for the 2nd time interval is as follows:

$$\frac{[1800 + (1800 - 399)]}{2} = 1600.5$$

The proportion of subjects with SAEs in the 2nd time interval, $P(t_2)$ is therefore 1/1600.5 or 0.0006. The 12-month cumulative SAE incidence rate is

$$P(t) = 1 - [(1 - 0.0000) \times (1 - 0.0006) \times (1 - 0.000) \times (1 - 0.0021) \times \ldots \times (1 - 0.0100)] = 0\ .055$$

which is 1 minus the cumulative probability of not having any SAE up to the 12th time interval.

Table 7: Example of Computing Cumulative Incidence Rates Using the Life Table Method

Interval (months)	Number Entering Interval	Number Lost to Follow-Up	Number with SAE	Number at Risk	Proportion with SAE	Cumulative Incidence Rate
0–1	3000	1200	0	2400	0.0000	0.0000
1–2	1800	399	1	1600.5	0.0006	0.0006
2–3	1400	400	0	1200	0.0000	0.0006
3–4	1000	98	2	951	0.0021	0.0027
4–5	900	100	0	850	0.0000	0.0027
5–6	800	95	5	752.5	0.0066	0.0094
6–7	700	92	8	654	0.0122	0.0215
7–8	600	91	9	554.5	0.0162	0.0374
8–9	500	98	2	451	0.0044	0.0416
9–10	400	100	0	350	0.0000	0.0416
10–11	300	99	1	250.5	0.0040	0.0454
11–12	200	0	2	200	0.0100	0.0550

Source: O'Neill, 1988.

Summaries of cumulative incidence rates will be presented for the OLE Safety Population, based on TEAEs experienced from the start of the original parent study (NEOD001-001). Cumulative incidence rates will be computed separately for each MedDRA SOC and each MedDRA PT within SOC.

9.2.2. Overall Summary of Adverse Events

An overall summary of crude AE incidences will be presented according to Table 7, including the number and percent of subjects with at least one of:

- Any TEAE
- TEAE by maximum CTCAE Grade
- CTCAE Grade ≥3 TEAE
- Serious TEAE
- Fatal TEAEs (outcome="Fatal" or severity=CTCAE Grade 5)
- Treatment-related TEAE
- Treatment-related serious TEAE
- Treatment-related TEAE of CTCAE ≥Grade 3
- TEAE leading to infusion interruption

- TEAE leading to dose reduction
- TEAE leading to dose being held
- TEAE leading to prolongation of infusion time (>2.5 hours)
- Infusion associated TEAE as determined by the Investigator
- TEAE leading to study drug withdrawal

9.2.3. Treatment-Emergent Adverse Events

The crude and cumulative incidences of TEAEs will be summarized. The following summaries will be presented:

- Subject incidence of TEAEs by MedDRA SOC and PT
- Subject incidence of TEAEs by MedDRA SOC and PT occurring in ≥5% of subjects

9.2.4. Severity of Adverse Events

The crude and cumulative incidences of TEAEs by maximum severity will be summarized. At each level of subject summarization, a subject is classified according to the highest severity if the subject reported 1 or more events. AEs with missing severity (CTCAE grade) will be considered Grade 3 (severe) for these summaries. The following summaries will be presented:

- Subject incidence of TEAEs by MedDRA SOC, PT, and highest severity (CTCAE grade)
- Subject incidence of CTCAE Grade 3 or higher TEAEs by MedDRA SOC and PT.

9.2.5. Relationship to Study Drug as Assessed by Investigator

The crude and cumulative incidences of TEAEs by strongest relationship to study drug (Related/Not Related) will be summarized. At each level of subject summarization, a subject is classified according to the closest relationship to study drug if the subject reported 1 or more events. AEs with a missing relationship will be considered related for this summary. The following summaries will be presented:

- Subject incidence of related TEAEs by MedDRA SOC and PT
- Subject incidence of related CTCAE Grade 3 or higher TEAEs by MedDRA SOC and PT

9.2.6. Adverse Events Leading to Dosing Changes

The crude and cumulative incidences of TEAEs leading to dosing changes will be summarized. The following summaries will be presented:

- Subject incidence of TEAEs leading to infusion interruption by MedDRA SOC and PT. This is a subset of the AEs where Action Taken with Study Treatment is checked as “Dose Interrupted” is checked.

- Subject incidence of TEAEs leading to dose reduction by MedDRA SOC and PT. This is a subset of the AEs where Action Taken with Study Treatment is checked as "Dose Reduced" is checked.
- Subject incidence of TEAEs leading to dose held by MedDRA SOC and PT. This is a subset of the AEs where Action Taken with Study Treatment is checked as "Dose Held" is checked.
- Subject incidence of TEAEs leading to prolongation of infusion time (>2.5 hours) by MedDRA SOC and PT.

9.2.7. Serious Adverse Events and Deaths

The crude incidences of serious TEAEs will be summarized. The incidence of fatal TEAEs will be summarized separately. In addition, the cumulative incidences of serious TEAEs and deaths will be summarized. The following summaries will be presented:

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

9.2.8. Adverse Events Leading to Study Drug Withdrawal

AEs leading to study drug withdrawal are those AEs where Action Taken with Study Treatment is checked as "Drug Discontinued". The crude and cumulative incidences of AEs leading to study drug withdrawal will be summarized. The following summaries will be presented:

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

9.2.9. Other Adverse Events: Infusion Reactions

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

If applicable, the crude incidence anaphylactic reaction, defined as the broad algorithmic standardized MedDRA query (SMQ) of "Anaphylactic reaction", defined in Appendix 5, will be summarized.

In order to explore the temporal relationship of TEAEs that may be associated with the infusion, the crude incidence of all TEAE occurring within 1 day (AE start date – infusion date + 1 = 1) of an infusion will be summarized.

9.3. Clinical Laboratory Evaluations

Laboratory parameters will be presented in Système International (SI) units.

Local laboratories were used during the original parent study NEOD001-001. A central laboratory (Covance Central Laboratory Services) was used for this open-label extension, NEOD001-OLE001. Data from the local and central labs will not be pooled. Summaries will only present data from the central laboratory for OLE Safety Population.

All clinical laboratory data will be presented in by-subject data listings. In addition, separate listings will be presented for any subject with a post OLE baseline CTCAE Grade 3 or 4 laboratory value.

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

- INR Upper Limit of Normal (ULN) = 1.1
- eGFR LLN = 90 mL/min/1.73m^2

9.3.1. Serum Chemistry, Hematology, and Coagulation

Quantitative serum chemistry, hematology, and coagulation results will be summarized using descriptive statistics at OLE baseline, each post OLE baseline visit, minimum OLE value, and maximum OLE value. The change and percentage change from OLE baseline will also be summarized.

9.3.2. Shifts in CTCAE Grade

Quantitative laboratory tests will be assigned grades based on CTCAE Version 4.03, where applicable. Shifts in CTCAE grade of laboratory tests will be presented from OLE baseline to worst post OLE baseline value, last post OLE baseline value, best post OLE baseline value, and at each post OLE baseline visit. Summaries will present the number and percentage of subjects with shifts in laboratory grade. Denominators for percentages will be the number of subjects with non-missing data at the specific assessment and OLE baseline.

In addition, the number and percent of subjects with a lab value with CTCAE Grade ≥3 and the number and percent of subjects with a CTCAE shift of ≥2 grades will be presented.

Where applicable, if the quantitative criteria for grading are equivalent for two grades, only differentiated by clinical interventions, the clinical intervention will be ignored and the highest CTCAE grade will be used.

9.3.3. Shifts in Normal Range

In addition, for laboratory tests that cannot be graded via CTCAE, shift tables (i.e., low-normal-high at baseline versus low-normal-high at post-baseline visit in a 3-by-3 contingency table) from OLE baseline to worst post OLE baseline value, last post OLE baseline value and at each post OLE baseline visit will be presented. Denominators for percentages will be the number of subjects with non-missing data at the specific assessment and baseline.

9.3.4. Pregnancy Testing and Urinalysis Dipstick

Pregnancy test results and urinalysis dipstick results will not be summarized and will be provided in a by-subject data listing.

9.4. Weight and BMI

Weight (kg), BMI (kg/m^2), and mBMI (kg/m^2 g/L), defined as a subject's weight (kg) ÷ subjects squared height (meters) × serum albumin (g/L), will be summarized using descriptive statistics at NEOD001 baseline, OLE baseline, at each post NEOD001 baseline visit, and at each post OLE baseline visit. In addition, changes and percent changes from NEOD001 and OLE baselines will be presented.

9.5. Vital Signs

Vital sign parameters including temperature (C), systolic and diastolic pressure (mmHg), pulse (beats/min), and respiratory rate (breaths/min) will be presented in a data listing. Method of collection will be provided in the listing; however, summaries will be generated without regard to the method of collection. Summaries of vital sign parameter results, change from NEOD001 baseline, change from OLE baseline, percent change from NEOD001 baseline, and percent change from OLE baseline, will be summarized using descriptive statistics at baseline and at each post-baseline visit. In addition, change and percent change from baseline will be presented from pre-dose to post-dose at infusion visit.

9.6. Electrocardiograms

ECGs measurements will be made in triplicate, 5 to 10 minutes apart and assessed by a central reader. For summary purposes, the mean of the three measurements will be used. ECG parameters including, time between 2 consecutive R waves [RR], PR interval, QRS duration, QT (uncorrected) interval, QT interval corrected by the Bazett's formula [QTcB], and QT interval corrected by the Fridericia's formula [QTcF], will be summarized using descriptive statistics will be presented for observed values, change from NEOD001 baseline, change from OLE baseline, at each NEOD001 post-baseline time point, and at each OLE post-baseline time point.

A categorical summary of the following abnormal maximum mean triplicate QTcF values will be presented: >450 msec, >480 msec, and >500 msec. Change from NEOD001 baseline and OLE baseline summaries will also be presented for measurements that represent a change from baseline >30 msec and >60 msec. Three separate listings for those subjects with any QTcF >450 msec or a QTcF change from either baseline >30 msec, any QTcF >480 msec or a QTcF change from either baseline >30 msec, and any QTcF >500 msec or a QTcF change from baseline >60 msec will be presented. The observation(s) meeting criteria for inclusion will be flagged in the listing.

Overall interpretation results for ECGs and the investigator interpretation results are collected as normal, abnormal not clinically significant, and abnormal clinically significant. Subjects whose interpretation shifts from normal to abnormal clinically significant or not clinically significant will be listed separately including description of the abnormality and any associated comments.

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

9.7. Physical Examination

Physical examination findings based on body systems entered on the eCRF will be included in a data listing only.

9.8. Immunogenicity

Immunogenicity of NEOD001 will be assessed by anti-NEOD001 antibody levels. Any sample found to be confirmed positive for anti-NEOD001 antibodies will be further evaluated by a neutralizing antibody assay. Serum anti-NEOD001 antibody levels will be listed.

10. PHARMACOKINETIC ANALYSES

Serum NEOD001 concentrations and elapsed time from the preceding NEOD001 dose will be listed.

11. CHANGES TO PROTOCOL PLANNED ANALYSES

Additional analyses of safety endpoints are included in this SAP.

Due to the discontinuation of the NEOD001 program, no summary tables or figures will be produced for the efficacy endpoints.

12. REFERENCES

American Heart Association. Classes of heart failure (last reviewed 06Apr2015). Available from: http://www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/Classes-of-Heart-Failure_UCM_306328_Article.jsp. Accessed 21 Oct 2015.

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Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649-55.

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13. APPENDICES

APPENDIX 1. EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS

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

Source: Oken, 1982.

APPENDIX 2. NEW YORK HEART ASSOCIATION (NYHA) FUNCTIONAL CLASSIFICATION

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

Source: American Heart Association, 2015.

APPENDIX 3. LABORATORY TESTS

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

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

APPENDIX 4. COAGULATION INDICES

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

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

APPENDIX 5. ANAPHYLACTIC REACTION SMQ

An Adverse Event or group of Adverse Events occurring on the same day should be flagged as Anaphylactic Reaction per SMQ if the AE(s) meets one or more of the following criteria:

- Any term from group A
- Any two terms, with one from group B and one from group C
- Any two terms, with one from group D and one from either group B or group C

Group A Terms	
Preferred Term	**Preferred Term Code**
Anaphylactic reaction	10002198
Anaphylactic shock	10002199
Anaphylactic transfusion reaction	10067113
Anaphylactoid reaction	10002216
Anaphylactoid shock	10063119
Circulatory collapse	10009192
Dialysis membrane reaction	10076665
Kounis syndrome	10069167
Shock	10040560
Shock symptom	10040581
Type I hypersensitivity	10045240

Group B Terms	
Preferred Term	**Preferred Term Code**
Acute respiratory failure	10001053
Asthma	10003553
Bronchial oedema	10056695
Bronchospasm	10006482
Cardio-respiratory distress	10049874
Chest discomfort	10008469
Choking	10008589
Choking sensation	10008590

Group B Terms	
Preferred Term	**Preferred Term Code**
Circumoral oedema	10052250
Cough	10011224
Cyanosis	10011703
Dyspnoea	10013968
Hyperventilation	10020910
Irregular breathing	10076213
Laryngeal dyspnoea	10052390
Laryngeal oedema	10023845
Laryngospasm	10023891
Laryngotracheal oedema	10023893
Mouth swelling	10075203
Nasal obstruction	10028748
Oedema mouth	10030110
Oropharyngeal oedema	10078783
Oropharyngeal spasm	10031111
Oropharyngeal swelling	10031118
Pharyngeal oedema	10034829
Respiratory arrest	10038669
Respiratory distress	10038687
Respiratory failure	10038695
Reversible airways obstruction	10062109
Sensation of foreign body	10061549
Sneezing	10041232
Stridor	10042241
Swollen tongue	10042727
Tachypnoea	10043089
Throat tightness	10043528
Tongue oedema	10043967
Tracheal obstruction	10044291

Group B Terms	
Preferred Term	**Preferred Term Code**
Tracheal oedema	10044296
Upper airway obstruction	10067775
Wheezing	10047924

Group C Terms	
Preferred Term	**Preferred Term Code**
Allergic oedema	10060934
Angioedema	10002424
Erythema	10015150
Eye oedema	10052139
Eye pruritus	10052140
Eye swelling	10015967
Eyelid oedema	10015993
Face oedema	10016029
Flushing	10016825
Generalised erythema	10051576
Injection site urticaria	10022107
Lip oedema	10024558
Lip swelling	10024570
Nodular rash	10075807
Ocular hyperaemia	10030041
Oedema	10030095
Periorbital oedema	10034545
Pruritus	10037087
Pruritus allergic	10063438
Pruritus generalised	10052576
Rash	10037844
Rash erythematous	10037855
Rash generalised	10037858

Group C Terms	
Preferred Term	**Preferred Term Code**
Rash pruritic	10037884
Skin swelling	10053262
Swelling	10042674
Swelling face	10042682
Urticaria	10046735
Urticaria papular	10046750

Group D Terms	
Preferred Term	**Preferred Term Code**
Blood pressure decreased	10005734
Blood pressure diastolic decreased	10005737
Blood pressure systolic decreased	10005758
Cardiac arrest	10007515
Cardio-respiratory arrest	10007617
Cardiovascular insufficiency	10065929
Diastolic hypotension	10066077
Hypotension	10021097