Statistical Analysis Plan for Protocol NEOD001-301 Double-blind Phase

A Phase 3, Randomized, Multicenter, Double-Blind, Placebo-Controlled, Efficacy and Safety Study of Birtamimab Plus Standard of Care vs Placebo Plus Standard of Care in Mayo Stage IV Subjects with Light Chain (AL) Amyloidosis

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Term
6MWD	6-Minute Walk Test distance
6MWT	6-Minute Walk Test
ADA	Anti-drug antibody
AE	adverse event
AL	amyloid light chain
ANCOVA	analysis of covariance
ANS	autonomic nervous system
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
C	Celsius
CI	confidence interval
cm	centimeter
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DOB	date of birth
DMC	Data Monitoring Committee
DOIC	date of informed consent
eCRF	electronic case report form
ECG	electrocardiogram
ETD	early treatment discontinuation
g	gram
in	inches
IRT	Interactive Response Technology
ITT	Intent-to-Treat
kg	kilogram
KM	Kaplan-Meier
L	liter
lb	pounds
LLN	lower limit of normal

Abbreviation	Term
LS	least squares
LSLV	last subject last visit
m	meter
m^2	meters squared
MAR	missing at random
MCS	Mental Component Score (SF-36v2)
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mg/dL	milligrams per deciliter
MH	Mental Health (SF-36v2)
MI	Multiple Imputation
mL	milliliters
mmHg	millimeters of mercury
MNAR	missing not at random
nAb	neutralizing antibody
ng	nanogram
ng/L	nanograms per liter
NT-proBNP	N-terminal pro-brain natriuretic peptide
OLE	Open-label Extension
PCS	Physical Component Score (SF-36v2)
PE	physical examination
PEY	patient exposure years
PF	Physical Functioning (SF-36v2)
PK	pharmacokinetics
PT	preferred term
QT	measure of time between start of Q wave and end of T wave
SAE	serious adverse event
SD	standard deviation
SEM	standard error of the mean

Abbreviation	Term
SF-36v2	Short Form-36 version 2 Health Survey
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 describes the statistical methods to be implemented during the analyses of Study NEOD001-301 data collected within the scope of the Double-blind Phase of the study protocol. The purpose of this plan is to provide specific guidelines from which the analyses will proceed. Any deviations from these guidelines will be documented in the clinical study report (CSR). A statistical analysis plan for the Open-label Extension (OLE) Phase will be provided separately.

2. INFORMATION FROM THE STUDY PROTOCOL DOUBLE-BLIND PHASE

2.1. Study Objective

2.1.1. Primary Objective

The primary objective is to evaluate the efficacy of birtamimab plus standard of care compared to placebo plus standard of care when administered intravenously in Mayo Stage IV subjects with AL amyloidosis by assessing time to all-cause mortality.

The primary estimand is the difference in survival distributions of the time-to-all-cause mortality between treatment groups in all randomized Mayo Stage IV amyloid light chain (AL) amyloidosis subjects who received any amount of study drug.

2.1.2. Secondary Objectives

The secondary efficacy objectives include the evaluation of birtamimab plus standard of care compared to placebo plus standard of care on the following:

2.1.2.1. Change in Functional Response

Objective: Change from baseline to Month 9 in the 6-Minute Walk Test (6MWT) distance during the Double-blind Phase

Estimand: The median difference in 6MWT distance changes from baseline between treatment groups at Month 9 in all randomized subjects with Mayo Stage IV AL amyloidosis who received any amount of study drug.

2.1.2.2. Change in Health-Related Quality of Life

Objective: Change from baseline to Month 9 in health-related quality of life using the Short Form-36 questionnaire Version 2 (SF-36v2)

Estimand: The median difference in SF-36v2 physical component score (PCS) changes from baseline between treatment groups at Month 9 in all randomized subjects with Mayo Stage IV AL amyloidosis who received any amount of study drug.

2.1.3. Exploratory Objectives

[redacted].

2.2. Study Design

2.2.1. Overall Study Design

This study comprises a multicenter, global, randomized, double-blind, placebo-controlled, efficacy and safety evaluation in Mayo Stage IV subjects with AL amyloidosis (i.e., Double-blind Phase), followed by a long-term, open-label extension (i.e., Open-label Extension [OLE] Phase).

In the Double-blind Phase, newly diagnosed Mayo Stage IV subjects with AL amyloidosis will be randomized in a 2:1 ratio to birtamimab or placebo. The initial first-line chemotherapy regimen must include bortezomib.

[redacted]

Subjects will remain in the Double-blind Phase until its completion, which will occur when approximately [redacted] primary endpoint events (all-cause mortality) have been reached.

An interim analysis for time to all-cause mortality will be conducted when approximately [redacted] (or [redacted]) of the events have occurred. Using the O'Brien-Fleming group sequential methodology, the interim analysis will be conducted with a significance level of [redacted] and the final analysis will be conducted with a significance level of [redacted], maintaining an overall study significance level of [redacted].

Each visit will be denoted by its "month" and "day" such that the first study drug infusion 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). "Cycle" is reserved to denote administration of chemotherapy. Assessment and visit windows are described in the Schedule of Events for Double-blind Phase (Table 1).

If a subject discontinues study drug prior to the end of the study, the subject should have an Early Treatment Discontinuation (ETD) Visit within 28 to 35 days after the last study drug administration (Table 1). If they are willing to continue to participate in study visits, they will then have assessments every third month for the remainder of the Double-blind Phase per Appendix 1.

All adverse events (AEs) and serious adverse events (SAEs) are reported from initiation of first administration of study drug through 28 days after the last dose of study drug during the Double-blind Phase or until the End of Treatment (EOT)/ETD Visit, whichever is later. New SAEs occurring beyond the EOT/ETD Visit or >28 days after the last administration of study drug, whichever is later, will be reported to the Sponsor or its designee only if, in the judgment of the Investigator, the SAE is associated with any protocol intervention (related to study procedure) or previous study drug exposure.

[redacted] The subject's vital status (survival information) will be collected accordingly in the study database to ensure adequate capture of endpoint events.

When approximately [redacted] events have been reported, all subjects still on study treatment will be considered for entry into the OLE Phase.

2.2.2. Study Drug

Study drug consists of intravenous birtamimab or placebo. The birtamimab dose is 24 mg/kg; however, the maximum dose administered is not to exceed [redacted]. Therefore, subjects with a weight of [redacted] or greater will receive the maximum dose of [redacted]. The subject's weight

during Screening may be used for calculation of the first dose. Subsequent doses may be calculated based on the current weight at that visit, baseline weight, or the most recent visit where weight was collected, based on the site's institutional guidelines. A change of ±10% from the weight being used for dosing should trigger recalculation of the dose based on the new weight.

[redacted]

A separate placebo will not be provided for this study. Subjects who are randomized to the placebo group will be administered a [redacted] intravenous bag of 0.9% saline, which will look identical to the birtamimab infusion bag.

Please refer to the protocol for complete product details.

2.2.3. Randomization Methodology

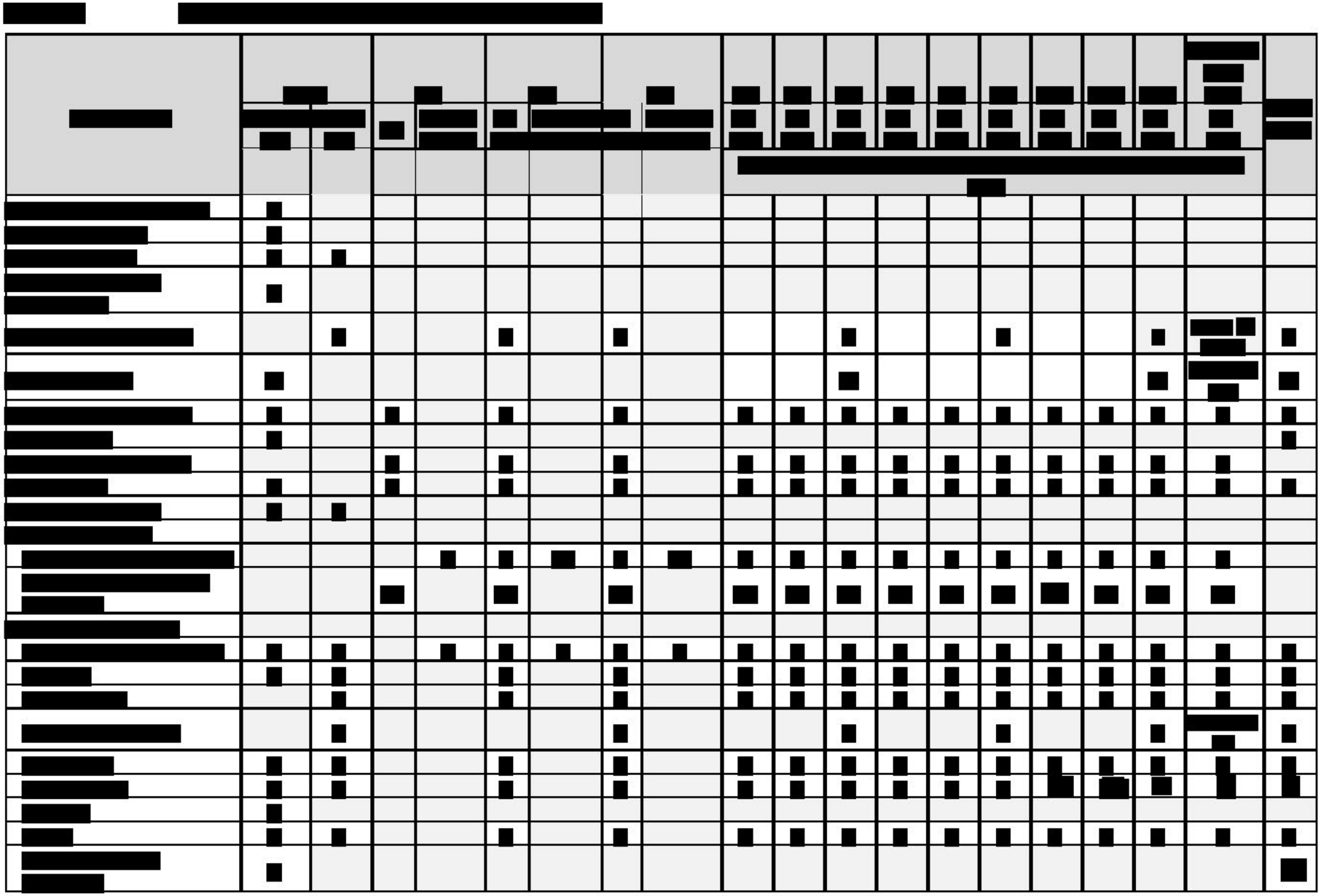
After a subject has completed all Screening requirements and meets all of the eligibility criteria, a Patient Eligibility Worksheet should be submitted within several days prior to Month 1-Day 1 for eligibility review and approval by the Medical Monitor or designee. If approved, randomization will be implemented through a phone call or via the Internet connection to an Interactive Response Technology (IRT) utilizing results from Screening assessments. Eligible subjects will be randomized in a 2:1 ratio into one of two arms, birtamimab 24 mg/kg or placebo.

[redacted]

Upon successful randomization, the Unblinded Pharmacist or their designee (henceforth collectively referred to as the Unblinded Pharmacy Staff) will be provided access to the treatment assignment. Approximately 220 subjects may be enrolled in the study (147 birtamimab, 73 placebo with a 2:1 randomization ratio).

2.2.4. Study Procedures

The schedule of assessments for Double-blind Phase, as outlined in the study protocol, is presented in Table 1.



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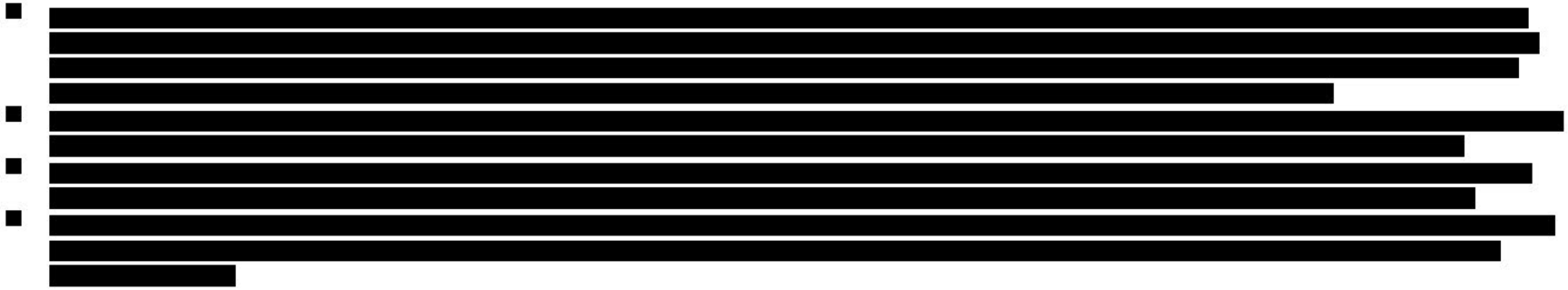

2.3. Study Endpoints

2.3.1. Primary Efficacy Endpoint

The primary efficacy endpoint is time to all-cause mortality.

For all-cause mortality, all deaths occurring after the first infusion of study drug (i.e. Month 1-Day 1) through the end of Double-blind phase will be included.

The following censoring rules will apply:

- Subjects who complete the Double-blind phase and are not known to have died will be censored at their last Double-blind phase assessment (visit, phone call or public record search) known to be alive.
- Subjects who withdraw from the Double-blind phase or are lost to follow-up prior to death during Double-blind phase will be censored at their last assessment (visit, phone call or public record search) where vital status was available.

2.3.2. Secondary Efficacy Endpoints

The following secondary efficacy endpoints are intended to evaluate response to treatment through the assessment of functional capacity and quality of life. The secondary endpoints, in order of priority are:

2.3.2.1. Change from Baseline to Month 9 in the 6-Minute Walk Test Distance (Meters)

The 6MWT is a test that requires a minimum walking length of 25 meters with no exercise equipment or advanced training for technicians. The walking track or area should be the same for all tests for a subject. Walking is an activity performed daily by all but the most severely impaired subjects. This test measures the distance that a subject can quickly walk on a flat, hard surface in a period of 6 minutes. The primary comparison will be at the Month 9 visit.

2.3.2.2. Change from Baseline to Month 9 in the Physical Component Score of the SF-36v2

The SF-36v2 is a 36-item self-report instrument that measures generic health-related quality of life in 8 specific dimensions plus one additional question that asks respondents to rate the amount of change experienced in their health in general (Maruish 2011; Appendix 2). It allows for the scoring of 2 component summary indices: the Physical Component Score (PCS) and the Mental Component Score (MCS). 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 United States (US) General Population. The standard deviation (SD) is 10 for all scales and both summary measures. The SF-36v2 will be scored using the algorithm provided by Optum, now QualityMetric, 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 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 Item Response Theory 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 7 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 applied to the calculation of the summary scores depends upon which particular scale score is missing from the eight-scale profile.

The secondary endpoint will include data from PCS score only, with the primary comparison at the Month 9 visit.

2.3.3. Exploratory Efficacy Endpoint

[redacted]

3. SAMPLE SIZE JUSTIFICATION

A two-sided log-rank test with a total of [redacted] events would achieve [redacted] power at a [redacted] significance level to detect a hazard ratio of [redacted] The hazard ratio of [redacted] is based on the post hoc analysis of Mayo Stage IV patients from the Phase 3 Study NEOD001-CL002, in which the birtamimab exponential hazard rate was [redacted] (corresponding to [redacted]% survival at 9 months) and the placebo exponential hazard rate was [redacted] (corresponding to [redacted]% survival at 9 months). The study will enroll approximately 220 subjects (147 birtamimab, 73 placebo with a 2:1 randomization ratio).

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. Pretreatment and on-treatment study days are numbered relative to the day of the first dose of study drug which is designated as Day 1. The preceding day is Day -1, the day before that is Day -2, etc.

All outputs will be incorporated into Microsoft Word rich text format (.rtf) files, sorted and labeled according to the International Council for Harmonisation 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 ITT or safety analysis population, as applicable, 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.

For continuous variables, the number of subjects, mean, SD, median, 25^{th} percentile (Q1), 75^{th} percentile (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 and standard error of the mean (SEM) 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 with the same decimal places as the point estimate, 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 98.0), while values <XX.5 will be rounded down to XX (e.g., 97.4 will round down to 97.0).

Time-to-event data will be summarized using Kaplan-Meier (KM) methodology using 25^{th}, 50^{th} (median), and 75^{th} percentiles with associated 2-sided 90% and 95% CIs (where estimable), as well as percentage of censored observations with rationale for censoring.

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, disease history, procedures, and AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA version 23.1 or newer). Concomitant medications including premedication and chemotherapy will be coded using World Health Organization (WHO, version Sep 2020 or newer) Drug Dictionary.

4.3. Definition of Baseline

To minimize the impact of variability in the 6MWT distance, the baseline for the 6MWT distance (meters) will be defined as the longest distance walked prior to first study drug infusion. If only one valid assessment is available prior to first study drug infusion, it will be used as the baseline value. The baseline for all other efficacy and safety parameters will be defined as the last non-missing assessment prior to the first study drug infusion.

4.4. Partial Dates

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

- Death (or Censoring) Date
  - For censoring of alive subjects, the last date that each subject was known to be alive will be identified as the latest 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 complete date, then the partial date will be imputed to equal the last known alive complete 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 complete date, then the partial date will be imputed to equal the last known alive complete date.
- Diagnostic Date
  - For missing day only – Day will be imputed as the first day of the month (i.e., 1).
  - For missing day and month – Day and month will be imputed as the first day of the year (i.e., 1 January).
- Start Dates (e.g., event date, AE onset date, start date of medication)
  - 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, and on or prior to the death date or last known complete date the patient was alive.

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 + 15 minutes. 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 recorded on the eCRF 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 – 5 minutes. 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.

4.5. Data Conventions

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

Quantitative laboratory tests containing less than (<) and/or 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 may be imputed and stored within the analysis datasets.

Variables (e.g., urine albumin/creatinine ratio) with a non-normal distribution that impacts the interpretation or validity of the planned analysis may have a data transformation applied (e.g., ln, $\log_{10}$). Only transformations that lead to clinically meaningful interpretations will be used.

4.6. 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 January 1 of the year of birth (*DOB*) to the specified date, e.g., date of informed consent (*DOIC*).

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

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

  height (cm) = height (in) × 2.54

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

  weight (kg) = weight (lb) / 2.205

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

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

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

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

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

  Change = post-baseline value – baseline value

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

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

4.7. Visit Windows

Each visit will be denoted by its "month" and "day" such that the first study drug (birtamimab or placebo) infusion 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 [redacted]

[redacted]). All visits, including scheduled visits, unscheduled visits, re-test, and ETD assessments, will be remapped to a scheduled visit for analysis purposes according to visit window as described in Table 2 and Table 3 below; the nominal visits will not be used for any by-visit analyses.

If multiple visits occur within a single visit window, unique assessments will be selected step-by-step as follows:

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. The most abnormal value is determined by taking the value that is the further from the lower limit of normal (LLN) or upper limit of normal (ULN).

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

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

	Target Study Day [a]	Analysis Window Study Day [a]	
		Low	High
Baseline[b]	1	Closest visit to Day 1, prior to first birtamimab/placebo dose	
Month 2	28	[redacted]	[redacted]
Month 3	56	[redacted]	[redacted]
Month x	28*[redacted]	[redacted]	[redacted]

[a] Study day will be calculated from first dose date.

[b] Baseline is defined Section 4.3.

Table 3 defines the visit windows for assessments taken at[redacted] intervals to be established with respect to relative day from the start of study drug.

Table 3: [redacted] Interval Visit Windows (Days)

Months	Target Study Day [a]	Analysis Window Study Day [a]	
		Low	High
Baseline[b]	1	Closest visit to Day 1, prior to first birtamimab/placebo dose [b]	
Month[redacted]	[redacted]	[redacted]	[redacted]
Month[redacted]	[redacted]	[redacted]	[redacted]
Month[redacted]	[redacted]	[redacted]	[redacted]

[a] Study day will be calculated from first dose date.

[b] Baseline is defined in Section 4.3.

"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.

5. ANALYSIS POPULATIONS

The [redacted] the Safety Population will include all randomized subjects with Mayo Stage IV AL amyloidosis who receive any amount of study drug (birtamimab or placebo). The [redacted] will be the primary population used for efficacy analyses, and patients will be analyzed according to the treatment assigned at randomization. The Safety Population will be the primary population used for safety analyses and patients will be analyzed based on the treatment received.

6. EXAMINATION OF SUBGROUPS

Subgroup analysis to examine the treatment effect for the primary endpoint will include, but is not limited to the following criteria:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Additional subgroup analyses based on baseline disease characteristics may be conducted as appropriate. Forest plot will be generated to visualize the subgroup analysis results. Important safety assessments such as TEAEs may be summarized by subgroups of interest.

7. STUDY POPULATION

7.1. Subject Disposition

Subject disposition will be summarized for all screened subjects and will include the number of subjects screened, the number screened but not randomized, the number randomized, the number randomized but not treated, the number in each subject population for analysis, the number who withdrew from study prior to completing the Double-blind phase and reason(s) for withdrawal, and the number who discontinued Double-blind phase treatment early and reason(s) for discontinuation of treatment.

A summary of randomization by region, country and site will be presented for the [redacted]. The randomization factors will be summarized and compared for IRT data and derived data.

Time on study in months will be calculated as (last known date of visit or successful phone call contact or date of death minus first infusion date plus one)/30.4375.

7.2. Demographics and Baseline Characteristics

Demographic variables will include the following:

- Age at informed consent
- Sex
- Race
- Ethnicity
- Region

Other baseline characteristics will include the following:

- Weight (kg)
- Height (cm)
- BMI (kg/m^2) including frequency of the following subgroups:
    - $<20, \geq 20 - <25, \geq 25 - <30, \geq 30$ kg/m^2

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

Demographics and baseline characteristics will be presented by treatment group and overall for the [redacted] and Safety Populations.

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

Baseline disease characteristics will be presented by treatment group and overall for the ITT population. No inferential statistical comparisons will be performed.

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

The following disease histories and baseline characteristics will be summarized:

- Age at AL amyloidosis diagnosis
- Duration (months) since AL amyloidosis diagnosis
- [redacted]
- Concurrent Monoclonal Gammopathy (yes/no)
- History of Familial Amyloidosis (yes/no/unknown)
- Organ involvement (liver, renal, ANS, other)
- Number of Non-cardiac Organ Involvements: descriptive and categorical (0, ≥1, ≥2, ≥3, ≥4 organs)
- Baseline N-terminal pro-brain natriuretic peptide (NT-proBNP)
- Baseline Troponin-T
- [redacted]
- Baseline 6MWT distance: [redacted]
- Baseline free light chains (FLC):
    - Ratio: descriptive and categorical (Low [redacted], Normal [redacted]), High ([redacted]))
    - Difference between involved and uninvolved free light chain (dFLC)
- [redacted]

7.4. Disease-Specific AL Symptoms

Disease-specific AL symptoms verbatim terms as recorded on the Disease-Specific Medical History eCRF will be mapped to preferred terms (PT) and system organ classes (SOC) using MedDRA.

Disease-specific AL symptoms will be presented in a by-subject data listing.

7.5. General Medical History

Verbatim terms on eCRFs will be mapped to PTs and SOCs using MedDRA.

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

7.6. Protocol Deviations

All protocol deviations will be collected by the clinical research associates.

Major protocol deviations are protocol deviations that might substantially affect the completeness, accuracy, and/or reliability of the study data or that might substantially affect a subject's rights, safety, or well-being. Important Protocol Deviations (IPDs) are a subset of major protocol deviations that especially and critically compromise study data and/or subject safety.

Important protocol deviations will be summarized by deviation category and treatment group using the ITT Population.

All major protocol deviations will be presented in a by-subject data listing.

7.7. Pretreatment, Prior Concomitant, and New Concomitant Medications

Verbatim terms on eCRFs will be mapped to Anatomical Therapeutic Chemical (ATC) class and Preferred Name using the WHO Drug Dictionary.

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

The concomitant medications (prior or new) will be summarized by treatment for the Safety population. Pretreatment medications, prior and new concomitant medications will be listed.

7.8. Chemotherapy

Chemotherapy regimens will be prescribed as per standard of care at the Investigator's discretion in accordance with study protocol. All chemotherapy recorded on the Prescribed Chemotherapy Regimens and Concomitant Chemotherapy Treatment Medications eCRFs will be listed. Section 9.1.3 details the analysis of concomitant chemotherapy.

8. EFFICACY ANALYSES

All efficacy analyses will use the [redacted]. All efficacy endpoints, recorded and derived, will be presented in by-subject data listings.

8.1. Adjustments for Covariates

For comparison of treatment groups with respect to median change from baseline to Month 9 based on [redacted]

8.2. Handling of Dropouts or Missing Data

At any point in the study, if a subject who received any amount study drug is unwilling to return to the study site for further visits but is willing to provide his/her health status (AEs if during treatment-emergent period, mortality, and hospitalizations) by phone, follow-up phone calls should be made to the subject or their caregiver, per protocol Sections 7.1.3 and 8.3. If a subject discontinues study drug prior to the end of the Double-blind Phase of the study but is willing to continue to participate in study visits, the subject should have an ETD Visit within 28-35 days after the last study drug administration and then have assessments performed every third month for the remainder of the Double-blind Phase. Vital status will be collected within legal and ethical boundaries for all enrolled subjects receiving any amount of study drug and will be searched in public sources. During the study close-out period, survival status will be collected within legal and ethical boundaries for all enrolled subjects who withdrew participation from the study. If vital status is determined, the subject will not be considered lost to follow-up and the vital status will be included in relevant analyses.

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

The following methods will be implemented to address missing data for the primary and secondary efficacy endpoint analyses.

8.2.1. Time-to-Event Endpoints

Subjects with no data after enrollment will be censored on Day 1 (first day of study drug dosing). Methods for handling missing data for time-to-event endpoints are included in the applicable study endpoint section because the censoring and event dates are specific to the events being analyzed.

8.2.2. Parametric Analyses

[redacted]

[redacted]

8.3. Interim Analyses and Data Monitoring Committee (DMC)

An interim analysis of time to all-cause mortality will be conducted when approximately [redacted] of the expected events [redacted] have occurred. The overall study significance level of [redacted] will be divided between the interim analysis ([redacted] and final analysis [redacted] O'Brien-Fleming group sequential methodology.

The primary objective of the independent DMC is to safeguard the interests of subjects in the study and to help ensure the integrity and credibility of the study. The DMC abides by the principles set forth in applicable regulatory guidance documents. The DMC is composed of individuals external to the study Sponsor, and those involved with organizing, conducting, and regulating the trial, and Investigators, and operates under the DMC's written Charter, which includes standard operating guidelines on its procedures and monitoring plans.

The DMC will conduct reviews of accumulating data from the study on a regular basis during the Double-blind Phase and will advise the Sponsor regarding the continuing safety of trial subjects and those yet to be recruited to the trial, as well as the continuing validity and scientific merit of the trial. It is possible that the DMC may advise the Sponsor to stop the study based on its review of the accruing data that indicate clear harm to subjects participating in the study.

The DMC will review the results of the interim analysis for efficacy (after approximately [redacted] events have occurred) and recommend whether the study should continue or be stopped for overwhelming efficacy.

In addition to the primary efficacy analysis in Section 8.6 , the following supportive analyses will be generated for interim data review:

- TFLs specified in the DMC charter for routine closed session DMC data review
- [redacted]
- [redacted]

If the superiority test is not significant (i.e., p-value from the primary analysis is greater than the interim alpha), DMC will inform the sponsor to continue the trial and plan to have final analysis occur when [redacted] events have been observed. No unblinded interim analysis data will be shared with the sponsor.

If the superiority test is successful (i.e., p-value from the primary analysis is less than the interim alpha), DMC will review complete interim analysis efficacy and safety data and may recommend declaration of early trial success if there is a clear difference in the efficacy profile of birtamimab and placebo indicative of overwhelming efficacy.

The DMC charter provides details of DMC meetings and interim data analysis review scope and decision-making strategy.

8.4. Multicenter Studies

The randomization is not stratified by site. Likewise, analyses of efficacy data will not be stratified by study site. The number and percentage of subjects randomized by geographical region and study site will be summarized by treatment group and for all subjects.

8.5. Multiple Comparisons/Multiplicity

For the primary efficacy analyses, the overall 2-sided level of significance will be controlled at [redacted] (two-sided) with alpha = [redacted] at the interim analysis and [redacted] at the final analysis using O'Brien-Fleming group sequential methodology. Secondary endpoints will not be tested at interim analysis. The hypothesis testing of key secondary endpoints will be conducted using a gatekeeping procedure based on a closed fixed-sequence test, provided the primary efficacy endpoint comparison is statistically significant at final analysis. If this comparison is not statistically significant, then the comparison of key secondary efficacy endpoints will be considered nominal, descriptive and exploratory. This procedure controls the study-wise type I error and is described below.

1. First, birtamimab and placebo will be compared with respect to the primary efficacy endpoint. If the comparison achieves statistical significance at the 2-sided [redacted] level in favor of birtamimab), then
2. Birtamimab and placebo will be compared with respect to median change from baseline to Month 9 in the 6MWT distance (meters) during the Double-blind Phase using the same alpha level as that for the primary endpoint analysis. If the comparison achieves statistical significance in favor of birtamimab, then
3. Birtamimab and placebo will be compared with respect to median change from baseline to Month 9 in the SF-36v2 PCS using the same alpha level as that for the primary endpoint analysis.

If at any step defined above, the comparison is not statistically significant, then the remaining comparisons in the stated hierarchy will be considered nominal, descriptive and exploratory. The study-wise type I error will be maintained with the above closed procedure.

8.6. Primary Efficacy Analysis

The primary efficacy endpoint is the time to all-cause mortality during the Double-blind Phase.

The primary estimand is the difference in survival distributions of the time-to all-cause mortality between treatment groups in all randomized Mayo Stage IV AL amyloidosis subjects who received any amount of study drug.

For all-cause mortality, all deaths occurring after the first infusion of study drug (i.e., Month1-Day 1) through the study's LSLV or follow-up phone call or public record search in the Double-blind Phase, whichever is later, will be included.

[redacted]

A sensitivity analysis using the [redacted]t may also be conducted. If, at the time of analysis (for both the interim analysis and the final analysis), any stratum of [redacted] has fewer than 5 deaths in either treatment arm, the unstratified analysis will be used as the primary analysis.

[redacted]

8.7. Secondary Efficacy Analyses

8.7.1. 6MWT Distance

The estimand for the 6MWT is the median difference in 6MWT distance change from baseline between treatment groups at Month 9 in all randomized subjects with Mayo Stage IV AL amyloidosis who received any amount of study drug.

This secondary efficacy analysis will test the following hypotheses:

- H0: The median change from baseline at Month 9 in 6MWT distance (meters) is equal between birtamimab and placebo treatment groups.
- H1: The median change from baseline at Month 9 in 6MWT distance (meters) is different between birtamimab and placebo treatment groups.

[redacted]

- [redacted]
- [redacted]

[redacted]

Descriptive statistics for 6MWT, change from baseline, and percent change from baseline will be presented by visit for each treatment group.

8.7.2. SF-36v2 PCS Score

The estimand for the SF-36v2 PCS is the median difference in SF-36v2 PCS change from baseline between treatment groups at Month 9 in all randomized subjects with Mayo Stage IV AL amyloidosis who received any amount of study drug.

This secondary efficacy analysis will test the following hypotheses:

- H0: The median change from baseline at Month 9 in SF-36v2 PCS score is equal between birtamimab and placebo treatment groups.
- H1: The median change from baseline at Month 9 in SF-36v2 PCS score is different between birtamimab and placebo treatment groups.

[redacted]

Descriptive statistics for SF-36v2 PCS scores, change from baseline, and percentage change from baseline will be presented by visit for each treatment group.

[redacted]

9. SAFETY ANALYSES

Safety analyses will be conducted using the Safety Population.

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

9.1. Extent of Exposure

9.1.1. Study Drug

The total patient exposure years (PEY) for each subject is defined as the time interval between the first dose and the last dose, inclusive, of study drug based on the subject's study drug administration information. One PEY is the equivalent of 1 subject exposed to study drug for 1 year. Two subjects who are exposed to study drug for half a year together contribute one PEY. The total PEY is the sum of the person exposure years of each subject in that treatment group. Duration of exposure is defined in months as (the date of the last infusion of study drug – the date of the first infusion of study drug + 1)/30.4375.

Study drug exposure summaries will include:

- The number of subjects exposed to birtamimab or placebo, the total PEY, and duration of exposure will be summarized using descriptive statistics. The number and percentage of subjects with exposure ≥ 6 months and ≥ 12 months will be summarized.
- Total number of infusions received will be determined for each subject by number of times the start time of drug infused is reported. If multiple infusion start times are reported on a single day, then only 1 infusion will be counted for that day. If the start time of drug infused is missing but total volume infused is greater than 0 mL, 1 infusion will be counted for that day. The number of infusions received will be summarized using descriptive statistics. In addition, cumulative number of subjects receiving infusions will be presented.

Infusion time will be summarized descriptively by treatment for the Safety Population. Categorical summary of infusion time may be presented.

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

9.1.2. Premedication

All subjects will be premedicated for each dose of study drug with 25 mg diphenhydramine (or an equivalent dose of a H1 antihistamine) and 650 mg acetaminophen (or an equivalent paracetamol dose) within 30 to 90 minutes prior to study drug administration. Pretreatment medications will be mapped to ATC class and Preferred Name using the WHO Drug Dictionary and listed.

9.1.3. Standard of Care Chemotherapy

All subjects will receive concomitant standard of care chemotherapy. The initial first-line chemotherapy regimen must include bortezomib, which must be administered subcutaneously on a weekly basis. Subsequent chemotherapy regimens may be prescribed as per standard of care at the Investigator's discretion (see protocol Section 6.5.3). The initial first-line chemotherapy regimen may also include daratumumab. The initiation of daratumumab treatment at

randomization is allowed at the discretion of the investigator; however, initiation at any other time during the study is prohibited (see protocol Section 6.8.2). Chemotherapy regimens including line of therapy, medication and dates administered will be listed. The standard of care therapy will be summarized by line of therapy and the regimen.

9.2. Adverse Events

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

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 the ETD / EOT Visit or 28 days after date of last dose, whichever is later.

Each AE summary will be displayed by treatment group. Summaries that are displayed by SOC and PT will be ordered by descending order of incidence of SOC and PT within each SOC in the birtamimab group.

The following listings will be presented by treatment group and subject:

- All AEs
- 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”)
- AEs leading to death (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)
- All AEs for subjects who received any dose of incorrect treatment, if applicable.

Additional AE listings may be generated as appropriate.

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.

9.2.1.2. Exposure-Adjusted Incidence Rates (EAIR)

Crude AE incidence will be corrected for differences in study drug exposure by using person-time in the denominator to calculate incidence rates. Adjusted incidence per 100 PEY is the number of subjects with an event for whom person-time is available divided by the total PEY and multiplied by 100. Each subject's PEY will be calculated as the last infusion date minus the first infusion date plus 1 divided by 365.25 days/year. One PEY is the equivalent of one subject exposed to study drug for one year. Two subjects who are exposed to study drug for half a year together contribute one PEY. The total PEY is the sum of the person exposure years of each subject in that treatment group.

9.2.2. Overall Summary of Adverse Events

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

- Any TEAE
- TEAE by maximum CTCAE Grade
- CTCAE Grade ≥3 TEAE
- Serious TEAE
- TEAE leading to death (outcome = "Fatal" or severity = CTCAE Grade 5)
- Chemotherapy-related TEAE
- TEAE due to disease progression
- Treatment-related TEAE
- Treatment-related serious TEAE
- Treatment-related TEAE of CTCAE ≥Grade 3
- Treatment-related TEAE leading to death
- TEAE leading to interruption of study drug
- TEAE leading to dose reduction of study drug
- TEAE leading to dose being held
- TEAE leading to prolongation of infusion time (>2.5 hours)
- Infusion-related reaction/hypersensitivity TEAE assessed by investigators
- TEAE leading to study drug withdrawal
- TEAE leading to study discontinuation

9.2.3. Treatment-Emergent Adverse Events

The crude subject incidences of TEAEs will be summarized by treatment group. In addition, the exposure-adjusted incidences of TEAEs will be summarized. The following summaries will be presented:

- Subject incidence of TEAEs by MedDRA SOC and PT
- Common TEAEs by MedDRA PT
- TEAEs by maximum toxicity grade and MedDRA PT
- Grade 3+ TEAEs by MedDRA PT
- Treatment-related TEAEs by MedDRA SOC and PT
- Treatment-related TEAEs by MedDRA PT
- Grade 3+ treatment-related TEAEs by MedDRA PT
- TEAEs leading to any dosing change by MedDRA PT

9.2.4. Serious Adverse Events and Deaths

The crude subject incidences of serious TEAEs and deaths will be summarized by treatment group. In addition, the exposure-adjusted 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 common serious TEAEs by MedDRA PT
- Subject incidence of treatment-related serious TEAEs by MedDRA SOC and PT
- Subject incidence of serious TEAEs by MedDRA PT and maximum toxicity
- TEAEs leading to death by MedDRA SOC and PT

In addition, a summary of death with causality (cardiac, non-cardiac, and unknown) will be presented.

9.2.5. Adverse Events Leading to Study Drug or Study Withdrawal

AEs leading to study drug withdrawal are those AEs where Action Taken with Study Treatment is checked as “Drug Discontinued”. The crude incidences of AEs leading to study drug withdrawal will be summarized by treatment group. The following summaries will be presented:

- Subject incidence of TEAEs leading to study drug withdrawal by MedDRA PT.
- Subject incidence of TEAEs leading to study discontinuation by MedDRA PT.

9.2.6. Infusion-Related/Hypersensitivity Adverse Events

The crude subject incidence of infusion-related reaction/hypersensitivity TEAEs assessed by investigators by MedDRA PT will be summarized by treatment group. This is a subset of the AEs where the question “Was the event an infusion-related reaction/hypersensitivity adverse event?” is checked “Yes”. In addition, the exposure-adjusted incidences of these TEAEs will be summarized.

9.3. Clinical Laboratory Evaluations

[redacted]

All clinical laboratory data will be presented in by-subject data listings using standard international (SI) system of units. In addition, separate listings will be presented for any subject with a postbaseline CTCAE Grade 3 or 4 laboratory value, or with a postbaseline value outside the normal range where CTCAE criteria cannot be applied to an analyte.

Absolute values, absolute changes, and percentage changes from baseline of chemistry, hematology, continuous urine parameters and other laboratory parameters will be summarized by treatment and visit. In addition, mean change from baseline will be summarized for the maximum and minimum post-treatment values and for the values at the EOT/ETD Visit (or last post-baseline visit if EOT/ETD visit is not available). Shift tables from baseline lab toxicity grade to the worst post-baseline grade will be presented for selected lab parameters. The number and percentage of subjects with CTCAE Grade ≥3 laboratory values will be presented. Boxplots may be generated for visualization of selected safety lab parameters.

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

- International normalized ratio (INR) ULN = 1.1
- Estimated glomerular filtration rate LLN = 90 mL/min/1.73m^2

9.3.1. Pregnancy Testing

All pregnancy test results will be provided in a by-subject data listing.

9.4. Weight and BMI

Weight (kg) and BMI (kg/m^2), defined as a subject's weight (kg) ÷ subjects squared height (meters), will be provided in a by-subject data listing.

9.5. Vital Signs

Vital sign parameters including temperature (°C), systolic and diastolic pressure (mmHg), heart rate (beats/min), and respiratory rate (breaths/min) will be presented in a data listing.

Absolute values, changes, and percentage changes from baseline of vital sign parameters will be summarized by treatment and visit, and also time point, as applicable.

9.6. Electrocardiograms

Electrocardiogram (ECG) measurements will be made in triplicate per protocol Section 7. ECG parameters include heart rate, time between 2 consecutive R waves [RR], PR interval, QRS duration, QT (uncorrected) interval, QT interval corrected by the Bazett's formula, and QT interval corrected by the Fridericia's formula.

Overall interpretation results for ECGs and the Investigator interpretation results are collected as normal, abnormal not clinically significant, and abnormal clinically significant.

All ECG results will be presented in by-subject data listings. Absolute values and changes from baseline of ECG parameters will be summarized by treatment and visit.

9.7. Physical Examination

Physical examination findings will be included in a data listing.

9.8. Immunogenicity Analyses

9.8.1. Anti-drug Antibody

Immunogenicity of birtamimab will be assessed by the presence of anti-birtamimab antibodies (anti-drug antibodies; ADA), which are antibodies that may be produced toward the drug by the body's immune system in response to drug treatment. Immunogenicity with the presence of confirmed positive ADA will be further characterized to assess whether those antibodies are neutralizing (neutralizing antibodies; nAb) with the potential to negatively impact therapeutic efficacy of birtamimab.

The ADA samples will undergo a screening test followed by a confirmatory test if screening result is positive. Positive ADA refers to a positive result from the confirmatory test. ADA positive samples will be further tested to determine the relative amount of ADA levels in a titer assay. A competitive plate-based assay will then be used to determine whether the ADAs that are detected are neutralizing.

A transient ADA response is defined as either of the following:

- A treatment-emergent ADA detected only at one postbaseline time point with the subject's last sampling time point being ADA negative, or
- A treatment-emergent ADA detected at 2 or more time points, with the first and last ADA-positive samples being separated by a period of <16 weeks (irrespective of any negative samples in between) and the subject's last sampling time point being ADA negative.

The Boosted ADA is defined as positive ADA at both baseline and post-baseline, with a titer at least 4-fold higher in the post-baseline sample(s). Missing titer values will not be imputed. Baseline assessment must be non-missing to assess boosted ADA status.

Treatment-emergent ADA is defined as a confirmed positive ADA result occurring after the first infusion of study drug, with a negative or missing ADA result at baseline. Treatment-emergent nAb is defined as post-baseline nAb with no nAb or negative nAb at baseline.

The following incidences (number and percentage of subjects) will be summarized by treatment group:

- Prevalence of ADAs as determined by positive ADA at any time over number of subjects with any ADA results (positive or negative)
- Positive neutralizing antibodies any time over number of ADA-positive subjects
- Pre-existing ADA (baseline positive) over number of subjects with any baseline ADA results

- Boosted ADA over number of subjects with pre-existing ADA.
- Pre-existing nAb (baseline positive) over number of subjects with pre-existing ADA
- Treatment-emergent ADA over number of subjects with a negative or missing baseline ADA result and any postbaseline ADA result.
- Treatment-emergent nAb over number of subjects with treatment-emergent ADA.
- Transient ADA over number of subjects with treatment-emergent ADA.

All treatment-emergent ADA responses will be further evaluated by use of ADA listings focused on subjects with treatment-emergent ADA detected at 2 or more timepoints or the last sampling timepoint being ADA positive.

A by-visit summary of the following will be provided:

- Number of subjects with any ADA results at each visit
- Number of subjects with confirmed positive ADA at each visit
- Number of subjects with neutralizing antibody at each visit

Line plots of ADA-positive subjects at any time, presenting titers over time in months, will be presented by treatment, birtamimab or placebo. The line plot will include baseline defined as Month 1 pre-dose and all-postbaseline assessments. Missing assessments will be represented by an open circle or a break in the line. Negative ADA assessments will be plotted as a titer value of 0.

9.8.2. ADA Impact on Pharmacokinetics, Efficacy and Safety

The PK concentration may be assayed if sufficient quantity/volume serum antibody samples are available for the PK analysis.

A listing of ADA results and available PK concentrations will be generated. Line plots of drug concentration by timepoint for subjects with treatment-emergent ADA and boosted ADA will be generated and compared to ADA-negative subjects. Summary of PK concentrations by visit may be generated for subjects with confirmed positive ADA results or negative ADA results.

An overall TEAE summary by treatment group and treatment-emergent ADA status will be provided. The primary efficacy analysis (time to all-cause mortality) will be conducted by treatment-emergent ADA status subgroup. Any further ADA impact on efficacy or safety may be evaluated, depending on incidences of treatment-emergent ADA.

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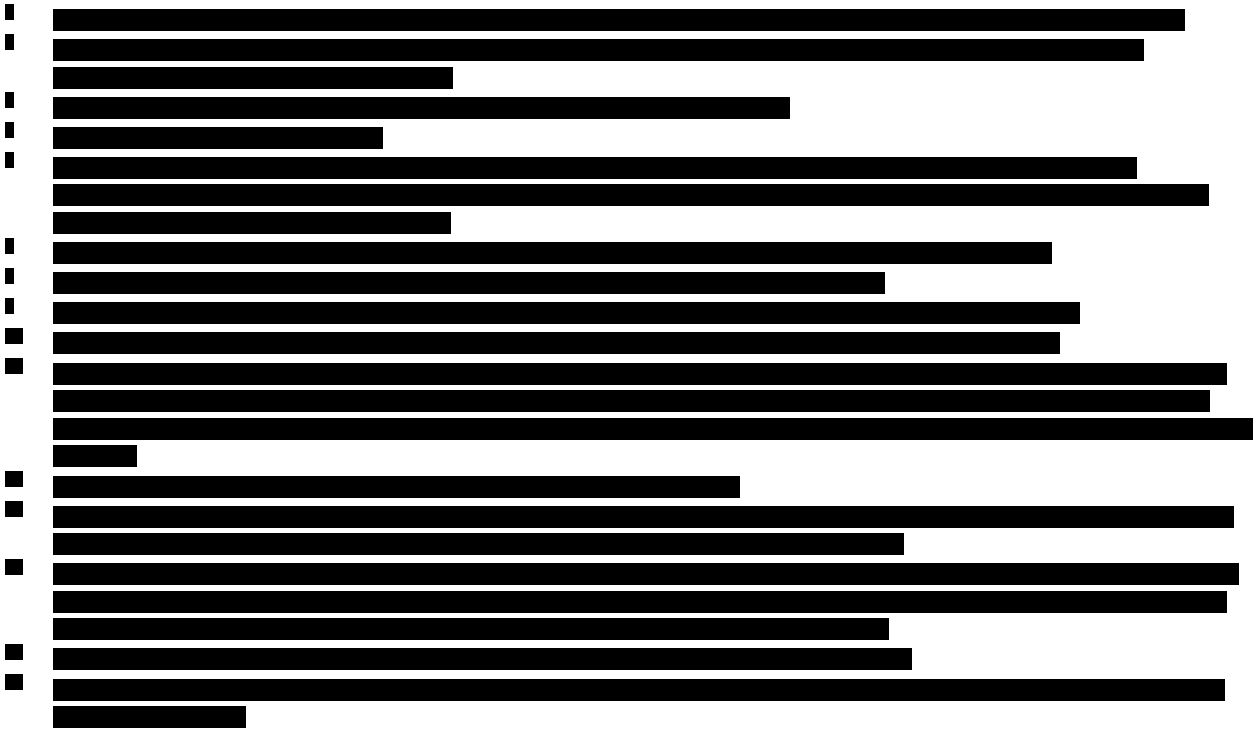
APPENDICES

[redacted]

[redacted]



Appendix 2: SF-36V2 Health Survey

Your Health and Well-Being

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

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

In general, would you say your health is:

Excellent
Very good
Good
Fair
Poor

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)? Not at all A little bit Moderately Quite a bit Extremely
This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks did you feel full of life? All of the time Most of the time Some of the time A little of the time None of the time
This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks have you been very nervous? All of the time Most of the time Some of the time A little of the time None of the time
This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks have you felt so down in the dumps that nothing could cheer you up? All of the time Most of the time Some of the time A little of the time None of the time

This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks have you felt calm and peaceful? All of the time Most of the time Some of the time A little of the time None of the time
This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks did you have a lot of energy? All of the time Most of the time Some of the time A little of the time None of the time
This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks have you felt downhearted and depressed? All of the time Most of the time Some of the time A little of the time None of the time

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

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

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

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

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

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

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

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

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

During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

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

How TRUE or FALSE is the following statement for you?

I seem to get sick a little easier than other people.

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

How TRUE or FALSE is the following statement for you?

I am as healthy as anybody I know.

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

How TRUE or FALSE is the following statement for you?

I expect my health to get worse.

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

How TRUE or FALSE is the following statement for you?

My health is excellent.

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

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Statistical Analysis Plan for the Open-label Extension Phase of Protocol NEOD001-301

A Phase 3, Randomized, Multicenter, Double-Blind, Placebo-Controlled, Efficacy and Safety Study of Birtamimab Plus Standard of Care vs Placebo Plus Standard of Care in Mayo Stage IV Subjects with Light Chain (AL) Amyloidosis

Investigational Product:	Birtamimab
US IND Number:	146070
EudraCT Number:	2021-000037-14
EU CT Number:	2024-511066-36-00
Protocol Version and Date:	Version 5.0, 27 March 2024
Phase:	Phase 3
Methodology:	Open-label
Sponsor:	Prothena Biosciences Limited 77 Sir John Rogerson's Quay, Block C Grand Canal Docklands, Dublin 2 D02 T804, Ireland
Sponsor Representative:	Prothena Biosciences Inc 1800 Sierra Point Parkway Brisbane, CA 94005 USA
Analysis Plan Version 1.0:	11 July 2025

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Term
AE	adverse event
AL	amyloid light chain
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DB	Double-blind
eCRF	electronic case report form
ETD	early treatment discontinuation
MedDRA	Medical Dictionary for Regulatory Activities
OLE	Open-label Extension
PEY	patient exposure years
PT	preferred term
SAE	serious adverse event
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event

1. INTRODUCTION

This document outlines the statistical methods to be implemented during the analyses of Study NEOD001-301 data collected within the scope of the Open-label Extension (OLE) phase of the study. The purpose of this plan is to provide specific guidelines from which the analyses will be proceeded. Any deviations from these guidelines will be documented in the abbreviated clinical study report (CSR).

The NEOD001-301 open-label phase was stopped early by the sponsor due to the outcome of the NEOD001-301 double-blind phase not meeting the primary endpoint. Therefore, the OLE analyses are limited to the following: Summary of disposition, exposure, and evaluation of Adverse Events (AEs) and serious adverse events (SAEs).

Changes from planned OLE phase analyses per protocol:

Primary rationale for the modifications: OLE phase was stopped early by sponsor.

2. STUDY INFORMATION

2.1. Primary Study Objective

The primary objective is to evaluate the long-term safety AEs of birtamimab plus standard of care in Mayo Stage IV subjects with amyloid light chain (AL) amyloidosis who participated in the OLE phase of NEOD001-301.

2.2. Overall Study Design and Study Drug

This study comprises a randomized, multicenter, global, double-blind, placebo-controlled, efficacy and safety evaluation in Mayo Stage IV subjects with AL amyloidosis (i.e., Double-blind Phase), followed by a long-term, open-label extension (i.e., OLE Phase).

After completion of the Double-blind Phase, eligible subjects may enter the optional OLE Phase, in which all subjects will receive open-label birtamimab treatment, regardless of Double-blind Phase randomized treatment assignment. Treatment in the OLE Phase will continue for an additional 24 months or until birtamimab is commercially available in a subject's country of residence, whichever occurs first (in accordance with country-specific regulations).

Each visit will be denoted by its "month" and "day" such that the first study drug infusion 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). "Cycle" is reserved to denote administration of chemotherapy.

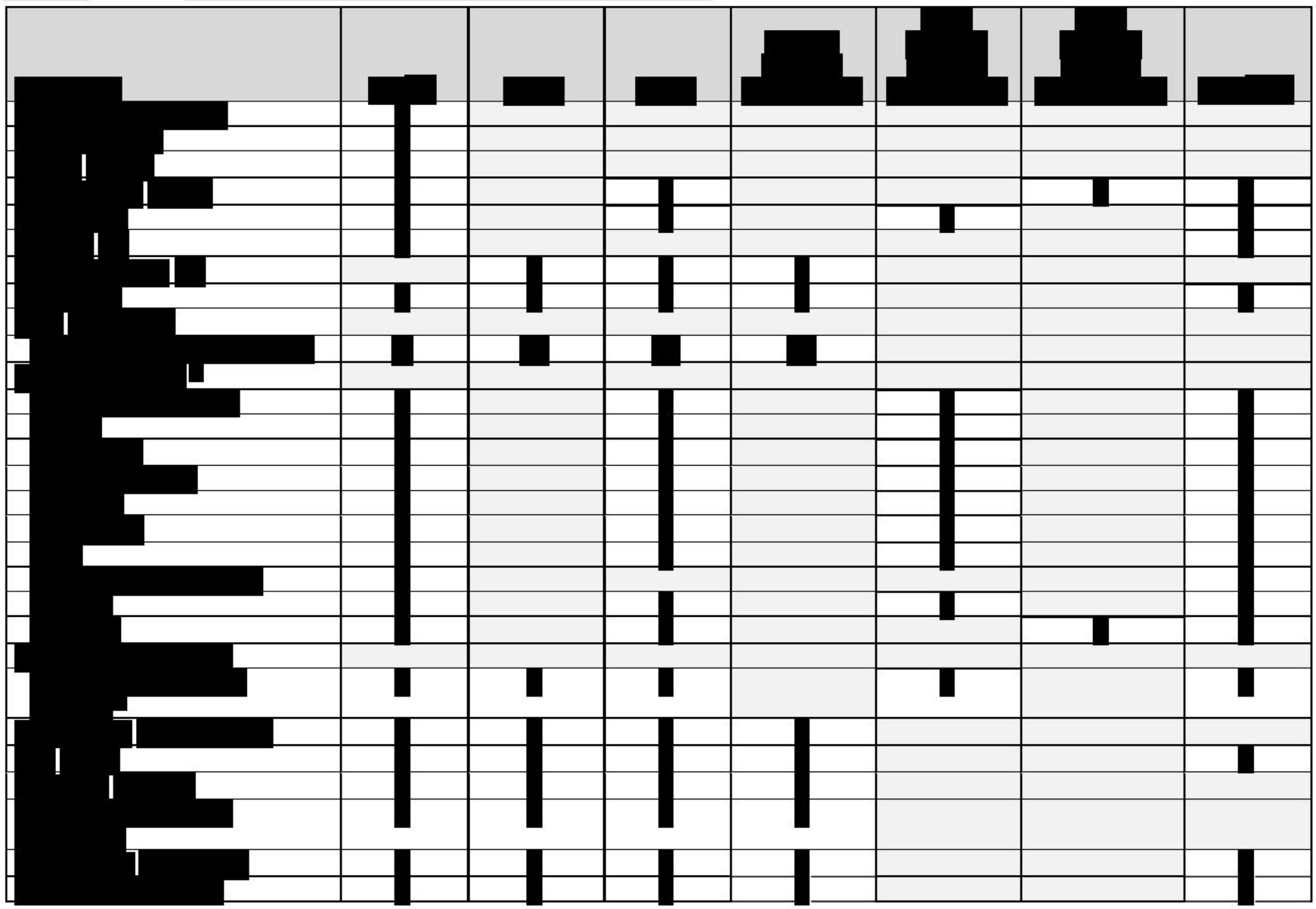
If a subject discontinues study drug prior to the end of the study, the subject should have an Early Treatment Discontinuation (ETD) Visit within 28 to 35 days after the last study drug administration (Table 1).

Study drug consists of intravenous birtamimab. The birtamimab dose is 24 mg/kg (not to exceed [redacted] The first dose of the OLE Phase should be calculated on the current weight at that visit. Subsequent doses may be calculated based on the current weight at that visit, baseline weight, or the most recent visit where weight was collected, based on the site's institutional guidelines. A change of ±10% from the weight being used for dosing should trigger recalculation of the dose based on the new weight.

[redacted].

For complete product details and complete study procedures details, please refer to the protocol.

The schedule of assessments is presented in Table 1.



3. GENERAL STATISTICAL METHODS

3.1. Reporting Conventions

Individual subject data obtained from electronic case report forms (eCRFs), 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. Pretreatment and on-treatment study days are numbered relative to the day of the first dose of study drug which is designated as Day 1. The preceding day is Day -1, the day before that is Day -2, etc.

All outputs will be incorporated into Microsoft Word rich text format (.rtf) files, sorted and labeled according to the International Council for Harmonisation 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 safety analysis population, as applicable, 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%.".

For continuous variables, the number of subjects, mean, SD, median, 25th percentile (Q1), 75th percentile (Q3), minimum, and maximum values will be presented. The precision of summary statistics, unless otherwise specified, will be as follows: mean, median, Q1 and Q3 to 1 more decimal place than the raw data, and SD and standard error of the mean to 2 decimal places more than the raw data. For derived variables, decimal places will be presented to the same number of decimal places as the underlying data. In general, the number of decimal places should not exceed 3 decimal places unless appropriate.

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 98.0), while values <XX.5 will be rounded down to XX (e.g., 97.4 will round down to 97.0).

3.2. Computing Environment

All descriptive statistical analyses will be performed using SAS statistical software Version 9.4 or higher, unless otherwise noted. AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA version 23.1 or newer).

3.3. Partial Dates

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

- Start Dates (e.g., event date, AE onset date, start date of medication)

  - For missing start day only – Day will be imputed as the first day of the month (i.e., 1) with the following exception: if the partial date falls in the same month and year as the date being used in the calculation (e.g., first infusion date, informed consent date), then the partial date will be imputed to equal the date being used for the calculation.
  - For missing start day and month – Day and month will be imputed as the first day of the year (i.e., 1 January) with the following exception: if the partial date falls in the same year as the date being used in the calculation (e.g., first infusion date, informed consent date), then the partial date will be imputed to equal the date being used for the calculation.
  - When applicable, imputed start dates must be prior to the stop date.
- Stop Dates (e.g., AE resolution date or stop date of medication)
  - For missing stop day only – Day will be imputed as the last day of the month (i.e., 28, 29, 30, or 31).
  - For missing stop day and month – Day and month will be imputed as the last day of the year (i.e., 31 December).
  - Imputed stop dates must be on or after the start date.

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

3.4. Data Conventions

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

3.5. 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

4. STUDY POPULATION

4.1. Subject Disposition

The Double-blind Safety Population will include all subjects who received any amount of study drug (birtamimab or placebo) in the Double-Blind Phase (NEOD001-301). This population will be displayed in disposition summary.

Subject disposition will be summarized for all subjects and will include:

- Number of subjects dosed in the Double-blind phase (DB Safety Population)
- Number of subjects Enrolled in the OLE phase (OLE Safety Population)
- Number Not Enrolled in the OLE phase
- Number who discontinued treatment early in the OLE phase and reason(s) for discontinuation of treatment as recorded on the OLE eCRF
- Number who withdraw from OLE phase prior to completing the study and reason(s) for withdrawal as recorded on the OLE eCRF
- Time in OLE Phase (Months)

  Time on study in months will be calculated as (last known date of visit or last known alive date or date of death minus first infusion date plus one)/30.4375.

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 for subjects enrolled in the OLE Phase. A listing of subjects not enrolled in the OLE phase will also be presented.

5. SAFETY ANALYSES

The OLE Safety Population will include all subjects who received any amount of birtamimab in the OLE phase of NEOD001-301.

Safety analyses will be conducted using the OLE Safety Population. Only safety data collected during the OLE phase will be included in any analysis.

5.1. Extent of Exposure

5.1.1. Study Drug

The total patient exposure years (PEY) for each subject is defined as the time interval between the first dose and the last dose during the OLE phase, inclusive, of study drug based on the subject's study drug administration information. One PEY is the equivalent of 1 subject exposed to study drug for 1 year. Two subjects who are exposed to study drug for half a year together contribute one PEY. The total PEY is the sum of the person exposure years of each subject. Duration of exposure is defined in months as (the date of the last infusion of study drug – the date of the first infusion of study drug + 1)/30.4375.

Study drug exposure summaries will include:

- The number of subjects exposed to birtamimab, the total PEY, and duration of exposure will be summarized using descriptive statistics. The number and percentage of subjects with exposure ≥ 6 months will be summarized.
- Total Number of Infusions received will be determined for each subject by number of times the start time of drug infused is reported. If multiple infusion start times are reported on a single day, then only 1 infusion will be counted for that day. If the start time of drug infused is missing but total volume infused is greater than 0 mL, 1 infusion will be counted for that day. The number of infusions received will be summarized using descriptive statistics. In addition, cumulative number of subjects receiving infusions will be presented.

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

5.2. Adverse Events

Verbatim terms on eCRFs will be mapped to preferred term (PT) and system organ class (SOC) using MedDRA. AEs will be reported, and severity will be categorized using the Common Terminology Criteria for Adverse Events (CTCAE).

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 the ETD / EOT Visit or 28 days after date of last dose, whichever is later.

Each AE summary will display the birtamimab group. Summaries that are displayed by SOC and PT will be ordered by descending order of incidence of SOC and PT within each SOC in the birtamimab group.

The following listings will be presented by subject:

- All AEs

- SAEs (this is a subset of the AEs where serious is marked as "Yes")
- AEs leading to death (this is a subset of the AEs where outcome is indicated as "Fatal" or the CTCAE grade is 5)

Additional AE listings may be generated as appropriate.

5.2.1. Overall Summary of Adverse Events

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

- Any TEAE
- TEAE by maximum Grade
- Grade 3 or higher TEAE
- Serious TEAE
- TEAE leading to death (outcome = "Fatal" or severity = Grade 5)
- Chemotherapy-related TEAE
- TEAE leading to study drug discontinuation
- TEAE leading to study withdrawal

5.2.2. Treatment-Emergent Adverse Events

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

- Subject incidence of TEAEs by MedDRA SOC and PT
- Common TEAEs by MedDRA PT
- TEAEs by maximum toxicity grade and MedDRA PT
- Grade 3 or higher TEAEs by MedDRA PT

5.2.3. Serious Adverse Events and Deaths

The crude subject 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 common serious TEAEs by MedDRA PT
- Subject incidence of serious TEAEs by MedDRA PT and maximum toxicity
- TEAEs leading to death by MedDRA SOC and PT

In addition, a summary of death with causality (cardiac, non-cardiac, and unknown) will be presented.

5.2.4. Adverse Events Leading to Study Drug or Study Withdrawal

AEs leading to study drug withdrawal are those AEs where Action Taken with Study Treatment is checked as "Drug Discontinued". The crude 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 discontinuation by MedDRA PT.
- Subject incidence of TEAEs leading to study withdrawal by MedDRA PT.