CLINICAL RESEARCH PROTOCOL

Study Title:	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
Protocol Number:	NEOD001-301
Version Number:	5.0
Investigational Product:	Birtamimab
US IND Number:	146070
EudraCT Number:	2021-000037-14
EU CT Number:	2024-511066-36-00
Indication:	Light Chain (AL) Amyloidosis
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
Sponsor's Responsible Signatory:	[redacted], MD, PhD
Coordinating Investigator:	[redacted], MD
Development Phase:	Phase 3
Date of Original Protocol:	26 January 2021
Date of Protocol Version 2.0:	10 January 2022
Date of Protocol Version 3.0:	30 November 2022
Date of Protocol Version 4.0:	18 October 2023
Date of Protocol Version 5.0:	27 March 2024

PROTOCOL APPROVAL PAGE

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Declaration of Sponsor

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

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

[redacted] Date

Chief Medical Officer

INVESTIGATOR SIGNATURE PAGE

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

Investigator Signature	Date
Investigator Name (Print)	

Please **sign, date, and return** this form to Prothena or its designee. Contact details will be provided to the Investigator. Please retain a copy for your study files.

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PROTOCOL SYNOPSIS

Title	A Phase 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
Study Phase	Phase 3
Indication	Birtamimab is indicated for the treatment of Mayo Stage IV patients with AL amyloidosis to reduce the risk of mortality.
Primary Objective	**Double-blind Phase** 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. **Open-label Extension Phase** To evaluate the long-term safety of birtamimab plus standard of care in Mayo Stage IV subjects with AL amyloidosis
Secondary Objectives	**Double-blind Phase** To evaluate birtamimab plus standard of care compared to placebo plus standard of care on the following: • Change from baseline to Month 9 in the 6-Minute Walk Test (6MWT) distance • Change from baseline to Month 9 in health-related quality of life using the Short Form-36 questionnaire Version 2 (SF-36v2) **Open-label Extension Phase** [redacted]
Exploratory Objectives	**Double-blind Phase** [redacted] **Open-label Extension Phase** To explore the long-term efficacy of birtamimab plus standard of care
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. 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). The primary efficacy endpoint is time to all-cause mortality during the Double-blind Phase. The distribution of survival times will be compared between treatment groups using a log-rank test. An interim analysis will be conducted when approximately 50% (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]. 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 (per Table 1 [Double-blind Phase] or Table 2 [OLE Phase]). If a subject who discontinues study drug during the Double-blind Phase is willing to continue to participate in study visits, they will then have assessments [redacted] for the remainder of the Double-blind Phase per Appendix 1. Vital Status Assessment Follow-up phone calls ([redacted]) should be made to all subjects (or their caregivers) who received a dose of study drug and are no longer receiving study drug nor completing assessments in the clinic, beginning approximately [redacted] months from the subject's last visit. The subject's vital status (survival information) will be collected.
Outline of Procedures	**Double-blind Phase** Subject screening will occur during the 28 days prior to the first administration of study drug on Month 1-Day 1. The Screening period may be extended up to a maximum of 7 days with prior approval by the Medical Monitor. Screening assessments are listed in Table 1. Individual test results that do not meet eligibility requirements may be repeated, with the exception of 6MWT; rescreening is allowed once per subject. Two Screening 6MWTs are required before the first administration of study drug. The first Screening 6MWT is required to be performed between Days -28 and -5, at least 4 days apart from the second Screening 6MWT, which should be performed within 3 days

	prior to Month 1-Day 1. The postbaseline 6MWTs may be administered on the same day as study drug administration and must be completed prior to study drug infusion. If all eligibility requirements are met, the subject will be randomized, Month 1-Day 1 assessments will be completed, and treatment will be initiated. 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). "Cycle" is reserved to denote administration of chemotherapy. Assessment and visit windows are described in the Schedule of Events (Table 1). All doses of study drug will be administered at the study site, starting on the day of randomization and then every 28 days [redacted] from the previous Month X-Day 1 visit until the End of Treatment (EOT)/ETD Visit. For Months [redacted] through [redacted] subjects will be assessed [redacted], although not all visits are required to be at the study site. For Month [redacted] and all subsequent months until the end of the study, subjects will only be required to return to the study site every 28 days for Day 1 dosing of study drug and study assessments. First-line chemotherapy must be a bortezomib-containing regimen, with bortezomib administered subcutaneously, weekly. The first administration of chemotherapy, including bortezomib, and daratumumab for those subjects who initiate daratumumab at randomization, will be administered after Month 1-Day 1 study drug administration ([redacted]) such that Month 1-Day 1 of the study will be equivalent to Cycle 1-Day 1 of chemotherapy. In addition to the visits outlined above, during the first cycle of chemotherapy, the subject must return to the study site for each weekly administration of bortezomib and for assessments prior to the administrations. During the second and third cycles of chemotherapy, bortezomib must be administered at the study site during the Month 2-Day 1, Month 2-Day 15, and Month 3-Day 1 visits (i.e., Cycle 2-Day 1, Cycle 2-Day 15, and Cycle 3-Day 1, respectively). If, for any reason in the opinion of the Investigator, the subject should continue to be seen weekly at the study site (e.g., toxicity that appears to exceed the anticipated side effects of the chemotherapy), then the other Cycle 2 and Cycle 3 weekly bortezomib administrations may be performed at the study site, as well. At the Investigator's discretion, if the subject is not experiencing any unanticipated or significant toxicity, the subject may be administered the Cycle 2-Days 8 and 22 and the Cycle 3 Days 8, 15 and 22 bortezomib by their local physician, rather than by the Investigator. Within 1 day prior to or on the day of each administration of bortezomib by the local physician, a Prothena-sponsored healthcare professional must obtain pre-dose vital signs and central laboratory samples in a homecare visit. However, if bortezomib is administered on a Monday (or there is an intervening

	holiday), then it is acceptable for the homecare visit to take place on the previous Friday. The number of cycles of first-line chemotherapy that is administered is at the discretion of the Investigator, and subsequent chemotherapy regimens may be prescribed as per standard of care at the Investigator's discretion. In the event that bortezomib doses are missed, the chemotherapy cycles may become misaligned with the monthly study drug dosing. In this case, the weekly visits during Months [redacted] through [redacted] should continue as described above in order to closely monitor subjects' health during the initial months of concomitant chemotherapy. Throughout the study, monthly doses of study drug should not be delayed or skipped due to adjustments that are made to chemotherapy dosing. Safety and efficacy assessments will be performed at each visit as outlined in the Double-blind Phase Schedule of Events (Table 1). [redacted] is not allowed during the Double-blind Phase. **Open-label Extension Phase** After the Double-blind Phase portion of the study, 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. The first visit (Month 1-Day 1) of the OLE Phase should be the same day as the Double-blind Phase EOT Visit but no later than 2 months after the last dose of randomized treatment, if feasible. If the first visit of the OLE Phase occurs on the same day as the Double-blind Phase EOT Visit or within 14 days of that visit, results of procedures performed at that visit may be used for the pre-infusion procedures for the first visit of the OLE Phase. All doses of study drug will be administered at the study site, starting at the first visit of the OLE Phase and then every 28 days [redacted] until the OLE Phase EOT/ETD Visit. During the OLE Phase, chemotherapy regimens (including daratumumab) should be prescribed per standard of care at the Investigator's discretion, [redacted]. Safety and efficacy assessments will be performed as outlined in the OLE Phase Schedule of Events (Table 2).
Number of Sites and Subjects	This is a multicenter, global study in approximately 120 centers. Approximately 220 subjects may be enrolled in the study, with approximately 147 and 73 subjects per arm (birtamimab and placebo, respectively).
Estimated Study Duration	The Double-blind Phase of the study is event-driven and will continue until approximately [redacted] primary endpoint events of all-cause mortality have occurred. All subjects who discontinue treatment during the Double-blind Phase will be followed until the last primary endpoint event has occurred. The estimated overall Double-blind Phase duration is approximately 42 months, including

	the screening, enrollment, treatment period, and postdose follow-up for subjects not entering the optional OLE Phase. For subjects who enter the OLE Phase, treatment will continue for an additional 24 months or until birtamimab is commercially available in the subject's country of residence, whichever occurs first (in accordance with country-specific regulations). For subjects not transitioning to commercially available birtamimab treatment, a postdose follow-up will occur 28 to 35 days after the last study drug administration. The estimated overall study duration is approximately 69 months, including the screening, enrollment, double-blind and open-label treatment periods, and postdose follow-up.
Summary of Subject Eligibility Criteria	**Inclusion Criteria** (subjects must meet ***all*** of the following criteria to be eligible for participation in the Double-blind Phase of the study): 1. Aged ≥18 years and legal age of consent according to local regulations 2. Newly diagnosed and AL amyloidosis treatment naive 3. [redacted] 4. Confirmed diagnosis of AL amyloidosis by the following: • [redacted] **AND** • [redacted] 5. If the subject meets any of the following: • [redacted] • [redacted] • [redacted] **AND** [redacted] **THEN** [redacted] **AND**

[redacted]

6. Cardiac involvement as defined by ***all*** of the following:
   - [redacted]
   - [redacted]
7. Confirmed Mayo Stage IV as defined by:
   - N-terminal pro-brain natriuretic peptide (NT-proBNP) ≥1800 pg/mL and
   - Troponin-T ≥0.025 ng/mL (mcg/L) or high sensitivity cardiac troponin T ≥40 ng/L and
   - Difference between involved and uninvolved free light chain ≥18 mg/dL
8. Planned first-line chemotherapy contains bortezomib administered subcutaneously weekly
9. [redacted]
   - [redacted]
   - [redacted]
   - [redacted]
   - [redacted]
   - [redacted]

	• [redacted] • [redacted] • [redacted] 10. [redacted] 11. [redacted] 12. [redacted] 13. [redacted] 14. Ability to understand and willingness to sign an informed consent form (ICF) prior to initiation of any study procedures To be eligible for the OLE Phase of the study, subjects must not have discontinued treatment in the Double-blind Phase and must meet the following criteria at the time of entry into the OLE Phase: 1. WOCBP must have a negative pregnancy test and must agree to use highly effective contraception through 90 days following last study drug administration 2. Male subjects must be surgically sterile or agree to use highly effective contraception through 90 days following last study drug administration 3. Ability to understand and willingness to sign an ICF prior to initiating the OLE Phase *Note: Patient screening in France will be reviewed by the French National Amyloidosis Reference Center in accordance with local requirements.* **Exclusion Criteria** (subjects must meet ***none*** of the following criteria to be eligible for the Double-blind Phase of the study):

	1. Non-AL amyloidosis 2. NT-proBNP >8500 pg/mL 3. Meets the International Myeloma Working Group (IMWG) definition of multiple myeloma, ***except*** for malignancy biomarker of involved/ uninvolved serum free light chain ratio ≥100 (Appendix 3). In France, the criterion also includes confirmed symptomatic multiple myeloma. 4. Subject is eligible for ***and*** plans to undergo ASCT or organ transplant during the study 5. Symptomatic orthostatic hypotension that in the medical judgment of the Investigator would interfere with the subject's ability to safely receive treatment or complete study assessments 6. Myocardial infarction, uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic (ECG) evidence of acute ischemia, within 6 months prior to the Month 1-Day 1 Visit 7. Severe valvular stenosis (e.g., aortic or mitral stenosis with a valve area <1.0 cm^2) or severe congenital heart disease 8. [redacted] 9. [redacted] 10. [redacted]

11. Prior treatment with hematopoietic growth factors, transfusions of blood or blood products within 1 week of Month 1-Day 1
12. Prior radiotherapy within 4 weeks of Month 1-Day 1
13. [redacted]
14. [redacted]
    - [redacted]
    - [redacted]
    - [redacted]
    - [redacted]
15. [redacted]
16. [redacted]
17. Prior treatment with plasma cell-directed chemotherapy, birtamimab, daratumumab, 11-1F4, anti-serum amyloid P antibody, doxycycline for amyloid, or other investigational treatment directed at amyloid
18. [redacted]
19. [redacted]
20. [redacted]

	21. [redacted] 22. [redacted] 23. Waldenström's macroglobulinemia and/or immunoglobulin M monoclonal gammopathy A subject will be excluded from the OLE Phase of the study if any of the following criteria are met at the time of entry into the OLE Phase: 1. Any medical condition or clinically significant abnormality on physical, neurological, laboratory, vital signs, or ECG examination that precludes treatment with birtamimab or participation in the study, in the medical judgment of the Investigator 2. Symptomatic orthostatic hypotension that in the medical judgment of the Investigator would interfere with subject's ability to safely receive treatment or complete study assessments. 3. History of Grade ≥3 infusion-related AEs during the Double-blind Phase or hypersensitivity to birtamimab 4. Unable or unwilling to adhere to the study-specified procedures and restrictions 5. Planning to receive any other investigational treatment during the study
Drug, Drug Dosage and Formulation	**Study Drug:** During the Double-blind Phase, study drug consists of birtamimab (24 mg/kg) or placebo. [redacted] During the OLE Phase, study drug consists of birtamimab (24 mg/kg), which will be supplied and prepared in the same manner as in the Double-blind Phase. In both the Double-blind and OLE Phases, study drug will be administered once every 28 days as an initial [redacted] minute intravenous infusion, including flush. If the subject tolerates the initial infusion, subsequent infusions may be administered over [redacted] minutes. The length of the infusion may be extended over a

	longer period of time if and when it is clinically indicated. [redacted] **Premedication:** [redacted] **Standard of Care Chemotherapy:** All subjects will receive concomitant standard of care chemotherapy, which must include bortezomib administered subcutaneously on a weekly basis for the initial, first-line chemotherapy regimen. Subsequent chemotherapy regimens may be prescribed as per standard of care, at the Investigator's discretion. Antiviral prophylaxis is required. The initiation of daratumumab treatment at randomization is allowed at the discretion of the Investigator; initiation at any other time during the Double-blind Phase is prohibited. [redacted]
Control Group	Normal saline will be used as the placebo control.
Route of Administration (Study Drug)	Intravenous infusion
Primary Efficacy Endpoint	Time to all-cause mortality during the Double-blind Phase
Secondary Efficacy Endpoints	Change from baseline to Month 9 of the Double-blind Phase in the 6MWT distance (meters) Change from baseline to Month 9 of the Double-blind Phase in the Physical Component Summary (PCS) score of the SF-36v2
Exploratory Efficacy Endpoints	[redacted] • [redacted] • [redacted] • [redacted]
Safety Endpoints	[redacted]
Statistical Considerations	**Analysis Populations** [redacted] The Safety Population will be the primary population used for the Double-blind Phase safety analyses. The OLE Population will include all subjects who

receive at least 1 dose of study drug in the OLE Phase and will be used for analyses of OLE Phase data.

Efficacy Analyses

Interim Analysis – An interim analysis of time to all-cause mortality during the Double-blind Phase will be conducted when approximately 50% (or [redacted]) of the events have occurred. Using the O'Brien-Fleming group sequential methodology, the overall significance level of 0.10 will be divided between the interim analysis (p< [redacted]) and final analysis (p< [redacted].

An independent Data Monitoring Committee (DMC) will review data on a regular basis at selected intervals to ensure that birtamimab is safe and well tolerated. The DMC will also evaluate the results of the interim analysis and determine if the Double-blind Phase can be stopped early for overwhelming efficacy. The guidelines for the DMC operations will be defined in a separate DMC Charter.

Primary Analysis – The primary endpoint is time to all-cause mortality during the Double-blind Phase. For all-cause mortality, all deaths occurring after the first infusion of study drug (i.e., Study Day 1) through the last subject last visit, follow-up telephone call, or public record search in the Double-blind Phase, whichever is later, will be included.

The distribution of the time to all-cause mortality will be summarized using the Kaplan-Meier method. [redacted]

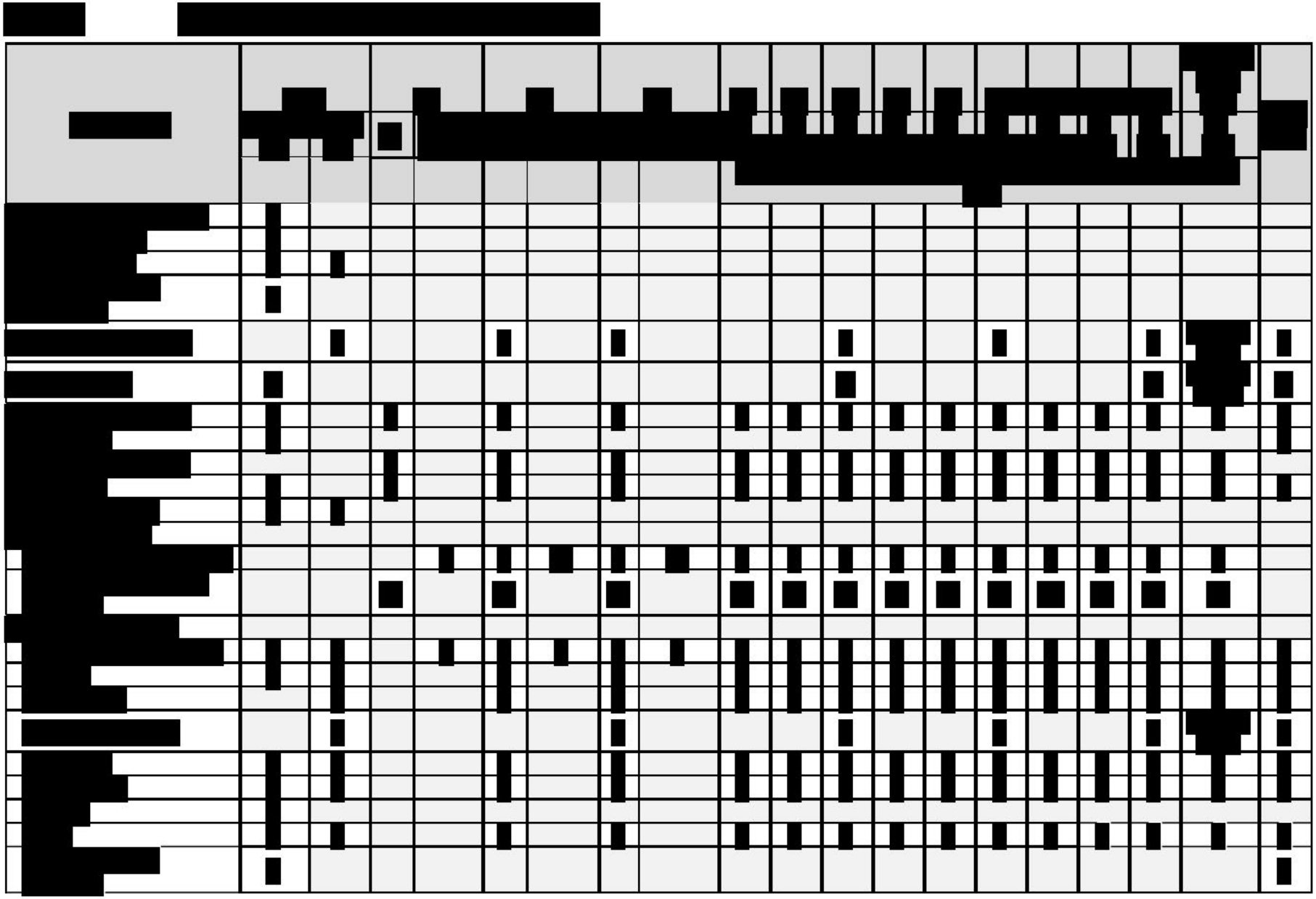
Using a log-rank test, birtamimab and the placebo control will be compared at a significance level of [redacted] at the final analysis.

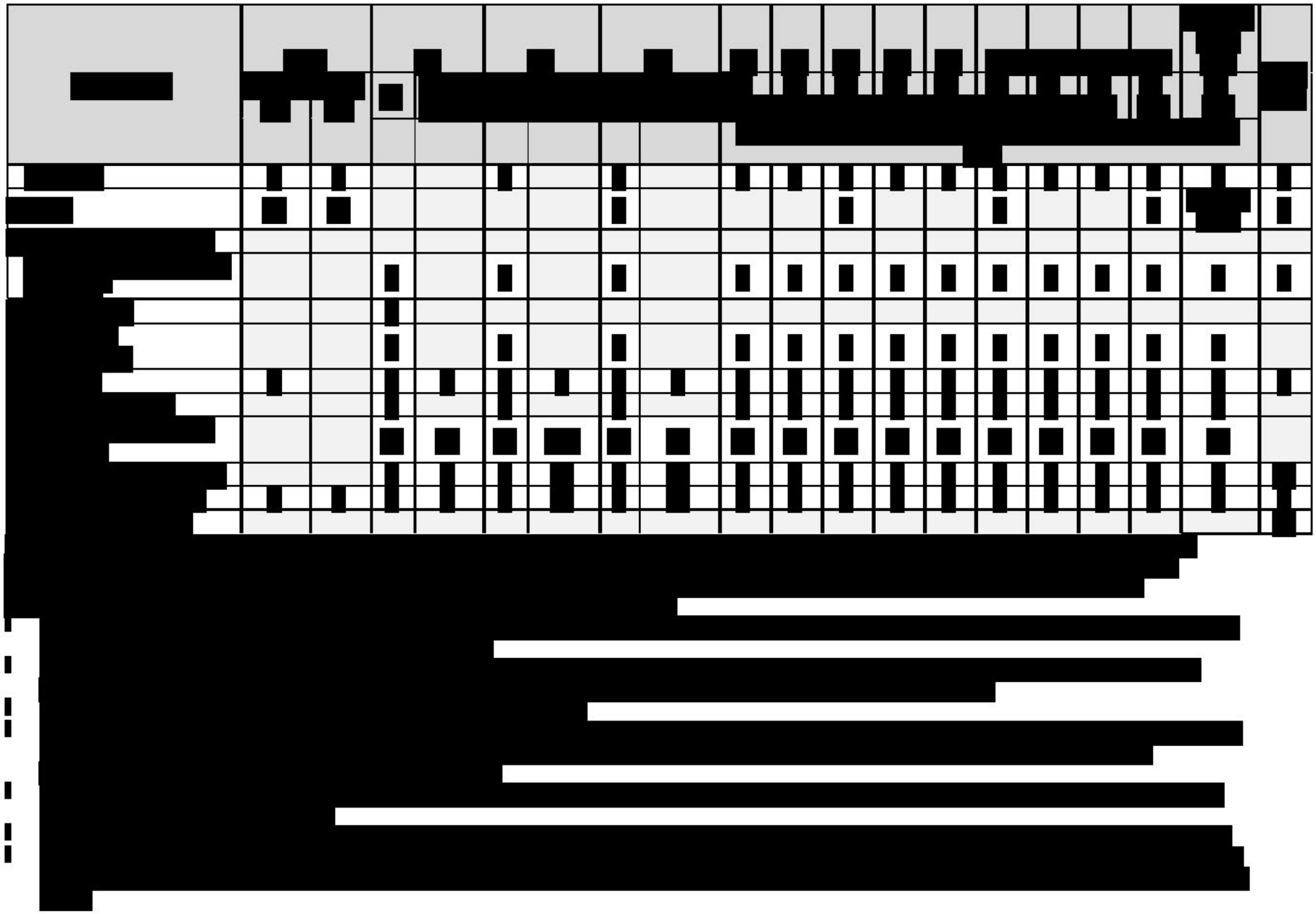
Secondary Efficacy Analyses – The following secondary endpoints will be evaluated:

- Change from baseline to Month 9 of the Double-blind Phase in the 6MWT distance (meters)
- Change from baseline to Month 9 of the Double-blind Phase in the PCS score of the SF-36v2

[redacted]

	Safety Analyses [redacted] ***Adverse Events*** – AEs will be coded using the Medical Dictionary for Regulatory Activities. Summary tables of treatment-emergent AEs (TEAEs) will be provided for each study phase. The incidence of TEAEs will be tabulated by system organ class and preferred term, and by severity and relationship to treatment. Tables of TEAEs leading to study drug discontinuation and treatment-emergent serious adverse events (SAEs) will be provided. NCI-CTCAE will be used for grading severity of AEs and laboratory values. ***Clinical Laboratory Evaluations*** – Descriptive statistics summarizing central laboratory data will be presented for all study visits. Changes from baseline to each study visit will also be summarized. 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. [redacted] **Immunogenicity** Serum anti-birtamimab antibody data for each study phase will be summarized and listed. [redacted] **Determination of Sample Size** [redacted] The study will enroll approximately 220 subjects (147 birtamimab, 73 placebo with a 2:1 randomization ratio).
Sponsor	Prothena Biosciences Limited





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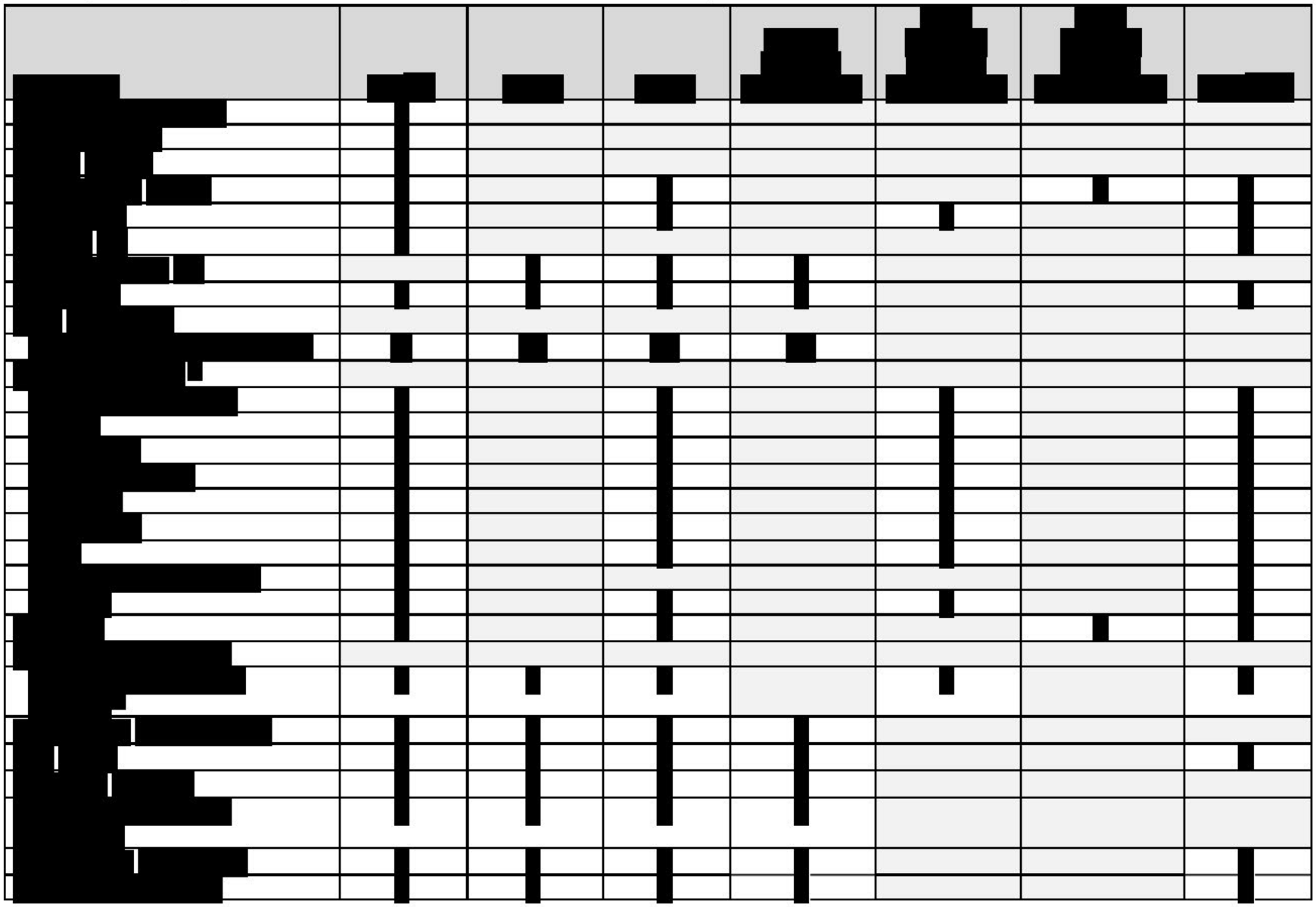

18 [redacted]

GLOSSARY OF TERMS

Abbreviation/Acronym	Definition
AA	amyloid A
AE	adverse event
AL	amyloid light chain
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
BP	blood pressure
[redacted]	[redacted]
[redacted]	[redacted]
CFR	Code of Federal Regulations
CI	confidence interval
[redacted]	[redacted]
dFLC	difference between involved and uninvolved free light chain
DMC	Data Monitoring Committee
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
[redacted]	[redacted]
EMA	European Medicines Agency
EOI	end of infusion
EOT	End of Treatment
ETD	Early Treatment Discontinuation
EU	European Union
FDA	Food and Drug Administration

Abbreviation/Acronym	Definition
GCP	Good Clinical Practice
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
HR	heart rate
ICF	informed consent form
ICH	International Council for Harmonisation
[redacted]	[redacted]
IMWG	International Myeloma Working Group
INR	international normalized ratio
IRB	Institutional Review Board
[redacted]	[redacted]
IXRS	Interactive Voice and Web Response System
[redacted]	[redacted]
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NT-proBNP	N-terminal pro-brain natriuretic peptide
[redacted]	[redacted]
OLE	Open-label Extension (Phase)
PCD	plasma cell dyscrasia
PCS	Physical Component Summary
PE	physical examination
PK	pharmacokinetic(s)
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
SAE	serious adverse event
SAP	statistical analysis plan

Abbreviation/Acronym	Definition
sFLC	serum-free light chain
SF-36v2	Short Form-36 questionnaire Version 2
SUSAR	suspected unexpected serious adverse reaction
6MWT	6-Minute Walk Test
TEAE	treatment-emergent adverse event
TRIAD	Transgenic Rapidly Inducible Amyloid Disease
[redacted]	[redacted]
ULN	upper limit of normal
US	United States
USP	United States Pharmacopeial Convention
[redacted]	[redacted]
WOCBP	women of childbearing potential

1. INTRODUCTION

1.1. Light Chain (AL) Amyloidosis

Systemic amyloidoses are a complex group of diseases caused by tissue deposition of misfolded proteins. The most common type, AL amyloidosis, is caused by amyloid deposits composed of insoluble light chain aggregates that infiltrate multiple organs and progressively affect organ structure and function. Soluble light chain aggregates have been shown in vitro to cause cellular toxicity and may be involved in the pathogenesis of AL amyloidosis. Approximately 75% of patients with AL amyloidosis present with 1 or 2 major organ systems involved (e.g., cardiac, renal, gastrointestinal tract, hepatic, autonomic nervous system, peripheral nervous system, soft tissues) while 25% of patients present with more than 2 systems involved (Palladini 2005; Gertz 2010). AL amyloidosis is most commonly associated with cardiac and/or renal dysfunction, with overt restrictive cardiomyopathy observed in approximately 50% to 70% of all cases, and subclinical cardiac involvement detected in almost every case on endomyocardial biopsy or at autopsy (Falk 2010; Siddiqi 2018; Shams 2022). In a study examining morbidity and mortality in patients with AL amyloidosis compared with matched disease-free controls within the Medicare population, common individual comorbidities for patients with AL amyloidosis were congestive heart failure (36.1% in patients with AL amyloidosis compared to 11.2% in controls), cerebrovascular disease (27.7% versus 16.1%, respectively), chronic pulmonary disease (37.8% versus 22.5%, respectively), moderate or severe liver disease (29.7% versus 10.2%, respectively), renal disease (35.7% versus 13.8%, respectively), diabetes without chronic complications (42.6% versus 29.2%, respectively), and malignancy/lymphoma/leukemia (35.7% versus 15.1%, respectively). Furthermore, hypothyroidism (cases: 32.1% versus controls: 22.2%) and hyperlipidemia (77.5% versus 65.6%, respectively) were common among Medicare beneficiaries with newly diagnosed AL amyloidosis (Quock 2018).

AL amyloidosis is a rare disease with an estimated incidence between 3 to 14 cases per million persons per year, which translates to approximately 30,000 to 45,000 patients in the United States (US) and European Union (EU). Overall, there are approximately 12,000 patients living with AL amyloidosis in the US (Hemminki 2012; Quock 2018). Patients with AL amyloidosis have a poor prognosis and median survival is estimated to range from 6 months to 3 years depending on the specific patient population and data assessed (Kyle 1992; Goodman 2006; Palladini 2016; Weiss 2016). The outcome of patients with AL amyloidosis is highly dependent on the spectrum and severity of organ involvement, especially cardiac involvement, which is the main determinant of survival (Milani 2018). Global longitudinal strain (GLS), measured by echocardiogram, was shown to be an independent predictor of overall survival in patients with AL amyloidosis (Buss 2012; Chuy 2020; Salinaro 2017). Patients who are categorized as Mayo Stage IV, defined as N-terminal pro-brain natriuretic peptide (NT-proBNP) ≥1800 pg/mL, Troponin-T ≥0.025 ng/mL and difference between involved and uninvolved free light chain (dFLC) ≥18 mg/dL, are at high risk for early death, with an overall median survival of 5.8 months and a 5-year survival rate of 14% (Kumar 2012).

AL amyloidosis has 2 important disease components. The first component is the plasma cell dyscrasia (PCD), which results in the overproduction of immunoglobulin light chain, and the second component is the impact of the soluble and insoluble amyloid on organ structure and function, leading to the clinical manifestations of the disease. There are currently no approved

treatments for AL amyloidosis that have been shown to reduce the risk of mortality in Mayo Stage IV patients with AL amyloidosis. The current standard of care for patients is aimed at reducing or eliminating the bone marrow disorder, i.e., the PCD. The most aggressive treatment options include autologous stem cell transplant (ASCT) and high-dose chemotherapy for those patients who can tolerate it. Other treatment regimens include combinations of drugs often used to treat hematological malignancies including melphalan, prednisone, dexamethasone, immunomodulatory drugs (e.g., thalidomide, lenalidomide), and proteasome inhibitors (e.g., bortezomib) in an attempt to reduce light chain production. Daratumumab, in combination with bortezomib, cyclophosphamide, and dexamethasone, has recently been approved by the US Food and Drug Administration (FDA) and other regulatory authorities, including European Medicines Agency (EMA), and Pharmaceuticals and Medical Devices Agency (PMDA) for the treatment of AL amyloidosis. However, there are no currently approved treatments for AL amyloidosis that directly target potentially toxic forms of the soluble and insoluble amyloidogenic light chain aggregate.

1.2. Rationale for the Clinical Study

Unlike other hematologic disorders such as multiple myeloma, the morbidity and mortality of AL amyloidosis is almost entirely related to organ dysfunction and not hematologic parameters. One of the major determinants of prognostic outcome in patients with AL amyloidosis is the extent of cardiac involvement; 75% of the deaths are due to cardiac amyloidosis (Merlini 2011). The process of amyloid formation results in cellular injury, tissue damage, and organ dysfunction through mechanisms that are not completely understood. Because the currently available treatment options are limited to treatment for the PCD component of the disease, the rate of organ function improvement or stabilization ("organ response") after achieving hematologic response from chemotherapy regimens is highly variable, ranging from 25% to 78% based on published information (Cohen 2007; Michael 2010; Cibeira 2011). Furthermore, the incidence of treatment-related mortality following high dose melphalan and ASCT was 13% within the first 100 days in patients with AL amyloidosis (Skinner 2004) and with the greatest mortality in patients with cardiac involvement. Though the ASCT approach is effective and results in rapid hematologic response, the average treatment-related mortality in 4 single-center studies ranged from 21% to 39% (Falk 2010). Given the high burden of morbidity and mortality in AL amyloidosis, as well as the significant impact on healthcare costs and health-related quality of life (Quock 2018), there is a substantial unmet need for effective treatments targeting patients with AL amyloidosis. This need is particularly acute for Mayo Stage IV patients, who represent the equivalent of an ultra-rare patient population of <2800 in the US with a median survival of only 5.8 months (Kumar 2012). Treatments that reduce or eliminate PCD in conjunction with treatments that target toxic soluble aggregates and insoluble amyloid such as birtamimab may be of great clinical benefit in the treatment of AL amyloidosis.

1.3. Background on Birtamimab

Birtamimab is an immunoglobulin G1 kappa monoclonal antibody that specifically binds to both insoluble and soluble light chain aggregates. The proposed mechanism of action of birtamimab is to neutralize soluble toxic aggregates and induce clearance of insoluble deposited fibrils (amyloid) through phagocytosis (Renz 2016). In vitro studies have shown that the murine precursor of birtamimab binds light chain aggregates deposited in multiple organs of patients

with AL amyloidosis, promoting clearance of amyloid by macrophages through antibody-dependent phagocytosis.

In Study NEOD001-001, pharmacokinetic (PK) samples were collected at prespecified time points, including full sampling profiles over the 28-day dosing interval in Infusions 1 and 3 in all enrolled subjects. The mean terminal elimination half-life of birtamimab in serum was approximately 13 to 16 days across all dose levels (0.5 to 24.0 mg/kg) (Gertz 2016). No nonlinear accumulation of birtamimab was observed over the dose range. The PK of birtamimab is consistent with dosing by intravenous infusion every 28 days across the dose range.

Imaging, autoradiography, and biodistribution studies demonstrated specific binding of birtamimab and its parent murine monoclonal antibody 2A4 to their amyloid target in 2 amyloidosis xenograft models. No evidence has been found that would indicate relevant off-target binding of birtamimab (e.g., to endogenous parent proteins of the amyloid). Further details can be found in the latest edition of the Birtamimab Investigator's Brochure.

1.3.1. Nonclinical Safety

Further details can be found in the latest edition of the Birtamimab Investigator's Brochure.

1.3.2. Clinical Experience

The efficacy, safety, and tolerability of birtamimab, administered intravenously every 28 days in subjects with AL amyloidosis, were evaluated in 5 clinical studies, including 2 completed studies and 3 terminated studies (Table 3). A total of [redacted] subjects received at least 1 dose of birtamimab. With the exception of [redacted] subjects in the Phase 1/2 Study NEOD001-001, the remaining [redacted] subjects received birtamimab at a dose of 24 mg/kg (up to maximum dose not to exceed [redacted]).

Table 3: Overview of Birtamimab Clinical Studies

Study ID; Status	Phase	Country	Study Title[a]	No. of Subjects Enrolled[b]
NEOD001-001 (NCT01707264) Completed	1/2	US	A Phase 1/2 Open Label, Dose Escalation Study of Intravenous Administration of Single Agent NEOD001 in Subjects with Light Chain (AL) Amyloidosis	[redacted]
NEOD001-OLE001 (NCT02613182); Terminated	2	US	Open-label Extension Study to Evaluate the Long-term Safety and Tolerability of NEOD001 in Subjects with Light Chain (AL) Amyloidosis	[redacted]
NEOD001-201 (PRONTO) (NCT02632786); Completed	2b	Australia, Austria, France, Germany, Greece, Israel, Italy, Spain, UK, US	A Phase 2b, Randomized, Double-blind, Placebo-controlled Study of NEOD001 in Previously Treated Subjects with Light Chain (AL) Amyloidosis who have Persistent Cardiac Dysfunction	[redacted] (66 subjects in birtamimab group and 63 subjects in control group)
NEOD001-OLE251 (NCT03154047); Terminated	2b	Australia, Austria, France, Germany, Greece, Israel, Italy, Spain, UK, US	A Phase 2b Open-label Extension Study to Evaluate the Long-term Safety and Efficacy of NEOD001 in Subjects with Light Chain (AL) Amyloidosis who were previously enrolled in Study NEOD001-201 (PRONTO)	[redacted] birtamimab and [redacted] placebo subjects from PRONTO study)
NEOD001-CL002 (VITAL) (NCT02312206); Terminated	3	Australia, Austria, Belgium, Canada, Denmark, France, Germany, Greece, Italy, Israel, Netherlands, Poland, Spain, UK, US	A Phase 3, Randomized, Multicenter, Double-Blind, Placebo-Controlled, 2-Arm, Efficacy and Safety Study of NEOD001 Plus Standard of Care vs Placebo Plus Standard of Care in Subjects with Light Chain (AL) Amyloidosis	[redacted] ([redacted] subjects in birtamimab group and [redacted] subjects in control group)

[a] In all clinical studies, study drug is administered by intravenous infusion every 28 days.

[b] Refers to total sample size, not number of subjects exposed to birtamimab.

Currently available safety data for birtamimab include the following:

- Study NEOD001-001: [redacted] subjects treated with birtamimab (0.5 mg/kg to 24 mg/kg) had mean number of infusions [redacted])
- Study NEOD001-OLE001: [redacted] subjects from Study NEOD001-001 treated with birtamimab had mean number of infusions [redacted]
- Study NEOD001-201 (PRONTO): [redacted] subjects (66 birtamimab/63 placebo); subjects treated with birtamimab had mean number of infusions [redacted]

- Study NEOD001-OLE251: [redacted] subjects from Study NEOD001-201 (PRONTO) (43 birtamimab/37 placebo) treated with birtamimab had mean number of infusions [redacted]
- Study NEOD001-CL002 (VITAL): [redacted] subjects (130 birtamimab/130 control); subjects treated with birtamimab had mean number of infusions = [redacted]

Further details of the 5 clinical birtamimab studies can be found in the latest edition of the Birtamimab Investigator's Brochure.

The Phase 2b Study NEOD001-201 did not meet its primary or secondary endpoints and subsequently Prothena Therapeutics Limited (Prothena) requested the independent Data Monitoring Committee (DMC) to review a futility analysis of the ongoing Phase 3 Study NEOD001-CL002. The DMC recommended discontinuation of Study NEOD001-CL002 for futility. Based on these findings, Prothena decided to discontinue all development of birtamimab, including Study NEOD001-CL002 as well as the open-label extension studies.

In Study NEOD001-CL002, the final hazard ratios, which favored birtamimab for the composite primary endpoint of all-cause mortality or cardiac hospitalization (occurring ≥91 days after a subject's first infusion of study drug), were largely attributable to all-cause mortality rather than cardiac hospitalization. Further post hoc evaluations included analyses by Mayo staging, a prognostic categorization system for mortality risk in newly diagnosed patients with AL amyloidosis; time to all-cause mortality, with survival censored at 9 months, revealed a potential survival benefit favoring birtamimab for those subjects categorized as Mayo Stage IV, with a hazard ratio of 0.413 (95% confidence interval [CI]: 0.191, 0.895; p=0.021, n=77) (Gertz 2023). At Month 9, the proportion of subjects surviving was 49% in the placebo group and 74% in the birtamimab group.

In the clinical studies conducted to date, birtamimab was safe and well-tolerated in subjects with AL amyloidosis and no clinically significant safety signals have been identified. In Study NEOD001-CL002, the safety profile of birtamimab in subjects with Mayo Stage IV AL amyloidosis was consistent with the overall study population.

[redacted]

Based on the data available to date, birtamimab is safe and well-tolerated in subjects with Mayo Stage IV AL amyloidosis and no clinically significant safety signals have been identified.

1.4. Rationale for Study Design and Dose Selection

As noted in Section 1.3.2, the post hoc analyses of time to all-cause mortality by Mayo Stage in Study NEOD001-CL002, with survival censored at 9 months, revealed a potential survival benefit favoring birtamimab for those subjects categorized as Mayo Stage IV, with a hazard ratio of 0.413 (95% CI: 0.191, 0.895; p=0.0251). At Month 9, the proportion of subjects surviving was 49% in the placebo group and 74% in the birtamimab group.

The Double-blind Phase of Study NEOD001-301, a randomized, double-blind treatment phase to support potential licensure of birtamimab in the Mayo Stage IV AL amyloidosis population, is designed to confirm the survival benefit demonstrated in Study NEOD001-CL002 by evaluating birtamimab plus standard of care treatment compared to the safety and efficacy of placebo plus standard of care treatment.

The Open-label Extension (OLE) Phase will be conducted to evaluate the long-term safety and explore the long-term efficacy of birtamimab plus standard of care treatment and additionally to

allow for continued access to birtamimab for subjects who completed treatment in the Double-blind Phase.

The highest dose of birtamimab tested in clinical studies was 24.0 mg/kg, which was deemed to be safe and well tolerated and is the same dose used in Study NEOD001-CL002 and the current Study NEOD001-301.

1.5. Benefit-Risk Assessment

Birtamimab is being developed for the treatment of patients with systemic AL amyloidosis. The ongoing Phase 3 study, NEOD001-301 AFFIRM-AL Study, is being conducted to confirm the observations from post hoc analyses for the previous Phase 3 NEOD001-CL002 VITAL study. In the VITAL study, post hoc analyses of time to all-cause mortality revealed a potential survival benefit favoring birtamimab (74%) compared to control (49%) for the subjects categorized as Mayo Stage IV, with a hazard ratio of 0.413 (91% CI: 0.191, 0.895; p=0.0251).

In the five previous studies completed or terminated by the Sponsor, a total of 302 subjects received birtamimab ([redacted] subjects at the recommended dose of 24 mg/kg dose level; not to exceed [redacted] total). Overall, there was no significant imbalance in events when compared to placebo and/or when considering the study population and background therapy. Furthermore, in the VITAL study, the safety profile of birtamimab in Mayo Stage IV subjects was consistent with the safety profile of the overall study population.

A favorable benefit/risk profile for birtamimab was shown in the post hoc analyses in Mayo Stage IV patients in the VITAL study together with the safety profile in the clinical studies conducted to date. Birtamimab offers the potential benefit for Mayo Stage IV patients of reducing mortality risk with relatively minimal safety risk based on the demonstrated safety profile to date, supporting the continued development of birtamimab in the Phase 3 NEOD001-301 AFFIRM-AL Study.

2. OBJECTIVES

2.1. Primary Objective

Double-blind Phase

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.

Open-label Extension Phase

To evaluate the long-term safety of birtamimab plus standard of care in Mayo Stage IV subjects with AL amyloidosis.

2.2. Secondary Objectives

Double-blind Phase

To evaluate birtamimab plus standard of care compared to placebo plus standard of care on the following:

- Change from baseline to Month 9 in the 6-Minute Walk Test (6MWT) distance
- Change from baseline to Month 9 in health-related quality of life using the Short Form-36 questionnaire Version 2 (SF-36v2)

3. STUDY PLAN

3.1. Study Design

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).

In the Double-blind Phase, newly diagnosed Mayo Stage IV subjects with AL amyloidosis will be randomized 2:1 to receive birtamimab plus local standard of care chemotherapy or placebo (saline) plus local standard of care chemotherapy. 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. 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 (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). "Cycle" is reserved to denote administration of chemotherapy. Assessment and visit windows are described in the Schedule of Events (Table 1 [Double-blind Phase] and Table 2 [OLE Phase]).

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 (per Table 1 [Double-blind Phase] or Table 2 [OLE Phase]). If a subject who discontinues study drug during the Double-blind Phase is willing to continue to participate in study visits, they will then have assessments [redacted] for the remainder of the Double-blind Phase per Appendix 1.

Vital Status Assessment Follow-up phone calls (every [redacted] months) should be made to all subjects (or their caregivers) who received a dose of study drug and are no longer receiving study drug or completing assessments in the clinic, beginning approximately [redacted] months from the subject's last visit. The subject's vital status (survival information) will be collected accordingly in the study database to ensure adequate capture of endpoint events.

3.2. Number of Sites and Subjects

This is a multicenter, global study in approximately 120 centers. Approximately 220 subjects may be enrolled in the study, which will continue until approximately [redacted] events (all-cause mortality) have occurred.

3.3. Endpoints

3.3.1. Efficacy Endpoints

3.3.1.1. Primary Efficacy Endpoint

- Time to all-cause mortality during the Double-blind Phase

3.3.1.2. Secondary Efficacy Endpoints

- Change from baseline to Month 9 of the Double-blind Phase in the 6MWT distance (meters)
- Change from baseline to Month 9 of the Double-blind Phase in the Physical Component Summary (PCS) score of the SF-36v2

3.3.1.3. Exploratory Efficacy Endpoints

The following endpoints will be explored during the OLE Phase:

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

3.3.2. Safety Endpoints

- [redacted]

3.4. Estimated Study Duration

The Double-blind Phase of this study is event driven and will continue until approximately [redacted] events of all-cause mortality have occurred. All subjects who discontinue treatment during the Double-blind Phase will be followed until the last event has occurred. The estimated overall Double-blind Phase duration is approximately 42 months, including the screening, enrollment, treatment period, and postdose follow-up for subjects not entering the optional OLE Phase.

For subjects who enter the OLE Phase, treatment will continue for an additional [redacted] months or until birtamimab is commercially available in the subject's country of residence, whichever occurs first (in accordance with country-specific regulations). For subjects not transitioning to commercially available birtamimab treatment, a postdose follow-up will occur 28 to 35 days after the last study drug administration.

The estimated overall study duration is approximately 69 months, including the screening, enrollment, double-blind and open-label treatment periods, and postdose follow-up.

3.5. Definition of Primary Endpoint and End of Study

The Double-blind Phase of the study will end when approximately [redacted] primary endpoint events have occurred and End of Treatment (EOT) Visits have been completed for all subjects who remain in the Double-blind Phase at that time. Events are defined as deaths due to any cause.

An interim analysis will be conducted when approximately 50% of the events ([redacted] have occurred. The O'Brien-Fleming group sequential methodology will be used to divide the overall study significance level between the interim (p=[redacted]) and the final analysis (p=[redacted]). If overwhelming efficacy (p<[redacted]) is achieved at the interim analysis, the Double-blind Phase may be stopped early.

The end of the study is defined as the date when the last subject last visit occurs in the OLE Phase.

3.6. Termination of the Clinical Study

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

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

- The discovery of an unexpected, relevant, or unacceptable risk to the subjects enrolled in the clinical study
- [redacted]
- A decision by the Sponsor to suspend the study, or to suspend or discontinue development of the study drug, for any reason

4. SUBJECT SELECTION

4.1. Inclusion Criteria

Subjects must meet ***all*** of the following criteria to be eligible for participation in the Double-blind Phase of the study:

1. Aged ≥18 years and legal age of consent according to local regulations
2. Newly diagnosed and AL amyloidosis treatment naive
3. [redacted]
4. Confirmed diagnosis of AL amyloidosis by the following:
   - [redacted]

     AND
   - [redacted]
5. If the subject meets any of the following:
   - [redacted]

   AND

   [redacted]

   THEN

   [redacted]

   AND

   [redacted]
6. [redacted]

[redacted]

7. Confirmed Mayo Stage IV as defined by:
   - NT-proBNP ≥1800 pg/mL and
   - Troponin-T ≥0.025 ng/mL (mcg/L) or high sensitivity cardiac troponin T ≥40 ng/L and
   - dFLC ≥18 mg/dL
8. Planned first-line chemotherapy contains bortezomib administered subcutaneously weekly
9. [redacted] as estimated by the Chronic Kidney Disease Epidemiology Collaboration equation
10. Seated systolic blood pressure (BP) [redacted]
11. Distance walked during each Screening 6MWT is [redacted]
12. [redacted]
13. [redacted]
14. Ability to understand and willingness to sign an informed consent form (ICF) prior to initiation of any study procedures

To be eligible for the OLE Phase of the study, subjects must not have discontinued treatment in the Double-blind Phase and must meet the following criteria at the time of entry into the OLE Phase:

1. WOCBP must have a negative pregnancy test and must agree to use highly effective contraception through 90 days following last study drug administration
2. Male subjects must be surgically sterile or agree to use highly effective contraception through 90 days following last study drug administration
3. Ability to understand and willingness to sign an ICF prior to initiating the OLE Phase

Note: Patient screening in France will be reviewed by the French National Amyloidosis Reference Center in accordance with local requirements.

4.2. Exclusion Criteria

Subjects must meet *none* of the following criteria to be eligible for the Double-blind Phase of the study:

1. Non-AL amyloidosis
2. NT-proBNP >8500 pg/mL
3. Meets the International Myeloma Working Group (IMWG) definition of multiple myeloma, ***except*** for malignancy biomarker of involved/uninvolved serum free light chain ratio ≥100 (Appendix 3). In France, the criterion also includes being confirmed with symptomatic multiple myeloma.
4. Subject is eligible for and plans to undergo ASCT or organ transplant during the study
5. Symptomatic orthostatic hypotension that in the medical judgment of the Investigator would interfere with the subject's ability to safely receive treatment or complete study assessments
6. Myocardial infarction, uncontrolled angina, severe uncontrolled ventricular arrhythmias, or ECG evidence of acute ischemia, within 6 months prior to the Month 1-Day 1 Visit
7. Severe valvular stenosis (e.g., aortic or mitral stenosis with a valve area <1.0 cm^2) or severe congenital heart disease
8. [redacted]
9. [redacted]
10. [redacted]

11. Prior treatment with hematopoietic growth factors, transfusions of blood or blood products within 1 week of Month 1-Day 1
12. Prior radiotherapy within 4 weeks of Month 1-Day 1
13. [redacted]
14. [redacted]
15. [redacted]
16. [redacted]
17. Prior treatment with plasma cell-directed chemotherapy, birtamimab, daratumumab, 11-1F4, anti-serum amyloid P antibody, doxycycline for amyloid, or other investigational treatment directed at amyloid
18. [redacted]
19. [redacted]
20. [redacted]
21. [redacted]
22. [redacted]
23. Waldenström's macroglobulinemia and/or immunoglobulin M monoclonal gammopathy

A subject will be excluded from the OLE Phase of the study if any of the following criteria are met at the time of entry into the OLE Phase:

1. Any medical condition or clinically significant abnormality on physical, neurological, laboratory, vital signs, or ECG examination that precludes treatment with birtamimab or participation in the study, in the medical judgment of the Investigator

2. Symptomatic orthostatic hypotension that in the medical judgment of the Investigator would interfere with subject's ability to safely receive treatment or complete study assessments
3. History of Grade ≥3 infusion-related AEs during the Double-blind Phase or hypersensitivity to birtamimab
4. Unable or unwilling to adhere to the study-specified procedures and restrictions
5. Planning to use any other investigational treatment during the study

5. SUBJECT SCREENING AND RANDOMIZATION

A Subject Number will be assigned via a phone- and/or web-based Interactive Voice and Web Response System (IXRS) for each subject who has signed an informed consent. This unique Subject Number will be utilized for submission of all lab samples, ECGs, and other study procedures.

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 IXRS 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] This 2-arm study will include approximately 147 subjects in the birtamimab group and 73 subjects in the placebo group for an estimated total of 220 subjects.

6. INVESTIGATIONAL MEDICINAL PRODUCT AND TREATMENT

6.1. Formulation, Packaging, and Labeling of Birtamimab

[redacted]

At a minimum, the label for each vial shipped to a clinical site will provide the following information: batch number/lot number, required storage conditions, directions for use, and any region-specific caution statements, e.g., "New Drug - Limited by United States Federal Law to Investigational Use."

6.2. Shipping, Storage, and Handling of Birtamimab

[redacted] Access to the study drug should be strictly limited to the Pharmacy Staff. Neither the Investigator nor any member of the study staff will distribute any of the study supplies to any person who is not participating in this study.

If a study staff member becomes aware that the study drug has not been properly handled (e.g., physical damage to carton/vial, temperature outside the [redacted] range in transit, or not stored at [redacted] in the clinic), follow the procedure outlined in the Pharmacy Manual or immediately contact the Site Monitor. [redacted]

See the Pharmacy Manual for further details about shipping, storage, and handling of birtamimab.

6.3. Placebo

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

6.4. Accountability and Return of Study Drug Supplies

[redacted]

6.5. Dosage, Administration, and Schedule

6.5.1. 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] g. The subject's weight during Screening may be used for calculation of the first dose in the Double-blind Phase. 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 (Double-blind or OLE, as applicable), 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.

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

Subjects who are randomized to the placebo arm in the Double-blind Phase will be administered a [redacted] IV bag of 0.9% saline, which will look identical to the birtamimab infusion bag.

All subjects will receive a flush of approximately [redacted] mL.

The Unblinded Pharmacy Staff at each site will be responsible for preparing the study drug; other study team members must remain blinded to study drug assignment during the Double-blind Phase. The Unblinded Pharmacy Staff will obtain the treatment assignment information from the IXRS, and will then prepare the study drug, providing the prepared IV bag to the Investigator for administration. The Unblinded Pharmacy Staff will maintain the records for drug accountability for audits or inspections. An Unblinded Monitor will be assigned as the Sponsor's designee to perform drug accountability and as such, will be the Unblinded Pharmacy Staff's primary point of contact for any study drug-related issues.

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

During the Double-blind Phase, all doses of study drug will be administered at the study site, starting on the day of randomization as an initial [redacted] minute intravenous infusion, including flush, and then once every 28 days [redacted]) from the previous Month X-Day 1 dosing visit until the EOT/ETD Visit. If the subject tolerates the initial administration without infusion-related AEs, subsequent infusions may be administered over [redacted] minutes, including flush. If there is concern about infusing [redacted] and flush over [redacted] minutes in any specific subject, the length of the infusion may be extended over a longer period of time as clinically indicated. If it is anticipated that the

infusion will extend beyond [redacted] hours, the reconstituted and diluted study drug should be split into multiple bags to ensure that no amount of reconstituted study drug will be at room temperature for longer than [redacted] hours (i.e., from the time of reconstitution of the vial to end of the infusion of a bag). [redacted] The volume contained in the administration tubing should be completely flushed using approximately [redacted] of 0.9% Sodium Chloride Injection (United States Pharmacopeial Convention [USP]) after administration of study drug. The infusion line should NOT be used for blood draws.

During the OLE Phase, all doses of study drug (birtamimab) will be administered at the study site, starting on OLE Month 1-Day 1 as an initial [redacted]) minute intravenous infusion (regardless of whether a subject was receiving [redacted]-minute infusions in the Double-blind Phase), including flush, and then once every 28 days [redacted] from the previous OLE Month X-Day 1 dosing visit until the EOT/ETD Visit. If the subject tolerates the initial administration without infusion-related AEs, subsequent infusions may be administered over [redacted]) minutes, including flush. If there is concern about infusing [redacted] and flush over these specified infusion times in any specific subject, the length of the infusion may be extended over a longer period of time as clinically indicated. If it is anticipated that the infusion will extend beyond [redacted] hours, the reconstituted and diluted study drug should be split into multiple bags to ensure that no amount of reconstituted study drug will be at room temperature for longer than [redacted] hours (i.e., from the time of reconstitution of the vial to end of the infusion of a bag). The additional bag(s) should remain refrigerated until ready for use. The volume contained in the administration tubing should be completely flushed using approximately [redacted] of 0.9% Sodium Chloride Injection (USP) after administration of study drug. The infusion line should NOT be used for blood draws.

In both phases of the study, every effort must be made to ensure doses are given 28 days from the previous dose. If logistic considerations intervene, a minimum of [redacted] days between doses is required. All subjects will be closely monitored for [redacted] minutes after completion of the study drug infusion. The Investigator may increase this standard monitoring time if deemed appropriate or per local standards. In the event of any clinical concerns or suspicious signs or symptoms after the infusion, the subject will remain under observation for as long as the Investigator deems it appropriate.

6.5.2. Study Drug Premedication

[redacted]

6.5.3. 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. Bortezomib should be administered according to the approved prescribing information and local institutional practices. 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; initiation at any other time during

the Double-blind Phase is prohibited (see Section 6.8.2). For subjects who did not initiate daratumumab at randomization during the Double-blind Phase, daratumumab may be initiated at any time during the OLE Phase at the Investigator's discretion. Antiviral prophylaxis is required.

[redacted]

The number of cycles of first-line chemotherapy that is administered is at the discretion of the Investigator; however, commonly accepted treatment practice suggests that a change in plasma cell-directed chemotherapy may occur in any of the following circumstances:

- Failure to attain at least a hematologic partial response by 6 weeks or a very good partial response by 3 months
- Withdrawal of consent
- Unacceptable toxicity
- Investigator decision

The Investigator may prescribe subsequent chemotherapy at his/her discretion as per standard of care. Particular care must be taken to accurately report chemotherapy administration, including missed doses, and dose reductions.

In the event that bortezomib doses are missed, the chemotherapy cycles may become misaligned with the monthly study drug dosing. In this case, the weekly visits during [redacted] should continue as described above in order to closely monitor subjects' health during the initial months of concomitant chemotherapy. Throughout the study, monthly doses of study drug should not be delayed or skipped due to adjustments that are made to chemotherapy dosing. Study drug dosing adjustments are described in Section 6.6.

6.6. Dosage Adjustments

6.6.1. Withholding of Study Drug

[redacted]

Throughout the study, monthly doses of study drug should not be delayed or skipped due to adjustments that are made to chemotherapy dosing.

6.6.2. Management of Suspected Infusion-Related/Hypersensitivity Adverse Events

In the event of a suspected infusion-related and/or hypersensitivity AE, the infusion should be immediately discontinued and appropriate supportive therapy should be administered per institutional practice, which may include epinephrine, intravenous fluids, corticosteroids, vasopressors, oxygen, bronchodilators, antihistamines, or acetaminophen/paracetamol. Subjects

should be evaluated and carefully monitored until there is complete resolution of the AE (i.e., all hypersensitivity signs and symptoms have resolved). In addition to the institution's recommended assessments, blood samples should be obtained in the event of a suspected infusion-related and/or hypersensitivity AE for assessment of the following: [redacted]. If a sample for anti-birtamimab antibody was collected prior to infusion, no additional serum will be collected for anti-birtamimab antibody. In the case where a reaction occurs on a month where a sample for anti-birtamimab antibody was not collected pre-dose, an anti-birtamimab antibody serum sample will be collected.

For subjects with a Grade 1 infusion-related and/or hypersensitivity AE, the infusion may be restarted upon resolution of the AE if deemed clinically appropriate.

For subjects with a Grade 2 infusion-related and/or hypersensitivity AE, if it is appropriate to restart the infusion, then this should be done at [redacted] of the original rate (i.e., if the initial infusion is administered over [redacted] minutes, the new rate should be based on administering [redacted] mL over [redacted] minutes). If the subject is to receive additional infusions in subsequent weeks, then the rate of these infusions should be discussed with and agreed upon prospectively by the Investigator and the Medical Monitor.

If a subject experiences a Grade 3 infusion-related and/or hypersensitivity AE, the infusion should not be restarted. The decision to continue dosing this subject at their next scheduled administration should be discussed with the Medical Monitor. [redacted] Subjects who have an infusion-related and/or hypersensitivity AE at the subsequent scheduled study drug administration must have study drug permanently discontinued and have an ETD Visit per Section 7.1.1.5.

Subjects who experience a Grade 4 infusion-related and/or hypersensitivity AE must have study drug permanently discontinued and have an ETD Visit per Section 7.1.1.5.

6.6.3. Dose Reductions

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

6.7. Treatment Compliance

Treatment compliance is assured as study drug will be administered at the study site. Any changes in volume or rate of administration will be recorded on the electronic case report form (eCRF), along with reasons why treatment was adjusted or not administered, if applicable.

6.8. Concomitant Therapy

Concomitant medication includes any drug (prescription or over-the-counter) or biological product (such as vaccines, blood or blood components) including herbal remedies or preparations. All medications that are taken by a subject from the first Screening Visit or within the 28 days prior to the Month 1-Day 1 Visit, whichever is earlier, through the subject's last visit, and any changes to concomitant medications during the study will be recorded on the appropriate eCRF.

6.8.1. Allowed Concomitant Therapy

The following concomitant medications and therapies are allowed at any time during the study:

- [redacted]

During the Double-blind Phase, the initiation of daratumumab treatment is allowed only at randomization at the discretion of the Investigator.

The following concomitant medications and therapies are allowed only during the OLE Phase:

- [redacted]

6.8.2. Prohibited Concomitant Therapy

The following concomitant medications and therapies are prohibited throughout the study:

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

The following concomitant medications and therapies are prohibited only during the Double-blind Phase:

- [redacted]
- Initiation of daratumumab treatment at any time other than at randomization
- [redacted]

7. STUDY PROCEDURES

7.1. Study Visits and Assessments

7.1.1. Double-blind Phase

7.1.1.1. First Screening Visit: Day -28 to Day -1

Subject screening will occur during the 28 days prior to the first administration of study drug on Month 1-Day 1. The Screening period may be extended up to a maximum of 7 days with prior approval by the Medical Monitor. Individual test results that do not meet eligibility requirements may be repeated, with the exception of 6MWT; rescreening is allowed once per subject.

[redacted]

Two Screening 6MWTs are required before the first administration of study drug. The first Screening 6MWT is required to be performed between Days -28 and -5, at least 4 days apart from the second Screening 6MWT, which should be performed within 3 days ***prior*** to Month 1-Day 1 (i.e., on Day -3 to Day -1). Although the entire Screening period does not need to be utilized, a minimum of 5 days must be allowed to accommodate the required 4-day interval between the 2 Screening 6MWTs. Subjects should plan to be able to return to the same clinical site for each 6MWT from first Screening through Month 9 and at EOT/ETD.

Written informed consent must be obtained before any study-specific screening evaluations are performed and should be documented in the subject's medical chart.

Note: Patient screening in France will be reviewed by the French National Amyloidosis Reference Center in accordance with local requirements.

The following will be performed between Days -28 and -1 prior to the Month 1-Day 1 Visit, unless otherwise noted:

- Obtain written informed consent
- Review inclusion and exclusion criteria to assess eligibility
- Obtain comprehensive cardiac, hematologic and oncologic medical history; additionally, for all other conditions, obtain relevant medical history for the past 5 years (including all major hospitalizations and surgeries), as well as the subject's current medical status
- [redacted]
- [redacted]
- 12-lead ECG performed in triplicate

- [redacted]
- [redacted]
- SARS-CoV-2 test (conduct within 14 days before dosing on Day 1, either during the first or second screening visit)
- [redacted]
- First Screening 6MWT – must be performed between Days -28 and -5, at least 4 days apart from the second Screening 6MWT, which should be performed within 3 days prior to Month 1-Day 1 (i.e., on Day -3 to Day -1); [redacted]
- [redacted]
- Record all medications and therapy beginning with the first Screening Visit

7.1.1.2. Second Screening Visit: Day -3 to Day -1

The following assessments will be conducted on Day -3 to Day -1 (i.e., 1-3 days prior to dosing on Month 1-Day 1):

- Administer SF-36v2 questionnaire (Appendix 4), [redacted]

- Assess any changes/additions to medical history since the first Screening Visit
- SARS-CoV-2 test (if not conducted during first Screening Visit)
- [redacted]
- Second Screening 6MWT; [redacted]
- Ensure all medications and therapy beginning with the first Screening Visit have been recorded

7.1.1.3. Treatment Visits

Subjects will receive study drug as an intravenous infusion every 28 days [redacted]) from the previous Month X-Day 1 visit until the EOT/ETD Visit. Assessment and visit windows are described in the Schedule of Events (Table 1) and in the sections below; the study drug dosing window is described in Section 6.5.1. The pre-dose assessments for each visit may be performed within the 2 days prior to the visit.

Central laboratory assessments will be performed [redacted] for study analysis. Both local laboratory assessments and central laboratory assessments (as applicable) will be performed for subject management. Results will be reviewed prior to dosing and prior to in-clinic bortezomib administration, to confirm that continued dosing is appropriate.

[redacted], which in the medical judgment of the Investigator would interfere with the subject's ability to safely receive treatment, will have the study drug withheld. If the study drug is withheld and subsequently rescheduled, central laboratory assessments required for that visit will need to be repeated if they were drawn more than 7 days prior to the rescheduled dosing date. However, a symptom-directed PE and vital signs need to be repeated prior to each dosing. [redacted]

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

If the subject discontinues study drug treatment prior to the end of the study, refer to Section 8.2.

7.1.1.3.1. Month 1-Day 1

Randomization in IXRS can occur up to one day prior to Month 1-Day 1 visit.

The subject must return to the study site for the following procedures:

Prior to Study Drug Infusion:

- [redacted]
- [redacted]
- Central laboratory assessment
  - [redacted]
- Local laboratory assessment:
  - Serum/urine pregnancy test for WOCBP within 24 hours prior to Month 1-Day 1 study drug administration; test results must be obtained prior to dosing and must be negative (see Section 9.8)
- Bioanalytical laboratory assessments – any time on Month 1-Day 1, prior to the start of the infusion:
  - Pre-dose anti-birtamimab antibody sample
- [redacted]
- [redacted]
- [redacted] Vital signs should be assessed in the same position at each assessment (i.e., pre-dose, during infusion, and after the infusion); if the subject will be supine during the infusion, then all of the vital signs should be assessed in the supine position.

Study Drug Administration:

- The initial dose of study drug, including flush, will [redacted]
- [redacted]

Assessments After Infusion:

- [redacted]
- [redacted]
- Closely monitor subject for [redacted] following completion of the study drug infusion per Section 6.5.1
- [redacted]
- Assessment of AEs
- Record all changes to concomitant medications and therapy

7.1.1.3.2. [redacted]

The subject must return to the study site for the following procedures:

Prior to Chemotherapy Administration:

- Local laboratory assessments:
  - Perform pre-dose local laboratory assessments, including hematology and chemistry, and review results prior to dosing
- Central laboratory assessments:
  - [redacted]

- [redacted]

Chemotherapy Administration:

- Administer bortezomib, antiviral prophylaxis, and other scheduled chemotherapy
- Assessment of AEs
- Record all changes to concomitant medications and therapy

7.1.1.3.3. [redacted]

The subject must return to the study site for the following procedures:

Prior to Study Drug Infusion:

- Administer SF-36v2 questionnaire (Appendix 4) [redacted]
- [redacted] performed in triplicate – [redacted]
- Symptom-directed PE should be as clinically indicated and also include weight and assessment of macroglossia, submandibular nodes/fullness, adenopathy, ecchymoses, liver/spleen size (palpable +/-), ascites (+/-), and edema (which should be quantified on a scale of 0-4)
- [redacted]
- Local laboratory assessments:
  - Perform local laboratory assessments, including hematology and chemistry, and review results prior to dosing
  - WOCBP: serum/urine pregnancy test; test results must be obtained prior to dosing and must be negative (see Section 9.8)
- Central laboratory assessments:
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

- [redacted]
  - Pre-dose anti-birtamimab antibody sample
- [redacted]
  - [redacted]
  - [redacted]
- [redacted]

Study Drug Administration

- The dose of study drug, including flush, may be delivered [redacted] minutes if the Month 1-Day 1 infusion was well tolerated without infusion-related AEs (Section 6.5.1)

Assessments After Infusion:

- [redacted]
  - [redacted]
  - [redacted]
- Closely monitor subject [redacted] following completion of the study drug infusion per Section 6.5.1
- [redacted]
- Assessment of AEs
- Record all changes to concomitant medications and therapy

7.1.1.3.4. [redacted]

If the subject had significant toxicities associated with previous chemotherapy administrations, then the subject should return to the study site for the following procedures and Cycle 2-Day 8 and/or Cycle 2-Day 22 bortezomib administration. If there were no significant toxicities associated with previous chemotherapy administration, then Cycle 2-Day 8 and/or Cycle 2-Day 22 chemotherapy may be administered by the subject's local physician, at the Investigator's discretion, and a homecare visit performed. The subject must return to the study site for Cycle 2-Day 15 bortezomib administration and assessments, regardless of previous tolerability.

Prior to Chemotherapy Administration:

The following assessments will be performed whether the visit is conducted at the study site or at the subject's local physician's clinic. If the visit is performed at the subject's local physician's clinic, a Prothena-sponsored homecare visit will take place either within 1 day prior to or pre-dose on the same day as bortezomib administration to perform vital signs and to collect central laboratory assessments. If bortezomib is administered on a Monday, then it is acceptable for the homecare visit to take place on the previous Friday.

- [redacted]

The following assessments will only be performed if the subject returns to the study site for the visit:

- Local laboratory assessments:
  - Perform local laboratory assessments, including hematology and chemistry, and review results prior to dosing
- Assessment of AEs
- Record all changes to concomitant medications and therapy

Chemotherapy Administration (Investigator or Local Physician):

- Administer bortezomib, antiviral prophylaxis, and other scheduled chemotherapy

7.1.1.3.5. [redacted]

The subject must return to the study site for the following procedures:

Prior to Study Drug Infusion:

- Administer SF-36v2 questionnaire (Appendix 4) [redacted]
- 12-lead ECG performed in triplicate - [redacted]
- [redacted]

- [redacted]
- [redacted]
- Local laboratory assessments:
  - Perform local laboratory assessments, including hematology and chemistry, and review results prior to dosing
  - WOCBP: serum/urine pregnancy test; test results must be obtained prior to dosing and must be negative (see Section 9.8)
- [redacted]
- 6MWT; [redacted]
- [redacted]
  - Pre-dose anti-birtamimab antibody sample
- Administer premedication within 30 to 90 minutes prior to the start of the infusion:
  - [redacted]
- [redacted]

Study Drug Administration:

- The dose of study drug, including flush, may be delivered over [redacted] minutes if the previous infusions were well tolerated without infusion-related AEs (Section 6.5.1)

Assessments After Infusion:

- [redacted]
  - [redacted]
  - [redacted]
- Closely monitor subject for [redacted] minutes following completion of the study drug infusion per Section 6.5.1
- [redacted]
- Assessment of AEs
- Record all changes to concomitant medications and therapy

[redacted]

If the subject had significant toxicities associated with Cycles 1 or 2 chemotherapy administrations, then the subject should return to the study site for the following procedures and Cycle 3-Days 8, 15, and 22 bortezomib administration. If there were no significant toxicities associated with previous chemotherapy administrations, Cycle 3-Days 8, 15, and 22 chemotherapy may be administered by the subject's local physician, at the Investigator's discretion, and a homecare visit performed within 1 day prior to or on the same day as bortezomib administration to conduct the following pre-chemotherapy assessments. If bortezomib is administered on a Monday, then it is acceptable for the homecare visit to take place on the previous Friday.

Prior to Chemotherapy Administration:

The following assessments will be performed whether the visit is conducted at the study site or at the subject's local physician's clinic:

- [redacted]
- Central laboratory assessments:
  - [redacted]
  - [redacted]

The following assessments will only be performed if the subject returns to the study site for this visit:

- Local laboratory assessments:

- Perform local laboratory assessments, including hematology and chemistry, and review results prior to dosing

- Assessment of AEs
- Record all changes to concomitant medications and therapy

Chemotherapy Administration (Investigator or local physician):

- Administer bortezomib, antiviral prophylaxis, and other scheduled chemotherapy

7.1.1.3.7. [redacted]

The subject must return to the study site for the following procedures:

Prior to Study Drug Infusion:

- Administer SF-36v2 questionnaire (Appendix 4) [redacted]
- [redacted]
- 12-lead ECG performed in triplicate - [redacted]
- [redacted]
- [redacted]
- Local laboratory assessments:
  - Perform local laboratory assessments, including hematology and chemistry, and review results prior to dosing
  - WOCBP: serum/urine pregnancy test; test results must be obtained prior to dosing and must be negative (see Section 9.8)
- [redacted]

- [redacted]
- 6MWT; [redacted]
- Bioanalytical laboratory assessments – any time on Day 1, prior to the start of the infusion:
  - Pre-dose anti-birtamimab antibody sample
- [redacted]
- [redacted]

Study Drug Administration:

- The dose of study drug, including flush, may be delivered over 60 (±10) minutes if previous infusions have been well tolerated without infusion-related AEs (Section 6.5.1)

Assessments After Infusion:

- [redacted]
  - [redacted]
- Closely monitor subject for [redacted] minutes following completion of the study drug infusion per Section 6.5.1
- [redacted]
- Assessment of AEs
- Record all changes to concomitant medications and therapy

7.1.1.3.8. [redacted]

The subject must return to the study site for the following procedures:

Prior to Study Drug Infusion:

- Administer SF-36v2 questionnaire (Appendix [redacted]
- [redacted]
- 12-lead ECG performed in triplicate - [redacted]
- [redacted]
- [redacted]
- Local laboratory assessments:
  - Perform local laboratory assessments, including hematology and chemistry, and review results prior to dosing
  - WOCBP: serum/urine pregnancy test; test results must be obtained prior to dosing and must be negative (see Section 9.8)
- [redacted]

- 6MWT; [redacted]
- Bioanalytical laboratory assessments – any time on Day 1, prior to the start of the infusion:
  - Pre-dose anti-birtamimab antibody sample
- [redacted]
- [redacted]

Study Drug Administration:

- The dose of study drug, including flush, may be delivered over [redacted] minutes if previous infusions have been well tolerated without infusion-related AEs (Section 6.5.1)

Assessments After Infusion:

- [redacted]
  - [redacted]
- Closely monitor subject for [redacted] minutes following completion of the study drug infusion per Section 6.5.1
- [redacted]
- Assessment of AEs
- Record all changes to concomitant medications and therapy

7.1.1.3.9. [redacted]

Prior to Study Drug Infusion:

- [redacted]

[redacted]

- [redacted]
- Local laboratory assessments:
  - If administering chemotherapy during this visit: perform local laboratory assessments, including hematology and chemistry, and review results prior to dosing with chemotherapy
  - WOCBP: serum/urine pregnancy test; test results must be obtained prior to dosing and must be negative (see Section 9.8)
- [redacted]
- Bioanalytical laboratory assessments – any time on Day 1, prior to the start of the infusion:
  - Pre-dose anti-birtamimab antibody sample
- [redacted]
- 12-lead ECG performed in triplicate within 45 minutes prior to infusion
- [redacted]

Study Drug Administration:

- The dose of study drug, including flush, may be delivered over [redacted] minutes if previous infusions have been well tolerated without infusion-related AEs (Section 6.5.1)

Assessments After Infusion:

- [redacted]
- Closely monitor subject for [redacted] minutes following completion of the study drug infusion per Section 6.5.1
- [redacted]
- Assessment of AEs
- Record all changes to concomitant medications and therapy

7.1.1.4. Concomitant Chemotherapy Visits

The first cycle of first-line, bortezomib-containing chemotherapy should be initiated on Month 1-Day 1, following administration of study drug and completion of the post-study drug observation period. Month 1-Day 1 is equivalent to Cycle 1-Day 1 of chemotherapy. Bortezomib should be given subcutaneously weekly on Days 1, 8, 15, and 22 according to the approved prescribing information and local institutional practices. Antiviral prophylaxis is required.

The subject must be closely monitored during at least the first 3 cycles of the first-line, bortezomib-containing chemotherapy regimen. ***During the first cycle of chemotherapy (i.e., Month 1 of the study), the subject must return to the study site for each administration of bortezomib and for assessments prior to each administration.*** In addition, subjects must receive Cycle 2-Day 1, Cycle 2-Day 15, and Cycle 3-Day 1 (i.e., Month 2-Day 1, Month 2-Day 15, and Month 3-Day 1, respectively) of bortezomib, along with any other chemotherapy, ***at the study site***.

During the second and third cycles, Cycle 2-Day 1, Cycle 2-Day 15, and Cycle 3-Day 1 will correspond to the Month 2-Day 1, Month 2-Day 15, and Month 3-Day 1 visits, respectively, during which visits, bortezomib, along with any other chemotherapy, will be administered ***at the study site*** and assessments will be performed prior to each administration. For chemotherapy on Cycle 2-Days 8 and 22, as well as Cycle 3-Days 8, 15, and 22, the subject should return to the study site for bortezomib administration and assessments ***if***, in the opinion of the Investigator, the subject is ***experiencing any significant toxicity*** that appears to exceed the anticipated side effects of the chemotherapy. At the Investigator's discretion, if the subject is ***not*** experiencing any unanticipated or significant toxicity, the subject may be administered bortezomib by their local physician, rather than by the Investigator.

In the event that bortezomib doses are missed, the chemotherapy cycles may become misaligned with the monthly study drug dosing. In this case, the weekly visits during Months 1 through 3 should continue as described above in order to closely monitor subjects' health during the initial

months of concomitant chemotherapy. Throughout the study, monthly doses of study drug should not be delayed or skipped due to adjustments that are made to chemotherapy dosing. Study drug dosing adjustments are described in Section 6.6.

When bortezomib administration takes place at the subject's local physician's office, vital signs, and central laboratory sample collection must be performed by a Prothena-sponsored healthcare professional within 1 day prior to or pre-dose on the same day as each administration of bortezomib. If bortezomib is administered on a Monday, then it is acceptable for the homecare visit to take place on the previous Friday. The central laboratory results should be reviewed by the study investigator or local physician to determine subject safety in order to proceed with bortezomib administration.

The number of cycles of first-line chemotherapy that is administered is at the discretion of the Investigator. The initial first-line chemotherapy regimen may also include daratumumab, which can only be initiated as a part of standard of care chemotherapy at the time the subject is randomized. If daratumumab is included, associated pre-medications and post-medications may also be included according to the approved label or local practices. Subsequent chemotherapy regimens may be prescribed as per standard of care at the Investigator's discretion.

Refer to Section 6.5.3 for guidance regarding cycles of chemotherapy beyond Month [redacted]

7.1.1.5. Double-blind Phase End of Treatment (EOT)/Early Treatment Discontinuation (ETD) (28 to 35 Days Post Final Dose)

After approximately [redacted] primary endpoint events of all-cause mortality have occurred, the Double-blind Phase of the study will conclude, and all subjects will have a Double-blind Phase EOT Visit. Subjects who discontinue study drug before the EOT should have an ETD Visit after they decide to end their treatment. The EOT/ETD Visit should be completed 28 to 35 days after the subject's final administration of study drug in the Double-blind Phase. [redacted]

- Administer SF-36v2 questionnaire (Appendix 4) [redacted]
- [redacted]
- 12-lead ECG performed in triplicate
- [redacted]
- [redacted]
- [redacted]

  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- 6MWT; [redacted]
- Bioanalytical laboratory assessments:
  - Anti-birtamimab antibody blood sample
- [redacted]
- Assessment of AEs
- Record all changes to concomitant medications and therapy

7.1.2. Open-label Extension Phase

7.1.2.1. Treatment Visits

Before any OLE Phase-specific evaluations are performed, written informed consent for participation in this phase of the study must be obtained.

Subjects participating in the OLE Phase will receive birtamimab as an intravenous infusion every 28 days [redacted] from the previous Month X-Day 1 visit until the EOT/ETD Visit. Assessment and visit windows are described in the Schedule of Events (Table 2) and in the sections below; the study drug dosing window is described in Section 6.5.1. The pre-dose assessments for each visit may be performed within the 5 days prior to the visit.

[redacted] The frequency may be increased if clinically indicated based on Investigator judgment. Both local laboratory assessments and central laboratory assessments (as applicable) may be performed for subject management.

[redacted] If the study drug is withheld and subsequently

rescheduled, central laboratory assessments required for that visit will need to be repeated if they were drawn more than 7 days prior to the rescheduled dosing date. However, a symptom-directed PE and vital signs need to be repeated prior to each dosing. [redacted]

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

If the subject discontinues study drug treatment prior to the end of the study, refer to Section 8.2.

7.1.2.1.1. Open-label Extension Month 1-Day 1

The first visit (Month 1-Day 1) of the OLE Phase should occur the same day as the Double-blind Phase EOT Visit but no later than 2 months after the last dose of randomized treatment, if feasible. If the first visit of the OLE Phase occurs on the same day as the Double-blind Phase EOT Visit or within 14 days of that visit, results of procedures performed at that visit may be used for the pre-infusion procedures for the first visit of the OLE Phase and do not need to be repeated.

[redacted]

The following procedures will be performed at the first visit of the OLE Phase:

Prior to Study Drug Infusion:

- Obtain written informed consent
- Review OLE Phase inclusion and exclusion criteria to assess eligibility
- Administer SF-36v2 questionnaire (Appendix 4), [redacted]
- Assess any changes/additions to medical history since the last visit
- 12-lead ECG performed in triplicate
- [redacted]
- [redacted]
- Local laboratory assessment:

- If administering chemotherapy during this visit, perform any local laboratory assessments necessary per standard of care, and review results prior to dosing with chemotherapy
- Serum/urine pregnancy test for WOCBP within 24 hours prior to Month 1-Day 1 study drug administration; test results must be obtained prior to dosing and must be negative (see Section 9.8)

- [redacted]
- 6MWT; [redacted]
- [redacted]
  - Pre-dose anti-birtamimab antibody sample
- [redacted]

Study Drug Administration:

- [redacted]
- [redacted]

Assessments After Infusion:

- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- [redacted]
- Closely monitor subject for [redacted] minutes following completion of the study drug infusion per Section 6.5.1
- [redacted]
- Assessment of AEs
- Record all changes to concomitant medications and therapy

7.1.2.1.2. Open-label Extension [redacted]

The subject must return to the study site for the following procedures:

Prior to Study Drug Infusion:

- [redacted]
- [redacted]
- Local laboratory assessment:
  - If administering chemotherapy during this visit, perform any local laboratory assessments necessary per standard of care, and review results prior to dosing with chemotherapy

  - Serum/urine pregnancy test for WOCBP; test results must be obtained prior to dosing and must be negative (see Section 9.8)
- [redacted]
  - Pre-dose anti-birtamimab antibody sample
- [redacted]
- [redacted]

Study Drug Administration

- The dose of study drug, including flush, may be delivered over [redacted] minutes if the Month 1-Day 1 infusion was well tolerated without infusion-related AEs (Section 6.5.1)

Assessments After Infusion:

- [redacted]
- Closely monitor subject for [redacted] minutes following completion of the study drug infusion per Section 6.5.1
- [redacted]
- Assessment of AEs
- Record all changes to concomitant medications and therapy

7.1.2.1.3. Open-label Extension [redacted]

[redacted]

The subject must return to the study site for the following procedures:

Prior to Study Drug Infusion:

- Administer SF-36v2 questionnaire (Appendix 4), [redacted]
- 12-lead ECG performed in triplicate - within 45 minutes prior to infusion
- [redacted]
- [redacted]
- Local laboratory assessment:
  - If administering chemotherapy during this visit: perform any local laboratory assessments necessary per standard of care, and review results prior to dosing with chemotherapy
  - Serum/urine pregnancy test for WOCBP; test results must be obtained prior to dosing and must be negative (see Section 9.8)
- [redacted]
- 6MWT; [redacted]
- [redacted]
  - Pre-dose anti-birtamimab antibody sample
- [redacted]

  - [redacted]
- [redacted]

Study Drug Administration

- The dose of study drug, including flush, may be delivered over [redacted] minutes if the previous infusions were well tolerated without infusion-related AEs (Section 6.5.1)

Assessments After Infusion:

- Vital signs, including BP, HR, RR, and temperature – in the same position as those assessed pre-dose, at the following time points:
  - Immediately at the EOI (+10 minutes), which includes completion of the saline flush
  - 1 hour (±10 minutes) post-EOI
- Closely monitor subject for 90 (±10) minutes following completion of the study drug infusion per Section 6.5.1
- Administer any scheduled antiviral prophylaxis and chemotherapy after the post-study drug infusion observation period and review of any local laboratory tests necessary to confirm that dosing is appropriate. Dexamethasone may be administered during the observation period if necessary, after the review of local laboratory tests
- Assessment of AEs
- Record all changes to concomitant medications and therapy

7.1.2.1.4. Open-label Extension [redacted]

Prior to Study Drug Infusion:

- [redacted]
- [redacted]
- Local laboratory assessment:
  - If administering chemotherapy during this visit, perform any local laboratory assessments necessary per standard of care, and review results prior to dosing with chemotherapy

- Serum/urine pregnancy test for WOCBP; test results must be obtained prior to dosing and must be negative (see Section 9.8)

- [redacted]

- [redacted]

Study Drug Administration

- The dose of study drug, including flush, may be delivered over [redacted] minutes if the previous infusions were well tolerated without infusion-related AEs (Section 6.5.1)

Assessments After Infusion:

- [redacted]

- Closely monitor subject for [redacted] minutes following completion of the study drug infusion per Section 6.5.1

- [redacted]

- Assessment of AEs
- Record all changes to concomitant medications and therapy

7.1.2.1.5. Open-label Extension Month [redacted]

[redacted]

Prior to Study Drug Infusion:

- 12-lead ECG performed in triplicate - [redacted]

- [redacted]

- [redacted]

- Bioanalytical laboratory assessments – any time prior to the start of the infusion:
  - Pre-dose anti-birtamimab antibody sample

7.1.2.1.6. Open-label Extension [redacted]

[redacted]

Prior to Study Drug Infusion:

- Administer SF-36v2 questionnaire (Appendix 4) [redacted]
- 6MWT; [redacted]

7.1.2.2. Open-Label End of Treatment/Early Treatment Discontinuation (28 to 35 Days Post-Final Dose)

After 24 months of open-label treatment or when birtamimab becomes commercially available in a subject's country of residence, whichever occurs first (in accordance with country-specific regulations), a subject's participation on the OLE Phase will conclude, and the subject will have an OLE Phase EOT Visit. Subjects who discontinue study drug before the EOT should have an ETD Visit after they decide to end their treatment. The OLE Phase EOT/ETD Visit should be completed 28 to 35 days after the subject's final administration of study drug in the OLE Phase.

- Administer SF-36v2 questionnaire (Appendix 4) [redacted]
- 12-lead ECG performed in triplicate
- [redacted]

- [redacted]
- [redacted]
- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- 6MWT; [redacted]
- Bioanalytical laboratory assessments:
  - Anti-birtamimab antibody blood sample
- [redacted]
- Assessment of AEs
- Record all changes to concomitant medications and therapy

7.1.3. Vital Status Assessment Every 3 Months

[redacted]. The subject's vital status (survival information) will be collected during telephone contact or through public record searches, if necessary, and entered accordingly in the study database to ensure adequate capture of primary endpoint events.

7.1.4. Unscheduled Visit

Assessments and procedures may also be conducted for an unscheduled visit/phone call (ie., a visit not specified by the protocol) as clinically indicated or if deemed necessary.

7.2. Order of Assessments

At each study visit, there are certain assessments that must be performed in a prescribed order, as follows:

[redacted]

7.3. Laboratory and Additional Evaluations

[redacted]

Local laboratory results (e.g., hematology, chemistry) will be obtained for subject management when necessary for obtaining results on a more immediate basis. Local laboratory results should also be obtained and reviewed for a safety assessment prior to each administration of chemotherapy at the study site. Results from these local laboratory tests will not be collected in the eCRFs or the clinical database.

In addition, a bioanalytical laboratory will be used for the analysis of anti-birtamimab antibody serum samples. A bioanalytical laboratory also will be used for associated PK analysis as applicable. Samples will be stored for up to [redacted] years, as required by this protocol and applicable regulatory requirements. After such time period, any remaining samples will be destroyed.

[redacted] Sites are expected to utilize assays that comply with all applicable local standards for health, safety, and environmental protection.

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

[redacted]

Hospitalization data, including admission and discharge dates, as well as reason(s) for admission will be collected from baseline through the subject's last visit.

7.4. 6-Minute Walk Test

[redacted] At least 4 days are required between the 2 Screening 6MWTs; therefore, the first Screening 6MWT must be performed between Day -28 and Day -5 and the second Screening 6MWT should be performed within 3 days ***prior*** to Month 1-Day 1 (i.e., on Day -3 to Day -1). Subjects should plan to be able to return to the same clinical site for each 6MWT.

[redacted]

As part of the 6MWT, [redacted]

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

7.5. Monitoring Anti-Birtamimab Antibodies During the Study

[redacted]

For any subject with a positive anti-birtamimab antibody result, PK analysis may be performed on both the sample with a positive antibody result (or the backup sample collected at the same time point) and a sample from the preceding collection time point if sufficient quantity/volume of the serum anti-birtamimab antibody samples is available for the PK analysis.

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

8. EMERGENCY UNBLINDING OF STUDY DRUG, EARLY DISCONTINUATION, OR TERMINATION FROM STUDY

8.1. Emergency Unblinding

In the event of an immediate medical emergency, the Investigator should implement emergency treatment to the subject, based on medical judgment and/or institutional policy. However, the Investigator has the ability to break the blind for a specific subject where knowledge of the subject's treatment (birtamimab or placebo) must be known in order to provide adequate medical treatment. In these situations, the breaking of the blind must be reported to the Sponsor within 24 hours.

Any other requests to reveal a subject's treatment must be requested of, and approved by, the Medical Monitor.

8.2. Early Treatment Discontinuation

If the subject discontinues study drug prior to the end of the Double-blind Phase, but is willing to continue to participate in study visits, the subject should have a Double-blind Phase ETD Visit within 28 to 35 days after his/her final administration of study drug (per Table 1 and Section 7.1.1.5) and then have assessments [redacted] during the remainder of the Double-blind Phase per Appendix 1.

If the subject discontinues study drug prior to the end of the Double-blind Phase and is not willing to continue to participate in study visits, the subject should return for an ETD Visit 28 to 35 days after his/her final administration of study drug (per Table 1 and Section 7.1.1.5).

If a subject discontinues study drug prior to the end of the OLE Phase, the subject should return for an ETD Visit 28 to 35 days after his/her final administration of study drug (Table 2 and Section 7.1.1.2).

If a subject fails to return for the scheduled Double-blind Phase or OLE Phase ETD Visit, a documented effort must be made to determine the reason. If the subject cannot be reached by phone after 2 attempts, a certified letter will be sent to the subject (or the subject's legally authorized representative, if appropriate) requesting contact with the Investigator. This information will be recorded in the study records.

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

- [redacted]
- Occurrence of an AE or clinically significant laboratory abnormality that, in the opinion of the Investigator, warrants the subject's permanent discontinuation from study drug treatment; the Medical Monitor should be notified as soon as possible of any discontinuation of study drug due to an AE.
- Suspected or confirmed pregnancy or nursing during the study treatment period. Female subjects who have a positive pregnancy test at the ETD Visit must be followed to term or until termination of the pregnancy (Section 9.8).

At any point in the study, if a subject who has received a dose of study drug is unwilling to return to the study site for further visits but is willing to discuss his/her health status by phone, conduct vital status assessments for the subject, per Section 7.1.2.

8.3. Early Termination from the Study

Subject participation in the Double-blind Phase of this study will continue until the end of the Double-blind Phase (i.e., until approximately [redacted] primary endpoint events of all-cause mortality have occurred). Early termination from the Double-blind Phase occurs if the subject fails to complete the entire Double-blind Phase and is no longer participating in study visits. Subject participation in the optional OLE Phase of this study will continue for 24 months or until birtamimab is commercially available in a subject's country of residence, whichever occurs first (in accordance with country-specific regulations). Early termination from the OLE Phase occurs if the subject fails to complete the entire OLE Phase and is no longer participating in study visits.

Subjects may withdraw their consent to participate in this study at any time without prejudice. The Investigator must withdraw from the study any subject who requests to be withdrawn. A subject's participation in the study may be discontinued at any time at the discretion of the Investigator in accordance with his/her clinical judgment. The Sponsor should be notified in a timely manner of all subject discontinuations.

Early termination from the study may occur if:

- Subject needs to receive any of the prohibited concomitant therapies listed in Section 6.8.2
- In the opinion of the Investigator, the subject cannot safely participate in the procedures required by the protocol
- Subject withdraws consent
- Subject is unwilling or unable to comply with the study requirements
- Subject is lost to follow-up
- Prothena reserves the right to discontinue the study at any time for any reason, including but not limited to, clinical or administrative reasons, or to discontinue participation of an individual Investigator or site for any reason, including but not limited to, poor enrollment or noncompliance.

Vital status will be collected within legal and ethical boundaries for all subjects receiving at least 1 dose of study drug and will be searched in public sources. During the Double-blind Phase close-out period and the final study close-out period, survival status will be collected within legal and ethical boundaries for all subjects who withdrew participation from the study. If vital status is determined, the subject will not be considered lost to follow-up.

8.4. Replacement of Subjects

Subjects who drop out of the study for any reason will not be replaced.

9. ADVERSE EVENTS/SERIOUS ADVERSE EVENTS AND REPORTING

9.1. Definitions

Consistent with the current regulatory guidance provided by the US Code of Federal Regulations (CFR) and the International Council for Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), AEs and serious adverse events (SAEs) are defined below.

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

This includes:

- The emergence of any signs and symptoms that were not present at baseline (an event present at baseline that has not changed is not considered an AE)
- Pre-existing conditions that are marked by a worsening from the subject's baseline/entry status (i.e., an increase in severity or frequency of the pre-existing abnormality or disorder)
- Reactions to study drug, sensitivity, or toxicity to study drug
- Apparently unrelated illnesses
- Injuries or accidents
- Extensions or exacerbations or symptomatology, subjective events reported by the subject, or new clinically significant abnormalities in clinical laboratory tests, physiological tests or PE

SAE Definition: An SAE is an AE that results in any of the following:

- Death
- Life threatening AE
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Inpatient hospitalization or prolongation of existing hospitalization
- A congenital anomaly or birth defect (in a child or fetus of a subject exposed to the study drug prior to conception or during pregnancy)
- An important medical event that, based on appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above (e.g., anaphylaxis)

An SAE may also include other event(s) that the Investigator or Sponsor deems to be serious based on medical judgment.

Death: Death, in and of itself, is not an AE; it is only an outcome. The cause of death is the AE. Therefore, the Investigator should make every effort to obtain and document the cause of death for all subjects who die during the study. If, despite all efforts, the cause of death remains unknown, the SAE should be documented as an "unspecified fatal event."

Life-threatening AE: Any AE that places the subject, in the view of the Investigator, at ***immediate*** risk of death from the event as it occurred. This does not include an event that, had it occurred in a more severe form, might have caused death.

Hospitalization: Hospitalization is defined by the Sponsor as a full admission to the hospital for diagnosis and treatment. This includes prolongation of an existing inpatient hospitalization. Examples of visits to a hospital facility that do ***not*** meet the serious criteria for hospitalization include:

- Emergency room visits that do not result in a full hospital admission or that last for a period of less than 24 hours
- Outpatient surgery
- Preplanned or elective procedures
- Protocol procedures

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

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

An untoward medical event occurring during the pre-scheduled elective procedure or routinely scheduled treatment should be recorded as an AE or an SAE, as appropriate.

Disability: A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.

9.2. Adverse Events – Detecting, Recording, and Reporting

9.2.1. Reporting Period for Adverse Events

The reporting period for AEs for both the Double-Blind and OLE Phases is as follows:

- All non-serious AEs and SAEs are reported from when the first administration of study drug is initiated through 28 days after the last dose of study drug or until the EOT/ETD Visit, whichever is later.
- After the ICF is signed but prior to the first administration of study drug: only SAEs related to any protocol-imposed intervention are reported. Other SAEs and AEs that occur between the signing of the ICF and first study drug administration should be captured as concurrent Medical History.

- 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 related to any protocol intervention (related to study procedure or previous study drug exposure).

9.2.2. Reporting of Adverse Events

All AEs (which includes SAEs), whether or not related to the study drug, must be fully and completely documented on the eCRF and in the subject's medical notes. Pre-existing conditions (noted before Screening) should not be reported as AEs unless they worsen (i.e., become more severe or more frequent) after the first administration of study drug is initiated. At each visit, the Investigator will ask the subject if any AEs were experienced since the last visit. The Investigator must follow all AEs until the events have resolved or until the condition has stabilized and no further medical follow-up is warranted. The Investigator may be asked to provide additional follow-up information to the Sponsor upon request. At the discretion of the Investigator, unscheduled visits and assessments may be performed during the study based on medical judgment and documented in the eCRFs.

If a subject is withdrawn from study drug treatment and/or the study because of an AE, it must be recorded on the AE and Disposition eCRFs. The subject should be followed and treated by the Investigator until the AE has resolved, stabilized, or a new chronic baseline has been established.

Whenever feasible, AEs should be documented as medical diagnoses and a unifying diagnosis should be provided. For example, symptoms including fever, productive cough, opacity in the left lower lobe of the lung on x-ray would be reported as a single AE of pneumonia. Otherwise, if reported AEs do not appear clearly inter-related as part of a diagnosis, individual signs or symptoms may be reported as separate AEs. Information recorded on the appropriate page of the eCRF will include the description of the AE, the date and time of onset and resolution (if applicable), severity, seriousness, relationship to the study drug, action taken, and the outcome.

When an AE resulting from disease progression meets the requirements to be considered serious the SAE verbatim term should be reported as the sign/symptom that best describes the event rather than as disease progression. For example, if a subject presents with worsening shortness of breath due to a pleural effusion from disease progression, the event term should be reported as "pleural effusion" instead of as disease progression.

9.3. Severity Assessment

Severity (e.g., NCI-CTCAE Grade 1, 2, 3, etc.) is not equivalent to seriousness, which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning.

The Investigator will determine the severity of each AE/SAE using the NCI-CTCAE Version 5.0. AEs that do not have a corresponding CTCAE term will be assessed according to the general guidelines for grading used in the CTCAE as stated in Table 4.

Table 4: Adverse Event Severity Grading Scale

CTCAE Grade	Description
1	Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate: minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[a]
3	Severe or medically significant but not immediately life-threatening: hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[b]
4	Life-threatening consequences; urgent intervention indicated
5	Death related to AE

ADL = activities of daily living; AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; SAE = serious adverse event

a. Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

b. Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Source: CTCAE.

The severity of the AE should be recorded in the appropriate section of the AE eCRF.

9.4. Relationship to Study Drug

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

Guidelines for "Related" Events

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

Guidelines for "Not related" Events

- There is little evidence to suggest there is a causal relationship. There is another reasonable explanation for the event.
- An AE will be considered "not related" to the use of the product if any of the following tests are met:

- An unreasonable temporal relationship between administration of the product and the onset on the AE (e.g., the event occurred either before, or too long after administration of the product for it to be considered product-related)
- A causal relationship between the product and the AE is biologically implausible (e.g., death as a passenger in an automobile accident)
- A clearly more likely alternative explanation for the AE is present (e.g., typical adverse reaction to a concomitant drug and/or typical disease-related event)

Consider the Following When Assessing Causality

- Temporal associations between the agent and the event
- Effect of dechallenge and/or rechallenge
- Compatibility with known class effect
  - The likelihood the AE can be attributed to the use of concomitant drugs, in particular chemotherapeutic agents used in treating the subject's underlying PCD (see the current prescribing information for chemotherapeutic products used as standard of care; refer to Appendix 6)
- Pre-existing risk factors
- A plausible mechanism
- Concurrent illnesses

9.5. Adverse Event Outcome Assessment

- Recovered/Resolved: The subject has recuperated or the event has improved.
- Recovered/Resolved with Sequelae: The subject recuperated but retained pathological conditions resulting from the prior disease or injury.
- Recovering/Resolving: Event is improving.
- Not Recovered/Not Resolved: Event has not improved or recuperated.
- Fatal: The termination of life as a result of an AE.
- Unknown: Not known, not observed, not recorded, or refused.

(Source: Clinical Data Interchange Standards Consortium [CDISC] in collaboration with the National Cancer Institute's Enterprise Vocabulary Services.)

9.6. Reporting of Serious Adverse Events

During both phases of the study, it is the responsibility of the Principal Investigator to report SAEs to the Sponsor or its designee.

- Any SAE that occurs at any time from the first study drug administration to 28 days after the last dose of study drug or until the EOT/ETD Visit, whichever is later, whether or not related to study drug, must be reported within 24 hours of discovery to the Sponsor or its designee.

- During the Screening period (e.g., after the ICF is signed but prior to the first administration of study drug, only) SAEs related to any protocol-imposed intervention are reported. Other SAEs and AEs that occur between the signing of the ICF and first study drug administration should be captured as concurrent Medical History.
- 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 related to any protocol intervention (i.e., related to study procedure or previous study drug exposure).

Do **not** delay in the reporting of an SAE in order to obtain additional information. Any additional information, if collected, can be reported to the Sponsor as a follow-up to the initial report. The SAE report should include the subject identification number or other appropriate terminology and the narrative should be comprehensive, including a chronology and assessment of the event. The SAE report should also include the Investigator's assessment of the relationship of the event to the use of study drug. This assessment can be changed as more information becomes available.

The Investigator is encouraged to discuss with the Medical Monitor any AEs for which the assessment of seriousness is unclear or questionable. Contact information for the Medical Monitor is found in the Study Manual.

9.6.1. SAE Reporting to Prothena via Paper Safety Reporting Form

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours. The Investigator will submit any updated or follow-up SAE data to the Sponsor within 24 hours of the receipt of information. Either facsimile (fax) transmission or a scan and email of the Investigator-signed hard-copy SAE paper form is the preferred method to transmit this information of SAE information to Prothena Drug Safety at ProthenaDrugSafety@Prothena.com.

In rare circumstances if fax or email transmission is not available, notification by telephone to the Medical Monitor is acceptable. Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE hard-copy pages within the designated reporting time frames.

Contacts for SAE reporting can be found in the Safety Reporting Completion Guideline.

9.6.2. Regulatory Reporting Requirements for SAEs

Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

During the study, the Sponsor or its designee will inform health authorities, central Institutional Review Boards (IRBs)/Ethics Committees (ECs), and the participating investigators of any suspected unexpected serious adverse reactions (SUSARs) occurring in other study centers or other studies of the active study drug, as appropriate, per local reporting requirements. In addition, the Sponsor or its designee will comply with any additional local safety reporting requirements.

Event expectedness for study drug is assessed by the Sponsor against the Reference Safety Information section of the Investigator's Brochure that is effective for expedited safety reporting.

An Investigator who receives an Investigator safety report describing an SAE/SUSAR or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file with the study records as appropriate and notify the IRB/EC, if appropriate, according to local requirements.

At the completion of the study, the Sponsor will report all safety observations made during the conduct of the trial in the Clinical Study Report to health authorities and IRBs/ECs as required.

9.7. Follow-up of Adverse Events

All AEs experienced by a subject, regardless of the suspected causality, will be followed until the event has resolved, until the Investigator and/or the Medical Monitor deems the event to be chronic or stable, until there is a satisfactory explanation for the changes observed, or until the subject is lost to follow-up.

9.8. Pregnancy

WOCBP are those who have experienced menarche and who are not permanently sterile or postmenopausal (12 consecutive months with no menses without an alternative medical cause). The inclusion of female subjects of childbearing potential requires use of a highly effective contraceptive measures, which when used consistently and correctly, result in low failure rates. Highly effective methods of birth control must be used in WOCBP from Screening through 90 days after the last dose of study drug administration and include: hormonal contraceptives (e.g., combined oral contraceptives, patch, vaginal ring, injectables, and implants); intrauterine device or intrauterine system; vasectomy and tubal ligation.

WOCBP must have 2 negative pregnancy tests during Screening (serum and urine with the second (i.e., urine) within 24 hours prior to the first administration of study drug). Serum or urine pregnancy testing for WOCBP is collected locally on dosing visits and the local laboratory result must be reviewed prior to dosing.

If a urine pregnancy test result is positive, a local serum pregnancy test must be done to confirm the pregnancy status. Subjects with a confirmed positive pregnancy test result will be discontinued (see Section 8.2).

For male subjects who are not surgically sterile with female partners of childbearing potential, a barrier method must be used while on treatment with birtamimab from the time of Screening through at least 90 days after the last dose of the study drug to prevent pregnancy of the female partner. In addition, a highly effective physician-approved method of birth control should be used by the female partner of childbearing potential.

Pregnancy in a subject or partner should be reported within 24 hours of the site becoming aware of the pregnancy by faxing or a scan and email of the Pregnancy Form in the study reference materials to the Sponsor or their designee. Any abnormal outcome of pregnancy that occurs during the study shall be reported as an SAE. The Investigator must make every effort to follow the subject through resolution of the pregnancy (delivery or termination) and to report the resolution on the Pregnancy Form in the study reference materials. In the event of pregnancy in

the partner of a study subject, the Investigator should make every reasonable attempt to obtain the woman's consent for release of protected health information.

Any subject who becomes pregnant during the study must be withdrawn from study drug and will be followed for the outcome of the pregnancy. The Investigator must follow-up and document the course and the outcome of all pregnancies even if the clinical study has ended. Pregnancies must be followed until birth, termination of the pregnancy, or loss of the subject to follow-up. If applicable, follow-up of a pregnancy will occur beyond the end of the study (e.g., clinical database lock) to observe for any significant safety issues.

9.9. Urgent Safety Measures

The Sponsor is required to follow global regulations including EU regulations which state that the appropriate regulatory bodies, including IRBs/ ECs /Research Ethics Boards, be notified according to their respective regulations of any new event resulting in the Sponsor and Investigator taking urgent safety measures to protect subjects against any immediate hazards.

For each phase of the study, the reporting period for these events, which may require the implementation of urgent safety measures, is the period from the first dose of study drug administration through the completion of the EOT/ETD Visit or for 28 days after the last dose of study drug, whichever is later. Investigators are required to report any events which may require the implementation of urgent safety measures to Sponsor within 24 hours. Examples of situations that may require urgent safety measures include the following:

- Immediate need to revise the study drug administration (e.g., modified dose amount or frequency not defined in protocol)
- Change in the study which has a significant impact on the scientific value of the clinical study
- Detrimental study conduct or management
- Discovery that the quality or safety of the study drug does not meet established safety requirements

10. STATISTICAL CONSIDERATIONS

A statistical analysis plan (SAP) for each study phase, providing details about the specific planned analyses and hypothesis tests, will be prepared and approved by the Sponsor and its designees prior to study database lock.

10.1. Analysis Populations

[redacted] and the Safety Population will include all randomized subjects with Mayo Stage IV AL amyloidosis who receive any amount of study drug (birtamimab or placebo). [redacted] will be the primary population used for the Double-blind Phase efficacy analyses, and subjects will be analyzed according to the treatment assigned at randomization. The Safety Population will be the primary population used for the Double-blind Phase safety analyses, and subjects will be analyzed based on the treatment received. The OLE Population will include all subjects who receive at least 1 dose of study drug in the OLE Phase. This population will be used for safety and exploratory efficacy analyses involving OLE Phase data, and subjects will be analyzed by treatment received in the Double-blind and OLE Phases.

10.2. General Considerations

For the Double-blind Phase, subject disposition will be summarized for all screened subjects and will include the number of subjects screened, the number screened but not enrolled with reasons for screen failure, the number in each subject population for analysis, the number who withdraw from study prior to completing the study and reason(s) for withdrawal, and the number who discontinued treatment early and reason(s) for discontinuation of treatment. The demographic and baseline characteristics will be presented for the [redacted] and Safety Populations. Duration of study drug exposure will be summarized using descriptive statistics for the Safety Population. For the OLE Phase, subject disposition, demographic and baseline characteristics, and study drug exposure will be summarized for the OLE Population.

[redacted]

10.3. Efficacy Analyses

10.3.1. Primary Analysis

The primary endpoint is time to all-cause mortality during the Double-blind Phase. For all-cause mortality, all deaths occurring after the first infusion of study drug (i.e., Study Day 1) through the last subject last visit, follow-up telephone call, or public record search in the Double-blind Phase, whichever is later, will be included.

The distribution of the time to all-cause mortality will be summarized using the Kaplan-Meier method. [redacted]

[redacted]

Using a log-rank test, birtamimab and the placebo control will be compared at a significance level of [redacted] at the final analysis.

10.3.2. Secondary Efficacy Analyses

If the primary analysis at the end of the Double-blind Phase (i.e., after approximately [redacted] primary endpoint events of all-cause mortality have occurred) is statistically significant in favor of birtamimab, the following key secondary endpoints will be analyzed using a fixed-sequence testing procedure with the same significance level as the primary endpoint in the order specified below to control the overall level of significance:

- Change from baseline to Month 9 of the Double-blind Phase in the 6MWT distance (meters)
- Change from baseline to Month 9 of the Double-blind Phase in the PCS score of the SF-36v2

[redacted]

10.3.3. Handling of Missing Data

Every effort must be made to avoid missing data. For all time-to-event endpoints, subjects with no data after first dose date will be censored on Day 1 (first day of study drug dosing).

Missing data for quantitative endpoints will not be imputed unless otherwise specified. Missing data imputation for analyses of the effects of missing data for primary and secondary endpoints will be provided in the SAP.

10.4. Safety Analyses

For the Double-blind and OLE Phases, safety data, including AEs, vital signs, ECGs, and clinical laboratory observations will be summarized by treatment received using the Safety and/or OLE Populations, as applicable.

10.4.1. Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities. Summary tables of TEAEs will be provided for each study phase. The incidence of TEAEs will be tabulated by system organ class and preferred term, and by severity and relationship to treatment. Tables of

TEAEs leading to study drug discontinuation and treatment-emergent SAEs will be provided. NCI-CTCAE will be used for grading severity of AEs and laboratory values.

10.4.2. Clinical Laboratory Evaluations

Descriptive statistics summarizing central laboratory data will be presented for all study visits. Changes from baseline (Double-blind and/or OLE Phase, as applicable) to each study visit will also be summarized. 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.

[redacted]

10.4.3. Vital Signs and Electrocardiograms

Descriptive statistics summarizing absolute values and changes from baseline (Double-blind and/or OLE Phase, as applicable) in vital sign and ECG parameters will be presented for all study visits.

10.5. Immunogenicity

Serum anti-birtamimab antibody data for each study phase will be summarized and listed. Serum anti-birtamimab antibody data may be correlated with select PK, safety, and efficacy data, if sufficient data exist.

[redacted]

10.6. Interim Analysis

An interim analysis of time to all-cause mortality during the Double-blind Phase will be conducted when approximately 50% (or [redacted] of the events have occurred. Using the O'Brien-Fleming group sequential methodology, the overall significance level of [redacted] will be divided between the interim analysis (p< [redacted]) and final analysis (p< [redacted].

An independent DMC will review data on a regular basis at selected intervals to ensure that birtamimab is safe and well tolerated. The DMC will also evaluate the results of the interim analysis and determine if the trial can be stopped early for overwhelming efficacy. The guidelines for the DMC operations will be defined in a separate DMC Charter.

10.7. Determination of Sample Size

A two-sided log-rank test with a total of [redacted] events would achieve [redacted]% power at a 0.1 significance level to detect a hazard ratio of 0.[redacted] The hazard ratio of 0.[redacted] is based on the post hoc analysis of Mayo Stage IV patients from the Phase 3 Study NEOD001-CL002 (Section 1.3.2), in which the birtamimab exponential hazard rate was 0.[redacted] (corresponding to [redacted]% survival at 9 months) and the placebo exponential hazard rate was 0.[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).

10.8. Data Monitoring Committee

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 members will review safety reports on a periodic basis. This will include review of aggregated data to assess SAEs. The DMC will meet at least twice a year starting when the first subject is exposed to study medication and continuing until the Double-blind Phase is complete and the database for that phase is locked and finalized, after which the DMC will be disbanded.

The DMC will review the study data at the interim analysis (after approximately [redacted] events have occurred) and recommend either continuing the study or stopping early for overwhelming efficacy.

11. DATA RECORDING, RETENTION, AND MONITORING

11.1. Case Report Forms

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

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

11.2. Availability and Retention of Records

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

Investigators are required to maintain all study documentation, including documents created or modified in electronic format, for the maximum period required by applicable regulations and guidelines, institution procedures, or at least 25 years, whichever is longer, following the completion of the study. ICFs, as well as all other study documents as specified as essential documents in ICH GCP, and adequate records for the receipt and disposition of all study drug must be retained for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated, or if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA and other applicable regulatory authorities are notified, unless a longer period is required by applicable law or regulation. The Investigator must not discard any records unless given written authorization by the Sponsor.

Study subjects' names and directly identifying personal information will be maintained by the Investigator for the maximum period required by institution procedures or at least 25 years, whichever is longer, unless applicable law or regulation requires a longer period.

Subject data will be collected, processed, and stored securely in the originating source systems (i.e., validated vendor systems maintained on secure data servers). Electronic records will be maintained per the requirements of Eudralex Volume 4 Annex 11, FDA 21 CFR Part 11, and the respective FDA Guidance Documents. Paper records and documents will be maintained under secure, controlled access, fireproof conditions (e.g., fireproof cabinet in locked room) to prevent theft, damage, or deterioration. Vendors will transfer encrypted data securely to the Sponsor/designee(s) according to written data transfer agreements. All study data, regardless of

format, will be collected, processed, stored, and transferred in accordance with applicable laws and regulations.

11.3. Quality Control and Quality Assurance

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

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

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

Source documentation may be accessed remotely for monitoring or audit purposes, if permitted by local regulations.

11.4. Subject Confidentiality

The Investigator must ensure that each subject's anonymity is maintained as described below. On the eCRFs or other documents submitted to the Sponsor or its designee, subjects must be identified by no more than year of birth or age, sex, and a unique Subject Identification Number.

Documents that are not for submission to the Sponsor (e.g., signed ICFs) shall be kept in strict confidence by the Investigator in compliance with applicable regulations and ICH GCP Guidelines. The Investigator and site must permit authorized representatives and agents of the Sponsor, study monitors and auditors, independent safety and expert oversight committees, regulatory agencies, and the IRB/EC direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are needed for the evaluation of the study. The Investigator shall inform each subject and further, secure each subject's consent in the ICF that the above-named persons and entities may have such direct access to the subject's study related records.

12. ETHICAL AND LEGAL ISSUES

12.1. Ethical Conduct of the Study

The Investigator and Sponsor will ensure that this study is conducted in full compliance with the "Declaration of Helsinki" ICH guidelines, the CFR, Regulation (EU) No. 536/2014 as applicable, and/or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject.

12.2. Regulatory Approval

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

12.3. Independent Review Board / Ethics Committee (EC) Approval

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

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

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

12.4. Subject Informed Consent

The Sponsor will prepare the master ICF for each phase of the study, which will be provided to the Investigator. The Sponsor or its designee must review and approve in writing, any amended ICFs prepared by the Investigator prior to submission to the IRB/EC for approval. An IRB/EC approved copy of each ICF and all amendments will be forwarded to Prothena or its designee for written approval prior to use by a site.

The ICFs document the study-specific information the Investigator provides to the subject and the subject's agreement to participate. Among other things, the Investigator will fully explain in layman's terms the nature of the study, along with the aims, methods, potential risks, and any discomfort participation in the study may entail. The subject will be informed that his/her participation is voluntary and that he/she may withdraw consent to participate at any time. In

France, patients will be allowed a 48-hour reflection period during which they can make a decision regarding their participation in the study. The subject must voluntarily, personally sign and date the ICF for each study phase before any study-related procedures for that phase are performed. The original and any amended, signed and dated ICFs must be retained in the subject's file at the study site and copies of the signed ICFs must be provided to the subject.

12.5. Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in the study will be limited to those data that are necessary to fulfill the objectives of the study. Subject data will be stored according to Section 11.2.

Such data must be collected and processed with adequate precautions to ensure compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures must be in place to protect the personal data against unauthorized access, disclosure, dissemination, alteration, or loss, such as being stored at the study site in encrypted electronic and/or paper form and password protected or secured in a locked room to ensure that only authorized study staff have access. With respect to information technology systems owned or controlled by the Sponsor, the Sponsor maintains policies and procedures on how to respond in the event of unauthorized access, use, or disclosure of Sponsor information or systems.

The informed consent obtained from the subject shall include explicit consent for the processing of his or her personal data by the study site, Sponsor and representatives and agents of the Sponsor, and for the Investigator and study site to allow direct access to the subject's medical records for study-related monitoring, audits, regulatory inspections, and IRB/EC review. The informed consent shall also provide for the subjects' explicit consent for the transfer of their personal data to the Sponsor and to other entities who may be located in other countries, where different data privacy laws apply.

12.6. Subject Compensation for Adverse Effects on Health

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

12.7. Protocol Amendments and Study Termination

The Sponsor or its designee may amend the protocol as needed to ensure that the clinical investigation is being conducted as intended. The Sponsor or its designee will initiate protocol amendments in writing if any change significantly affects the safety of subjects, the scope of the investigation, or the scientific quality of the study. Protocol changes must be submitted to the IRB/EC as a protocol amendment. If necessary, the ICF(s) will be revised to reflect the changes in the amendment and will be submitted to the IRB/EC for review and approval. A copy of the amendment signature page must be signed by the Investigator and returned to the Sponsor or its designee. Written documentation of IRB/EC approval is required before the amendment is implemented.

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

12.8. Finance, Insurance, and Indemnity

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

12.9. Serious Breaches of the Protocol or ICH GCP

The Investigator will inform Prothena immediately of any serious breaches of this protocol or of the ICH GCP guidelines that the Investigator becomes aware of, reporting the serious breach to seriousbreachGCP@prothena.com.

13. PUBLICATION

All publication rights are delineated in the Clinical Study Agreement. The study results will be posted in clinical trial databases in accordance with local requirements.

14. REFERENCES

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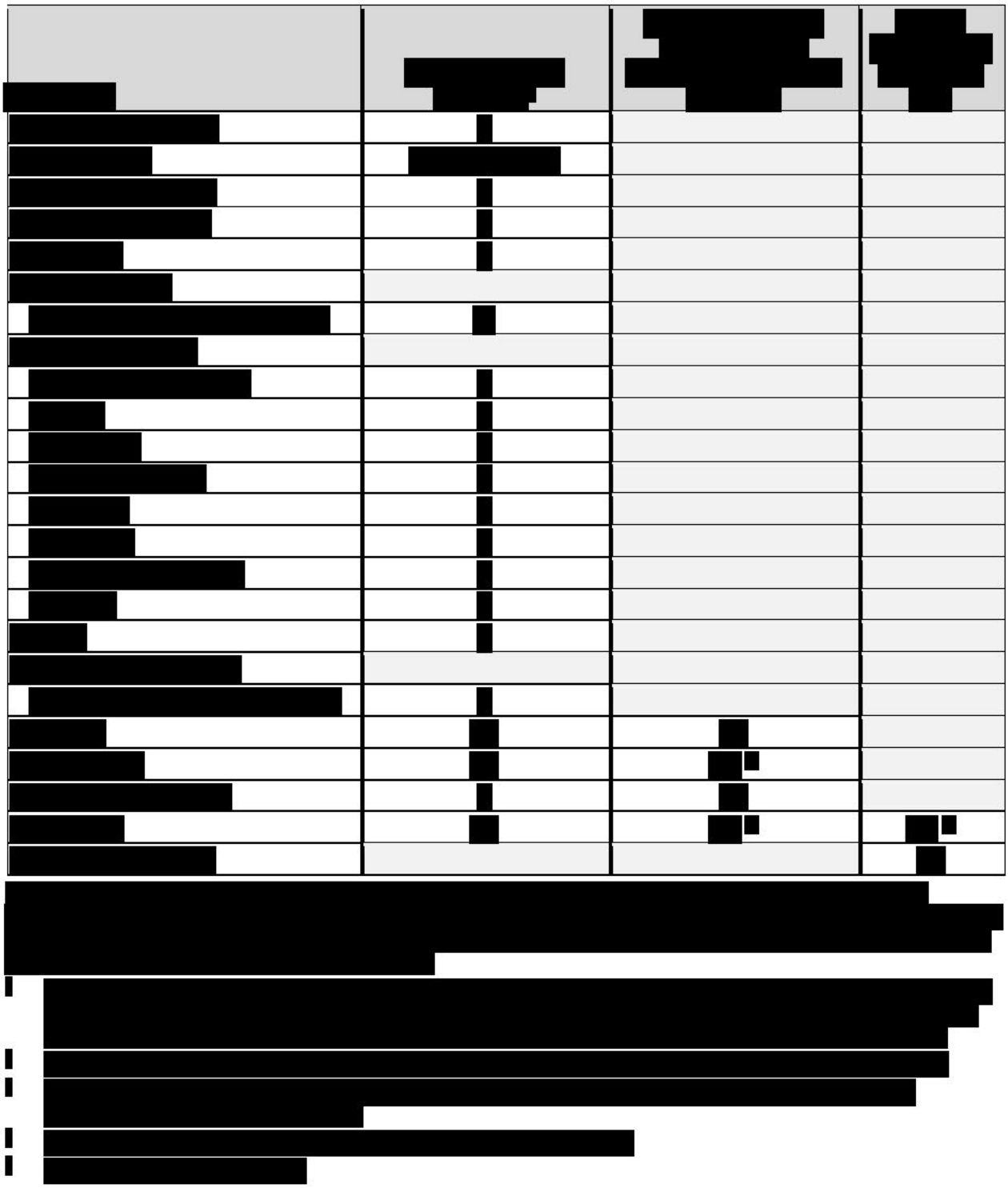
15. APPENDICES

APPENDIX 1.



APPENDIX 2. EXAMPLES OF HIGHLY EFFECTIVE CONTRACEPTION METHODS

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

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

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

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

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

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

Source: Clinical Trial Facilitation Group (CTFG): Recommendations related to contraception and pregnancy testing in clinical trials (Final Version 15Sep2014). Available from: http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf. Accessed 02Aug2015.

APPENDIX 3. REVISED INTERNATIONAL MYELOMA WORKING GROUP DIAGNOSTIC CRITERIA FOR MULTIPLE MYELOMA

Definition of Multiple Myeloma

Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma[1] and any one or more of the following myeloma defining events:

Myeloma defining events:

- Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
  - Hypercalcemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal (ULN) or >2.75 mmol/L (>11 mg/dL)
  - Renal insufficiency: creatinine clearance <40 mL per min[2] or serum creatinine >177 μmol/L (>2 mg/dL)
  - Anemia: hemoglobin value of >20 g/L below the lower limit of normal, or a hemoglobin value <100 g/L
  - Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT[3]
- Any one or more of the following biomarkers of malignancy:
  - Clonal bone marrow plasma cell percentage[1] ≥60%
  - Involved/uninvolved serum free light chain ratio[4] ≥100
  - >1 focal lesions on magnetic resonance imaging studies[5]

CT = computed tomography; PET = positron emission tomography; PET-CT = ^{18}F-fluorodeoxyglucose PET with CT; ULN = upper limit of normal.

1 Clonality should be established by showing κ/λ-light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and core biopsy, the highest value should be used.

2 Measured or estimated by validated equations.

3 If bone marrow has less than 10% clonal plasma cells, more than 1 bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement.

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

5 Each focal lesion must be 5 mm or more in size.

Source: Rajkumar 2014.

APPENDIX 4. SHORT FORM-36 QUESTIONNAIRE (SF-36V2)

Your Health and Well-Being

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

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

In general, would you say your health is:

Excellent
Very good
Good
Fair
Poor

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

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

SAMPLE

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

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

APPENDIX 6. PACKAGE INSERTS FOR CHEMOTHERAPEUTIC AGENTS COMMONLY PRESCRIBED FOR INDIVIDUALS WITH AL AMYLOIDOSIS

Package Inserts for many chemotherapeutic agents commonly prescribed for individuals with AL amyloidosis and which have been approved by the US Food and Drug Administration (FDA) may be found at the FDA website, Drugs@FDA, at the following link: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/

The Summary of Product Characteristics for all products approved via the Centralized procedure in the European Union (EU) can be found on the European Medicines Agency (EMA) website as follows: https://www.ema.europa.eu/en/medicines

The above website states that EMA does not evaluate all medicines currently in use in Europe. If a specific medicine cannot be found on the website, it may be found on that of the national health authority of a specific EU country. For example, in the United Kingdom, refer to the electronic Medicines Compendium (https://www.medicines.org.uk/emc/about-the-emc).

For countries outside of the US and EU, the package inserts may be found on the website of the country's national health authority.

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