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

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This study has been transitioned to CTIS with ID 2024-511066-36-00 check the CTIS register for the current data. Double-blind Phase:Primary Objective:To evaluate the efficacy of birtamimab plus standard of care compared to placebo plus standard of...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Metastases
Study type	Interventional

Summary

ID

NL-OMON54039

Source
ToetsingOnline

Brief title
Efficacy and Safety of Birtamimab in Mayo Stage 4 AL; NEOD001-301

Condition

- Metastases

Synonym
Mayo Stage IV Light Chain (AL) Amyloidosis

Research involving
Human

Sponsors and support

Primary sponsor: Prothena Biosciences Limited
Source(s) of monetary or material Support: Prothena Biosciences Limited

Intervention

Keyword: Birtamimab, efficacy, Mayo Stage 4 AL, safety

Outcome measures

Primary outcome

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

Secondary outcome

• Change from baseline to Month 9 of the Double-blind Phase in the 6-Minute

Walk Test (6MWT) distance

• Change from baseline to Month 9 of the Double-blind Phase in health related

quality of life using the Short Form 36 questionnaire Version 2 (SF 36v2)

Study description

Background summary

Subjects are being asked to take part in this study because they have been newly diagnosed with Mayo Stage IV AL amyloidosis. This is a relatively rare blood disease in which deposits of abnormal proteins, called amyloid, can build up in the organs. This build up can cause progressive damage so that the organs no longer work properly. Organs that can be affected include: heart, kidneys, liver, spleen, digestive or gastrointestinal tract, and nervous system. Antibodies are proteins that make up part of the immune system, the body*s own natural defense system. They recognize foreign or unwanted material, such as infections or even some cancers, and help destroy them without causing too much harm to normal cells. Birtamimab is an antibody that was developed to destroy the abnormal protein (amyloid) that is believed to be involved in AL amyloidosis. Reduction in the amount of amyloid build up has been observed in

animal studies in which mice. In these studies mice were treated with a mouse version of the birtamimab antibody. Birtamimab may reduce the amyloid build-up and/or the damage caused by amyloid and may improve your abnormal organ function.

Study objective

This study has been transitioned to CTIS with ID 2024-511066-36-00 check the CTIS register for the current data.

Double-blind Phase:

Primary Objective:
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.

Secondary Objectives:
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)

Exploratory Objectives:
None

Open-label Extension Phase:
Primary Objective:
To evaluate the long-term safety of birtamimab plus standard of care in Mayo Stage IV subjects with AL amyloidosis

Secondary Objectives:
None

Exploratory Objectives:
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.
Subjects will be stratified at randomization based on their 6MWT distance (<300 meters vs. >=300 meters) and initiation of daratumumab treatment at randomization (yes vs. no).
Subjects will remain in the Double-blind Phase until its completion, which will occur when approximately 47 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 24) of the events have occurred. Using the O*Brien-Fleming group sequential methodology, the interim analysis will be conducted with a significance level of 0.0108 and the final analysis will be conducted with a significance level of 0.0984, maintaining an overall study significance level of 0.10.
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 every third month for the remainder of the Double-blind Phase per Appendix 1.
Vital Status Assessment Follow-up phone calls (every 3 months) 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 3 months from the subject*s last visit. The subject*s vital status (survival information) will be collected.

Intervention

Study Drug:
During the Double-blind Phase, study drug consists of birtamimab (24 mg/kg) or placebo. The active study drug, birtamimab, is supplied as a sterile, single use, lyophilized dosage form in a 20 mL vial containing 500 mg/vial birtamimab. Each vial will be reconstituted with 9.6 mL sterile water for injection to a concentration of 50 mg/mL resulting in a buffered, isotonic, preservative-free solution. Birtamimab will be prepared in a 250-mL intravenous bag of 0.9% saline. For subjects who are randomized to placebo, an IV infusion of 250 mL of 0.9% saline will be administered. All subjects will receive a flush of approximately 30mL.
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 120 (±20) minute intravenous infusion, including flush. If the subject tolerates the initial infusion, subsequent infusions may be administered over 60 (±10) minutes. The length of the infusion may be extended over a longer period of time if and when it is clinically indicated. A minimum of 21 days between doses is required.
Premedication:
All subjects will be premedicated for each dose of study drug with 25 mg diphenhydramine (or equivalent dose of an H1 antihistamine) and 650 mg acetaminophen (or equivalent paracetamol dose in accordance with local practice) within 30 to 90 minutes prior to study drug administration.
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. 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.

Study burden and risks

See ICF section 7.0

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Double-blind Phase:
1.Aged >=18 years and legal age of consent according to local regulations
2.Newly diagnosed and AL amyloidosis treatment naive
3.Bone marrow demonstrating clonal plasma cells
4.Confirmed diagnosis of AL amyloidosis by the following:
-Histochemical diagnosis of amyloidosis determined by polarizing light microscopy of green birefringent material in Congo red-stained tissue specimens OR characteristic electron microscopy appearance AND
-Confirmatory immunohistochemistry OR immunoelectron microscopy OR mass spectroscopy of AL amyloidosis
5.If the subject meets any of the following:
-Is black or of African descent
-Is over 75 years of age
-Has a history of familial transthyretin amyloidosis
-No cardiac tissue is available for typing, THEN the subject must have gene sequencing consistent with transthyretin (TTR) wild type (i.e., no TTR mutation present) AND must score 0 in technetium-99m-3,3-diphosphono-1,2 propanodicarboxylic acid (99mTc DPD; Rapezzi 2011), hydroxymethylenediphosphonate (99mTc HMDP; Galat 2015), OR pyrophosphate (99mTc PYP; Bokhari 2013) scintigraphy
6.Cardiac involvement as defined by all of the following:
-Past documented or presently noted clinical signs and symptoms supportive of a diagnosis of heart failure in the setting of a confirmed diagnosis of AL amyloidosis in the absence of an alternative explanation for heart failure
-Either an endomyocardial biopsy demonstrating AL amyloidosis OR an echocardiogram demonstrating a mean left ventricular wall thickness at diastole >12 mm in the absence of other causes (e.g., severe hypertension, aortic stenosis), which would adequately explain the degree of wall thickening OR

cardiovascular magnetic resonance imaging findings reported as characteristic of amyloidosis
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
-Difference between involved and uninvolved free light chain >=18 mg/dL
8.Planned first-line chemotherapy contains bortezomib administered subcutaneously weekly
9.Adequate bone marrow reserve, hepatic function, and renal function, as demonstrated by:
-Absolute neutrophil count >=1.0 × 10e9/L
-Platelet count >=75 × 10e9/L
-Hemoglobin >=9 g/dL
-Total bilirubin <= 2 × the upper limit of normal (ULN) (except for subjects with Gilbert*s syndrome, in which case direct bilirubin <=2 × ULN)
-Aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase <=3 × ULN
-Alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase <=3 × ULN
-Alkaline phosphatase (ALP) <=5 × ULN
-Estimated glomerular filtration rate (eGFR) >=30 mL/min/1.73 m2 as estimated by the Chronic Kidney Disease Epidemiology Collaboration equation
10.Seated systolic blood pressure (BP) 90 to 180 mmHg
11.Distance walked during each Screening 6MWT is >30 meters and <550 meters
12.Women of childbearing potential (WOCBP) must have 2 negative pregnancy tests during Screening, the second within 24 hours prior to the first administration of study drug, and must agree to use highly effective physician-approved contraception from Screening to 90 days following the last study drug administration
13. Male subjects must be surgically sterile or must agree to use a barrier method, together with the use of highly effective physician-approved contraception (Appendix 2) by their female partner of childbearing potential, from Screening to 90 days following the last study drug administration
14.Ability to understand and willingness to sign an informed consent form (ICF) prior to initiation of any study procedures

Open label extension phase:
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

Exclusion criteria

Double-blind Phase:
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)
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 cm2) or severe congenital heart disease
8. ECG evidence of acute ischemia or active conduction system abnormalities with the exception of any of the following:
• First degree AV-block
• Second degree AV-block Type 1 (Mobitz Type 1 / Wenckebach type)
• Right or left bundle branch block
• Atrial fibrillation with a controlled ventricular rate (uncontrolled [>110 bpm] ventricular rate is not allowed [determined by an average of 3 beats in Lead II or 3 representative beats if Lead II is not representative of the overall ECG])
9. Peripheral neuropathy assessed as National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Grade 2 with pain, Grade 3, or Grade 4
10. Subject is receiving oral or intravenous antibiotics, antifungals, or antivirals within 1 week of Month 1-Day 1 with the exception of prophylactic agents
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. Major surgery within 4 weeks of Month 1-Day 1 or planned major surgery during the study
14. Active malignancy with the exception of any of the following:
• Adequately treated cutaneous basal cell carcinoma, squamous cell carcinoma, or in situ cervical cancer
• Adequately treated Stage I cancer from which the subject is currently in remission and has been in remission for 2 years
• Low-risk prostate cancer with Gleason score <7 prostate-specific antigen <10 ng/mL, and a stage of cancer at most cT2a, cN0, and CM0
• Any other cancer from which the subject has been disease-free for >=2 years

15. History of severe allergy to any of the components of birtamimab such as histidine/L histidine hydrochloride monohydrate, trehalose dehydrate, or polysorbate 20 or history of Grade >=3 infusion-related adverse events (AEs) or hypersensitivity to another monoclonal antibody, or known hypersensitivity to diphenhydramine (or an equivalent H1 antihistamine) or acetaminophen (or its equivalent, paracetamol)
16. Known unresolved or active HIV, hepatitis B, hepatitis C, or SARS-CoV-2 infection
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. Treatment with another investigational agent within 30 days of Month 1-Day 1
19. Women who are pregnant or lactating
20. Any condition which could interfere with, or the treatment for which might interfere with, the conduct of the study or which would, in the opinion of the Investigator, unacceptably increase the subject*s risk by participating in the study
21. Subject is under legal custodianship
22. History of uncontrolled epilepsy or seizure disorder
23. Waldenström's macroglobulinemia and/or immunoglobulin M monoclonal gammopathy

Open label extension 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

Study design

Design

Study phase:	3
Study type:	Interventional

Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	30-06-2022
Enrollment:	11
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	Birtamimab
Generic name:	Birtamimab

Ethics review

Approved WMO Date:	04-08-2021
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	22-02-2022
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	23-03-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-06-2022

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	06-08-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	28-02-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	23-03-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-04-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	02-06-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	30-12-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	09-04-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-05-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	03-07-2024

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2024-511066-36-00
EudraCT	EUCTR2021-000037-14-NL
ClinicalTrials.gov	NCT04973137
CCMO	NL77501.042.21