# 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

Published: 19-06-2015
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To evaluate the efficacy of NEOD001 plus standard of care vs. placebo plus standard of care when administered intravenously in subjects with AL amyloidosis by assessing time to all-cause mortality or cardiac hospitalizationSecondary ObjectivesIn...

| | |
|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Other condition |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON44130

**Source**
ToetsingOnline

**Brief title**
NEOD001 AL

### Condition

- Other condition

**Synonym**
rare blood disease - heart failure

**Health condition**

Light Chain (AL) Amyloidosis

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Prothena Therapeutics
**Source(s) of monetary or material Support:** Prothena Therapeutics Ltd

## Intervention

**Keyword:** Light Chain (AL) Amyloidosis, Monoclonal Antibody, NEOD001, Placebo Controlled

## Outcome measures

### Primary outcome

Time to all-cause mortality or cardiac hospitalization as adjudicated by the

CEC

### Secondary outcome

* NT-proBNP best response from baseline to Month 9

* Change from baseline to Month 9 in the Physical Component Score of the SF-36

* Change from baseline to Month 9 in the 6MWT

* For renal-evaluable subjects, renal best response from baseline to Month 9

* For subjects with peripheral neuropathy due to AL amyloidosis, change from

baseline to Month 9 in the NIS LL score

* For hepatic-evaluable subjects, hepatic best response from baseline to Month

9

* Change from baseline to Month 9 in the KCCQ

* Time to cardiac mortality or cardiac hospitalization as adjudicated by the CEC

* Time to all-cause mortality

# Study description

### Background summary

Antibodies are proteins that make up part of the immune system, your body*s natural defence system. They recognize foreign or unwanted material, such as infections or even some cancers and help destroy those things while causing little or less harm to normal cells. NEOD001 is an antibody that was developed to target the abnormal protein (amyloid) that is believed to be involved in AL amyloidosis. NEOD001 might reduce the amyloid build up and/or the damage caused by amyloid, and may improve your abnormal organ function.

See also Protocol Pages 31-35

### Study objective

To evaluate the efficacy of NEOD001 plus standard of care vs. placebo plus standard of care when administered intravenously in subjects with AL amyloidosis by assessing time to all-cause mortality or cardiac hospitalization

Secondary Objectives
In subjects with AL amyloidosis, comparing NEOD001 plus standard of care vs. placebo plus standard of care:
* To evaluate the safety of NEOD001
* To evaluate the cardiac response rate as assessed by N terminal pro B-type natriuretic peptide (NT-proBNP)
* To evaluate health-related quality of life using the Short Form-36 (SF-36)
* To evaluate cardiac functional response using the 6-Minute Walk Test (6MWT)
* To evaluate the renal response rate using established criteria
* To evaluate peripheral neuropathy using the Neuropathy Impairment Scale * Lower Limbs (NIS-LL)
* To evaluate the hepatic response rate according to consensus criteria
* To evaluate cardiac-specific quality of life using the Kansas City Cardiomyopathy Questionnaire (KCCQ)
* To evaluate time to cardiac mortality or cardiac hospitalization
* To evaluate time to all-cause mortality

Exploratory Objectives
* To evaluate time to cardiac mortality
* To evaluate time to cardiac hospitalization
* To evaluate time to hematologic treatment failure
* To evaluate time to organ progression
* To evaluate change in liver size (i.e., craniocaudal dimension)
* To evaluate the pharmacokinetics (PK) of NEOD001

* To evaluate the immunogenicity of NEOD001
* To evaluate the change in cardiac function
* To evaluate painful peripheral neuropathy using the Visual Analog Scale * Pain Intensity (VASPI)

## Study design

This is a multicenter, international, randomized, double-blind, placebo-controlled, two-arm efficacy and safety study in subjects with AL amyloidosis.
Newly diagnosed subjects with AL amyloidosis will be randomized in a 1:1 ratio to NEOD001 or placebo. Subjects will be stratified at randomization based on three factors:
* Mayo Clinic Stage: Stages I and II vs. Stages III and IV
* Renal Stage: Stage I vs. Stages II and III
* 6MWT distance: < 300 meters vs. * 300 meters
Subjects will remain on study until study completion, which will occur when approximately 156 primary endpoint events (all-cause mortality or cardiac hospitalizations as adjudicated by the Clinical Events Committee [CEC]) have been reached.
If the subject discontinues study drug prior to the end of the study but is willing to continue to participate in study visits, the subject should have an ETD Visit within 28-35 days after his/her final administration of study drug and then have assessments every third month. The most important visit is the Month 9-Day 1 Visit, so if a subject is unwilling to continue visits every third month, every effort should be made for the subject to return and complete the Month 9-Day 1 Visit on schedule. All visits after the ETD Visit should occur on schedule, that is, at the time when the visit would have occurred had the subject remained on study drug.
Follow-up phone calls should be made to randomized subjects who received a dose of study drug (or his/her caregiver) every 3 months, beginning approximately 3 months from the subject*s last visit. The subject*s health status, as well as details of any hospitalizations should be discussed.
At the time of study completion (i.e., once approximately 156 events have been reached), subjects still receiving study drug (i.e., NEOD001 or placebo) treatment may be considered for entry into a separate open-label extension study of NEOD001.

## Intervention

IP+ See above

## Study burden and risks

The purpose of this study is to learn more about the safety and the effects of NEOD001 on the disease. The knowledge gained from this study may help other

people with AL Amyloidosis in the future.

NEOD001 is a monoclonal antibody. There is the possibility of a reaction to the monoclonal antibody as it is being infused (given) through your vein; these are called infusion reactions. Symptoms can include fever, chills, rash, and/or hives, changes in blood pressure, temperature and heart rate. If infusion reactions are severe, they can be potentially life-threatening or even fatal. Your temperature, breathing rate, heart rate, and blood pressure will be measured prior to, during, and after the infusion. You will be given some medications within 30-90 minutes prior to the start of the infusion to try to prevent you from getting infusion reactions. You will be watched closely during the infusion and for approximately 90 minutes after the completion of the infusion. If you do have a reaction to the study drug, your study doctor may need to give the study drug at a slower rate (over a longer period of time), give you a lower dose, and /or give you additional medications to prevent the reaction, or you may have to stop taking study drug.

NEOD001 is currently being tested in a Phase 1/2 clinical study that was designed to test different dose levels to find the highest dose that could be given safely. The highest dose tested was 24 mg/kg which was considered to be safe, and that dose will be used in this study. The most common side effects that were seen in the Phase 1/2 study (those that were experienced by 10% or more of the people in the study) based on information that was collected as of 30 September 2015, were as follows: fatigue, upper respiratory tract infection (a cold), diarrhea, nausea, edema (swelling), anemia (a low number of red blood cells), cough, increased blood creatinine, headache, peripheral edema (swelling in the hands or feet) and rash. In addition, in a subset of 27 patients who participated in the first part of the study (which is referred to as the Dose Escalation Phase), 10% or more patients experienced dyspnea (shortness of breath) and hyponatremia (low sodium levels in the blood). Your health status, including organ function and immune function will be monitored by your study doctor/staff at least monthly during the study.

# Contacts

**Public**
Prothena Therapeutics

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**Scientific**
Prothena Therapeutics

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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

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

## Inclusion criteria

Subjects must meet all of the following criteria:
1. Aged * 18 years
2. Newly diagnosed and AL amyloidosis treatment naïve
3. Bone marrow demonstrating clonal plasma cells
4. Confirmed diagnosis of AL amyloidosis by the following:
* Histochemical diagnosis of amyloidosis determined bypolarizing light microscopy of green birefringent material in Congo red-stained tissue specimens OR characteristic electron microscopy appearance
AND
* Confirmatory immunohistochemistry OR mass spectroscopy of AL amyloidosis
5. Confirmed diagnosis of AL amyloidosis by mass spectrometry or immunoelectron microscopy of amyloid material in tissue biopsy if the subject meets any of the following:
* Is black or African American
* Is over 75 years of age with concurrent monoclonal gammopathy
* Has a history of familial amyloidosis and has concurrent monoclonal gammopathy
OR
* If the subject meets any of the above 3 conditions and has echocardiographic evidence of amyloidosis, biopsyproven amyloidosis with a monoclonal gammopathy and no tissue is available for mass spectrometry or immunoelectron microscopy, the subject must have gene sequencing consistent with transthyretin (TTR)wild type (e.g., 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
* NT-proBNP * 650 pg/mL and * 8500 pg/mL
7. Planned first-line chemotherapy contains bortezomib administered weekly and subcutaneously (SC)
8. Adequate bone marrow reserve, hepatic function, and renal function, as demonstrated by:
* Absolute neutrophil count (ANC) * 1.0 × 109/L
* Platelet count * 75 × 109/L
* Hemoglobin * 9 g/dL
* Total bilirubin * 2 times the upper limit of normal (× ULN)
* Aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase (SGOT) * 3 × ULN
* Alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase (SGPT) * 3 × ULN
Alkaline phosphatase (ALP) * 5 × ULN (except for subjects with hepatomegaly and isozymes specific to liver, rather than bone)
* Estimated glomerular filtration rate (eGFR) * 30 mL/min/1.73 m2 as estimated by the Chronic Kidney Disease Epidemiology Collaboration (CKDEPI)
equation
9. Seated systolic blood pressure 90-180 mmHg
10. Distance walked during each Screening 6MWT
11. Women of childbearing potential (WOCBP) must have two 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 (Appendix 4) from Screening to 90 days following the last study drug administration
12. Male subjects must be surgically sterile or must agree to use highly effective physician-approved contraception (Appendix 4) from Screening to 90 days following the last study drug administration
13. Ability to understand and willingness to sign an informed consent form prior to initiation of any study procedures

## Exclusion criteria

Subjects must meet none of the following criteria:
1. Non-AL amyloidosis
2. NT-proBNP < 650 pg/mL or > 8,500 pg/mL
3. Meets the International Myeloma Working Group (IMWG) definition of Multiple Myeloma (Appendix 5)
*Note that subjects who meet the IMWG definition of symptomatic multiple myeloma with signs and/or symptoms attributable only to associated amyloidosis are potentially eligible upon approval of the Sponsor.

4. Subject is eligible for and plans to undergo ASCT or organ transplant
5. 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
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 [i.e., >110 bpm] ventricular rate is not allowed [determined by an average of three beats in Lead II or three representative beats if Lead II is not representative of the overall EKG])
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 IV antibiotics, antifungals or antivirals within 1 week of Month 1-Day 1 with the exception of prophylactic oral 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 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 and prostate-specific antigen < 10 mg/mL
* 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 NEOD001 such as histidine/L histidine hydrochloride monohydrate, trehalose dehydrate, or polysorbate 20 or history of Grade * 3 infusion-related 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 or history of uncontrolled, active HIV, hepatitis B or hepatitis C infection
17. Prior treatment with plasma cell-directed chemotherapy, NEOD001, 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 epilepsy or seizure disorder with the exception of childhood febrile seizures
23. Waldenström's macroglobulinemia and/or immunoglobulin M (IgM) monoclonal gammopathy

# Study design

## Design

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|---|---|
| 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: | Recruitment stopped |
| Start date (anticipated): | 28-06-2016 |
| Enrollment: | 10 |
| Type: | Actual |

## Medical products/devices used

| | |
|---|---|
| Product type: | Medicine |
| Brand name: | NEOD001 |
| Generic name: | NEOD001 |

# Ethics review

Approved WMO

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|---|---|
| Date: | 19-06-2015 |
| Application type: | First submission |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |

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|---|---|
| Approved WMO Date: | 21-03-2016 |
| Application type: | First submission |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 22-09-2016 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 20-10-2016 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 17-02-2017 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 12-06-2017 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 27-06-2017 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 17-07-2017 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 02-02-2018 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 17-04-2018 |
| 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 |
|---|---|
| EudraCT | EUCTR2014-003865-11-NL |
| ClinicalTrials.gov | NCT02312206 |
| CCMO | NL52890.042.15 |