A Phase 1, First-in-Human, Double-Blind, Placebo-Controlled, Multicenter, Single and Multiple Ascending Dose Study of NI006 in Patients with Amyloid Transthyretin Cardiomyopathy Followed by an Open-Label Extension

Published: 18-12-2019
Last updated: 10-04-2024

Primary objective:Determine the short- and long-term safety and tolerability of single and multiple doses of NI006 in subjects with ATTR-CM by evaluating adverse events (AE) and serious adverse events (SAE) and changes in laboratory parameters (...

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

Summary

ID

NL-OMON52809

Source
ToetsingOnline

Brief title
NI006 in Patients with Amyloid Transthyretin Cardiomyopathy

Condition

- Other condition
- Cardiac disorders, signs and symptoms NEC

Synonym
Heart failure caused by Amyloid Cardiomyopathy, Transthyretin Amyloid Cardiomyopathy

Health condition

Cardiovascular Diseases

Research involving

Human

Sponsors and support

Primary sponsor: Neurimmune AG
Source(s) of monetary or material Support: Sponsor: Neurimmune AG

Intervention

Keyword: Amyloid Transthyretin, Cardiomyopathy, First-in-Human, Human monoclonal IgG1 antibody

Outcome measures

Primary outcome

Primary endpoints:

• Number and proportion of treatment emergent adverse events (TEAEs)

• Number and proportion of SAEs

• Changes in clinical laboratory parameters (continuous parameters)

• Change from baseline in cardiac biomarkers

• Changes by visit for vital signs

• Changes by visit for ECG parameters (continuous parameters)

• Summary of echocardiogram results

Secondary outcome

Secondary endpoints:

• PK parameters for the SAD phase:

Maximum observed serum concentration (Cmax), time to maximum observed serum

concentration (Tmax), area under the serum concentration-time curve from zero

to infinity (AUCinf),serum clearance (CL), apparent volume of distribution during terminal phase (Vz), apparent volume of distribution at steady state (Vss), terminal elimination half-life (t*)

• PK parameters for the MAD phase:

Cmax, Tmax, area under the serum concentration-time curve from time zero to the end of the dosing interval after the first dose (AUC*), CL, Vz, Vss, t*, accumulation ratio for maximum concentration (RaccCmax), accumulation ratio calculated from AUC (RaccAUC)

•PK parameters for the OLE and OLE 2 phase: Minimum observed serum concentration (Ctrough), dose normalized Ctrough, accumulation ratio compared to SAD/MAD calculated from dose-normalized Ctrough

Exploratory endpoints:

• 6-Minute Walk Test (6-MWT)

• Kansas City Cardiomyopathy Questionnaire (KCCQ)

• Echocardiography (contractile function [strain], thickness and filling pressure, left ventricular ejection fraction [LVEF])

• Estimation of amyloid load by imaging method in a subset of subjects

• Changes in biomarkers

• Determination of TTR, free thyroxine (T4), Vitamin A levels and Retinol-binding protein (RBP)

• Determination of anti-drug antibody (ADA) response

• Immunohistochemistry (IHC) of cardiac or salivary gland biopsies in in a

subset of subjects (OPTIONAL)

Study description

Background summary

Amyloid Transthyretin (ATTR)-Cardiomyopathy (CM) is an age-associated fatal disease with a mean subject survival of 3 to 5 years and limited treatment options available. There is currently (July 2019) no specific treatment for ATTR-CM approved in Europe. Standard treatments for heart failure such as beta-blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers are poorly tolerated in ATTR-CM and should be avoided. Heart transplantation is in principle the only available approach to restore cardiac function but has poor applicability to this elderly and fragile subject population. Liver transplantation, which is used for patients with hereditary ATTR amyloidosis with peripheral neuropathy, unfortunately does not prevent progression of cardiac amyloidosis. Tafamidis (Vyndaqel® and Vyndamax®) has been approved by the Food and Drug Administration (FDA) in May 2019 for the treatment of patients with ATTR-CM based on clinical trial data showing higher survival rates and reduced number of hospitalizations for cardiovascular problems in the tafamidis group than in the placebo group. Approval of tafamidis is also expected in Europe.
NI006, a human monoclonal immunoglobulin-1 (IgG1) antibody derived using Neurimmune*s proprietary technology, binds ATTR in cardiac and non-cardiac tissues from subjects with sporadic and hereditary forms of the disease, including binding similarly wild-type (WT) and mutant ATTR fibrils. NI006 has the capacity to activate the elimination of ATTR fibrils by immune cells. Removal of ATTR deposits from tissues, especially in the heart, is expected to reduce myocardium stiffness, leading to improved cardiac function and symptom regression in subjects.

Study objective

Primary objective:
Determine the short- and long-term safety and tolerability of single and multiple doses of NI006 in subjects with ATTR-CM by evaluating adverse events (AE) and serious adverse events (SAE) and changes in laboratory parameters (hematology,clinical chemistry, immunology, and urinalysis), cardiac biomarkers, vital signs, electrocardiogram (ECG), and echocardiogram

Secondary objective:
Determine the pharmacokinetic (PK) profile and PK parameters of NI006 in subjects with ATTR-CM

Exploratory objective:
-Explore the efficacy of multiple doses of NI006 in subjects with ATTR-CM on clinical, imaging, ECG and laboratory variables
-Confirm absence of effect on physiological TTR
-Evaluate the immunogenicity of NI006
-Characterize target engagement and immune activation on tissue biopsies (OPTIONAL)

Study design

This is a randomized, placebo-controlled, double-blind trial combining SAD and MAD phases, followed by an OLE phase in subjects with ATTR-CM.
Subjects completing the SAD phase will be enrolled in the MAD phase upon evaluation of all available safety data by the DEC.
Subjects completing the MAD phase will have the possibility to continue in an OLE phase with dose up-titrations and switch from placebo to NI006 treatment, upon cumulative safety data evaluation by the DEC.
About 30 to 36 subjects are planned to be enrolled in 5 to 6 ascending dose cohorts of 6 subjects each. This number does not include subjects who need to be replaced as explained in section 6.3.3 of the protocol.
The dose cohorts planned in mg/kg body weight are: 0.3 mg/kg (cohort 1), 1 mg/kg (cohort 2), 3 mg/kg (cohort 3), 10 mg/kg (cohort 4), 30 mg/kg (cohort 5), and potentially 60 mg/kg (cohort 6, in case of absence of safety signals at 30 mg/kg).
The trial schema is provided in Table 5 and Table 6 of the protocol. These schemata are to visualize the planned trial but are presenting a best-case scenario and do not take possible delays into account.

SAD Phase
For each dose cohort, the first 2 subjects are randomized in a 1:1 ratio to receive a single dose of NI006 or placebo. The decision to dose additional subjects at the same dose level is based on 5-day post-dose safety data. The following 4 subjects are randomized in a 3:1 ratio to receive a single dose of NI006 or placebo, with a minimum 7-day enrolment interval. When at least 5 subjects were dosed in a dose cohort, with a minimum of 29 days after the first subject was treated with IMP in the dose cohort, the DEC will review all available safety data and decide on the initiation of the next higher dose cohort (regular DEC meeting). Under specific circumstances the DEC will be convened earlier than 29 days after the first subject was treated with IMP in the dose cohort (ad-hoc DEC meeting).
If 5 SAD cohorts are performed, 20 subjects will receive 1 dose of NI006, and 10 subjects will receive placebo. If 6 SAD cohorts are performed, 24 subjects will receive 1 dose of NI006 and 12 subjects will receive placebo; both cases listed are excluding replacement subjects.

MAD Phase
Subjects completing the SAD phase will continue in the MAD phase of the trial

35 calendar days after their first dose of NI006 and receive 3 additional administrations of NI006 at their assigned dose or placebo with an inter-treatment interval of 28 days (±2 days - all procedures on the same day).
The decision to enter the MAD phase will rely on the evaluation of the cumulative safety data available by the DEC. In case no DEC decision is available at this time or the DEC decided to postpone start of the MAD for specific subject(s), the first treatment of the subjects in the MAD must be delayed accordingly until the decision to enter the MAD is taken.
If all 5 SAD and MAD cohorts are performed, 20 subjects will receive 4 doses of NI006, and 10 subjects will receive 4 doses of placebo. If 6 SAD and MAD cohorts are performed, 24 subjects will receive 4 doses of NI006 and 12 subjects will receive 4 doses of placebo; both cases listed are excluding potential replacement subjects.

OLE Phase
Subjects completing the MAD phase will have the possibility to continue in the OLE phase of the trial. Subjects who received placebo during SAD and MAD phases will be switched to NI006 during the OLE phase. During the OLE, based on the evaluation of the cumulative safety data by
the DEC, subjects will be up-titrated continuously to the highest doses deemed safe and well tolerated in repeated dosing (as evaluated in the MAD of the specific dose cohort) at their dosing visit. During the OLE phase all subjects may have the chance to be dosed with the maximum tolerated dose (MTD) depending on the timepoint when the MTD is reached.
The OLE phase includes 8 additional administrations of NI006 with an inter-treatment interval of 28 days (±2 days; all procedures on the same day).

Hospitalization for Safety Surveillance
The hospitalization schedule for safety surveillance is summarized in Table 4 of the protocol.
-SAD: 5 days (4 nights) (first IMP administration on the first day [V1] and discharge on the 5th day [V5])
-MAD: For the second IMP administration, all subjects will be hospitalized for 3 days (2 nights) (drug administration on the first day [V9] and discharge on the 3rd day [V11]); For the third and fourth drug administration, all subjects will be hospitalized for 2 days (1 night) (drug administration on first day [V14, V18] and discharge on the second day [V15, V19])
-OLE: 5 days (4 nights) after the first treatment in the OLE phase (drug administration on the first day [V23] and discharge on the 5th day [V27]); No hospitalization is mandatory for all following treatments provided no safety issues have previously been detected and according to the Investigator*s judgement

Intervention

Patients will receive the following interventions:

-NI006/placebo dosing
-vital signs and physical examination
-Questionnaires & 6-minute walking test
-MRI or Bone Scintigraphy
-Echocardiography
-continuous ECG telemonitoring
-5-days holter
-12-lead ECG
-salivary gland biopsy (optional) - note: no cardiac biopsy in The Netherlands
-Blood / urine draws
-pregnancy testing (serum/urine for WOCBP)

Study burden and risks

Risk-benefit assessment:
The available non-clinical data indicate that NI006 selectively binds pathological WT and mutant ATTR amyloid. This was confirmed by IHC with NI006 showing selective staining of amyloid deposits in tissues collected from subjects with both sporadic and hereditary ATTR amyloidosis.
NI006 binding selectivity was further evaluated in good laboratory practice (GLP) tissue crossreactivity experiments using frozen human tissue panels. An ex vivo assay was developed consisting of human subject-derived cardiac tissue sections incubated with human-derived macrophages in the presence of NI006. In this assay, NI006 triggered rapid, dose-dependent and nearly complete removal of ATTR amyloid from heart tissues by macrophages within 14 days, which confirmed expected MOA.
Proof-of-mechanism for antibody-mediated removal of amyloid deposits has been recently established in Alzheimer disease (Panza et al, 2014; Ostrowitzki et al, 2012; Sevigny et al, 2016) and in treatment with anti-serum amyloid P antibody (Richards et al, 2015; Richards et al, 2018).
The capacity of NI006 to bind amyloid deposits in subject*s cardiac tissues and trigger their elimination by macrophages demonstrated ex vivo indicate a promising therapeutic potential for the treatment of diseases caused by ATTR amyloidosis.
The sentinel dosing at the beginning of each dose cohort, the proposed clinical safety monitoring, and the use of a Data Evaluation Committee (DEC), provide for a comprehensive safety risk minimization to address any uncertainties with the administration of NI006.
Based on the current absence of approved treatment options for ATTR-CM in Europe, the limited numbers of therapeutic mechanisms currently tested in clinical studies, the rapid lethality of this disease, and the promising non-clinical data observed with NI006, there is a demand from the medical community to move forward with the clinical evaluation of NI006.

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

1. Written informed consent obtained from the subject prior to any trial-related procedure indicating that he/she understands the purpose of and procedures required for the trial and is willing to participate in it
2. Male or female subjects aged >=18 years (and < 85 years only for cohort 7) at the time of obtaining informed consent and with confirmed availability for the scheduled trial visits
3. Confirmed ATTR-CM diagnosis established by:
• Polarizing light microscopy of green birefringent material in Congo red-stained tissue specimens and confirmed diagnosis of ATTR amyloidosis by IHC or mass spectrometry
OR
• positive bone scintigraphy using either 99mTc

-3,3-diphosphono-1,2-propanodicarboxylic acid (DPD), 99mTc-hydroxyl-methylenediphosphonate (HMDP) or 99mTc-pyrophosphate (PYP), with cardiac signal intensity indicative of ATTR-CM (early phase imaging: cardiac mediastinum ratio > 1.21; late phase imaging: Perugini Grade 2 or 3) and absence of gammopathy (negative serum and urine immunofixation electrophoresis plus normal free light chain serum ratio). If a gammopathy is detected, diagnosis must be established based on tissue biopsy as indicated above
4. Known genotype as follows:
a) Known pathogenic TTR mutation for subjects with hereditary ATTR-CM
b) Known negative genetic testing for a TTR mutation for subjects with sporadic, WT-ATTR-CM
5. Chronic Heart Failure with all of the following characteristics:
a) LVEF >=40%
b) Left ventricular wall thickness (LVWT) >=14 mm, measured by echocardiography
c) N-terminal pro b-type natriuretic peptide (NT-proBNP) level >=600 pg/mL
d) Able to walk >=150 meter in the 6-MWT
e) New York Heart Association (NYHA) class III (applicable only for cohort 7)
f) No hospitalizations for cardiac disease for at least 30 calendar days prior to screening
6. General health status acceptable for a participation in a clinical trial with a Karnofsky Performance Status >=60%
7. Stable pharmacological treatment of any other chronic condition for at least 30 calendar days prior to screening, with the exclusion of immunomodulatory and immunosuppressive treatments
8. Absolute neutrophil count (ANC) >=1000 cells/mm^3, platelet count >=100,000 cells/mm^3, and hemoglobin >=10 g/dL
9. Women of childbearing potential (WOCBP) must have a negative serum pregnancy test at screening and must agree to use highly effective physician-approved contraception from screening to 5 months after ending trial participation
10. Males must be surgically sterile or must agree to use highly effective physician-approved
contraception throughout of the trial participation, and for 5 months after ending trial participation

Inclusion Criteria for OLE2
1.Participation in the OLE in cohorts 1 to 5 with a minimum of one administration of NI006 during OLE
2.Written informed consent for OLE2 obtained from the subject prior to any OLE2-related procedure indicating that he/she understands the purpose of and procedures required for the trial and is willing to participate in it
3.Availability for all scheduled visits
4.WOCBP must have a negative serum pregnancy test at screening and must agree to use highly effective physician-approved contraception from screening to 5 months after ending trial participation
5.Males must be surgically sterile or must agree to use highly effective physician- approved contraception throughout of the trial participation, and

for 5 months after ending trial participation

Exclusion criteria

1. Amyloid light-chain (AL) amyloidosis or any other non ATTR amyloidosis
2. Heart failure corresponding to NYHA class IV
3. Uncontrolled hypertension with systolic pressure >=180 mmHg or diastolic pressure >=110 mmHg confirmed by 3 measurements in supine position recorded with 5 minutes break in between the measurements
4. Hypotension with systolic pressure <= 90 mmHg or diastolic pressure <= 60 mmHg confirmed by 3 measurements in supine position recorded with 5 minutes break in between the measurements
5. NT-proBNP >=6000 pg/mL (NT-proBNP >=8'500 pg/mL applicable only for cohort 7)
6. Heart failure not predominantly caused by ATTR-CM
7. Any severe uncorrected valve disease
8. Chronic liver disease with liver function test abnormalities:
a) Alanine transaminase (ALT) and aspartate aminotransferase (AST) > 2.5 × upper limit of normal (ULN)
b) Total bilirubin > 2 × ULN
9. Respiratory insufficiency requiring oxygen therapy
10. Renal insufficiency with estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m2 using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation
11. Active malignancy with exception of the following:
a) Adequately treated basal cell carcinoma
b) Squamous cell carcinoma of the skin
c) In situ cervical cancer
d) Low risk prostate cancer with Gleason score < 7 and prostate specific antigen < 10 mg/mL
e) Any other cancer from which the subject has been disease-free for >= 2 years
12. Uncontrolled infection as per Investigator*s judgement
13. Known human immunodeficiency virus (HIV) infection, seropositivity for HIV, hepatitis B and C as well as active hepatitis A
14. Autoimmune disease requiring immunosuppressive/modulating treatment in the last 2 years
15. History of organ transplantation or ventricular assist device (VAD)
16. Polyneuropathy disability (PND) score > IIIA
17. Suspected or known intolerance/allergy to proteins or any components of the investigational medicinal product (IMP)
18. Concomitant immunosuppressant therapy e.g., corticosteroids, prednisone, dexamethasone except as indicated in low dose (i.e., up to 10 mg prednisone or equivalent daily is allowed) for other medical conditions such as inhaled steroid for asthma
19. Use of the following drugs acting on TTR or ATTR: tolcapone, diflunisal, patisiran, inotersen, and long-term doxycycline, in the 30 calendar days prior

to signing informed consent form (ICF). Tafamidis is permitted if it is given as standard of care in a stable dose for at least 30 calendar days prior to signing the ICF
20. Participation in another investigational clinical trial or intake of investigational drug within 30 calendar days before signing the ICF
21. Suspected or known drug or alcohol abuse
22. Serious psychiatric or any other medical condition (including laboratory abnormalities), which, in the opinion of the Investigator, makes the subject unsuitable for inclusion and puts the subject at an unacceptable risk
23. Subject is nursing or is considering becoming pregnant during the trial or in the 5 months after ending trial participation
24. Unwillingness or inability to adhere to the trial requirements
25. If subject is in any way dependent on Neurimmune AG or the principal Investigator or if the subject is accommodated in an establishment on judicial or administrative order
26. Employee or immediate family (spouse, parent, child or sibling, whether biological or legally adopted) of an employee of Neurimmune AG, the contract research organization (CRO) or the trial site

Exclusion Criteria for OLE2
1.Life-threatening allergic hypersensitivity reactions (Grade 3 or higher) to proteins or any components of the IMP
2.Heart failure corresponding to New York Heart Association (NYHA) class IV at the time of screening
3.Occurrence of severe treatment-related adverse reactions to the IMP that led to previous trial discontinuation
4.Infection with SARS-CoV2 confirmed by reverse transcriptase polymerase chain reaction (RT-PCR) in the 30 calendar days prior to signing informed consent form is an exclusion criterion. A negative SARS-CoV2 test is required to enter the trial. Completed SARS-CoV2 vaccination is recommended prior to randomization, but not a requirement
5. LVEF < 30%
6. Uncontrolled hypertension with systolic pressure >=180 mmHg or diastolic pressure >=110 mmHg confirmed by 3 measurements in supine position recorded with 5 minutes break in between the measurements
7.Hypotension with systolic pressure <= 90 mmHg or diastolic pressure <= 60 mmHg confirmed by 3 measurements in supine position recorded with 5 minutes break in between the measurements
8.Liver disease with liver function test abnormalities:
a) ALT and AST > 2.5 × upper limit of normal (ULN)
b) Total bilirubin > 2 × ULN
Please refer to Prot Amd 4 for further exclusion criteria

Study design

Design

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):	08-10-2020
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	NI006
Generic name:	NI006

Ethics review

Approved WMO Date:	18-12-2019
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	23-07-2020
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	05-11-2020

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	06-01-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	27-01-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	07-06-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	26-06-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-07-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	12-08-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	01-12-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	07-12-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-01-2022

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	10-03-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	06-04-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	08-10-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	23-11-2022
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
Other	2019-001932-80
EudraCT	EUCTR2019-001932-80-NL
CCMO	NL70819.042.19