Efficacy and safety of NNC6019-0001 at two dose levels in participants with transthyretin amyloid cardiomyopathy (ATTR CM)

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This study has been transitioned to CTIS with ID 2023-506824-96-00 check the CTIS register for the current data. • safety and tolerability from baseline to week 64 in participants with hATTR or wtATTR cardiomyopathyPrimary • To compare the effect of...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Heart failures
Study type	Interventional

Summary

ID

NL-OMON51443

Source
ToetsingOnline

Brief title
NN6019-4940

Condition

- Heart failures

Synonym
cardiomyopathy

Research involving
Human

Sponsors and support

Primary sponsor: Novo Nordisk

Source(s) of monetary or material Support: Novo Nordisk

Intervention

Keyword: NNC6019-0001, two dose levels

Outcome measures

Primary outcome

Change in 6-minute walktest (6-MWT) From baseline (week 0) to visit 15 (week 52) - Meters

Change in NT-proBNP From baseline (week 0) to visit 15 (week 52) - Percentage

Secondary outcome

Supportive secondary endpoints

Change in myocardial extracellular volume (ECV) From baseline (week 0) to visit 15 (week 52) - %-points

Change in Kansas City Cardiomyopathy Questionnaire (KCCQ) Clinical Summary Scorea (CSS)2 From baseline (week 0) to visit 15 (week 52) - Score

Change in neuropathy impairment scoreb (NIS) From baseline (week 0) to visit 15 (week 52) - Score

Change in troponin I From baseline (week 0) to visit 15 (week 52) - ng/mL

Change in global longitudinal strain (GLS) on echocardiography From baseline

(week 0) to visit 15 (week 52) - %-points

Number of treatment emergent adverse events From baseline (week 0) to visit 16

(week 64) - Count

Time to occurrence of allcause mortality From baseline (week 0) to visit 16

(week 64) - Weeks

Number of CV events comprising hospitalisation due to CV events or urgent heart

failure visits From baseline (week 0) to visit 16 (week 64) - Count

Study description

Background summary

Transthyretin amyloid cardiomyopathy (ATTR CM)
Transthyretin amyloid (ATTR) amyloidosis is a rare and progressive disease characterised by deposition of aggregates of misfolded transthyretin protein (amyloid). Transthyretin (TTR) is a naturally occurring protein, which may misfold to form toxic soluble monomers that subsequently may aggregate and form fibrils with resultant TTR amyloid deposition into tissues (e.g., heart, nerves, gastrointestinal tract) with disrupted organ structure and function as the consequence. The TTR protein is produced primarily in the liver and in its normal tetrameric form serves as a carrier for thyroxin and vitamin A, the latter via the binding of retinol binding protein.
ATTR amyloidosis can be hereditary (hATTR) due to rare genetic variants or occur sporadically as wild type (wtATTR).
In hATTR amyloidosis, the body makes a mutant form of the TTR protein. There are more than 100 reported types of TTR mutations that promote amyloid fibril formation. The predominant organ involvement for hATTR amyloidosis is either the nervous system (hATTR PN amyloidosis) or the heart (hATTR CM amyloidosis), although other organ systems are also often involved. Depending on the specific mutation, some patients predominantly have cardiac symptoms, some predominantly have symptoms from the nervous system, and some have a combination of both. In one study of approximately 500 patients with the hATTR V30M mutation, one third

of patients had clinical nephropathy based on elevated levels of proteinuria, and 10% progressed to end-stage renal disease. A significant number of TTR mutations associated with a clinical phenotype cause a restrictive cardiomyopathy.
Wild-type ATTR is similar to hATTR except that the protein that is deposited is the misfolded, non-mutated transthyretin protein. The misfolding is thought to be caused by age-related impaired proteostasis. The predominant effect of wtATTR amyloidosis is on the heart.

Study objective

This study has been transitioned to CTIS with ID 2023-506824-96-00 check the CTIS register for the current data.

• safety and tolerability from baseline to week 64 in participants with hATTR or wtATTR cardiomyopathy

Primary
• To compare the effect of two dose levelsof NNC6019-0001 (30 mg/kg and 100 mg/kg) versus placebo on:
• change in 6-minute walk test and
• change in NT-proBNP
from baseline to week 52 in participants with hATTR or wtATTR cardiomyopathy.

Secondary
• To compare the effect of two dose levels of NNC6019-0001 (30 mg/kg and 100 mg/kg) versus placebo on:
• biomarkers
• pharmacodynamic endpoints
from baseline to week 52 in participants with hATTR or wtATTR cardiomyopathy.

Study design

This is an interventional, randomised, multinational, multicentre, three-arm parallel-group, double-blind, placebo-controlled study comparing i.v. NNC6019-0001 Q4W at two dose levels (30 mg/kg and 100 mg/kg) versus placebo in participants with hATTR or wtATTR CM.
The study consists of a screening period of up to 8 weeks, followed by a 52-week intervention period. When participants discontinue study intervention according to protocol, an end of treatment visit should be carried out 4 weeks after administration of the last dose and a follow-up visit should be carried out 16 weeks after administration of the last dose.

Intervention

Patient will be randomised 1:1:1 to receive i.v. 30 mg/kg NNC6019-0001, 100

mg/kg NNC6019-0001 or placebo Q4W added to standard of care accroding to the following treatment arms:

30 mg/kg NNC6019-0001
100 mg/kg NNC6019-0001
placebo

Study burden and risks

Potential risk:
Hypersensitivity: As expected for a protein-based drug, participants treated with NNC6019-0001 may develop localised (to the infusion site) or generalised hypersensitivity reactions.
Myocardial Inflammation: The intended action of the NNC6019-0001 in clearing amyloid through macrophage activation and phagocytosis may result in a theoretical risk of myocardial inflammation.
Pro-arrhythmic risk: Based on the potential mechanism of action of NNC6019-0001 and the underlying disease pathophysiology of ATTR cardiomyopathy, there is a theoretical risk of arrhythmogenicity.
To mitigate these potential risks participants will be followed closely and carefully by qualified medical staff. Additionally standard safety surveillance activities and medical monitoring will be performed by Novo Nordisk.
Preliminary efficacy results from the FHD study (study NN6019-4965) for 7 evaluable participants treated with NNC6019-0001 were favourable. NNC6019-0001 was associated with a mean change of - 1.21% in GLS from baseline to 9 months indicating a possible benefit in cardiac systolic function. Six (6) of the 7 efficacy evaluable participants had no change in their baseline New York Heart Association (NYHA) class at month 9. Participation in this study is contributing to the process of developing a new therapy option for patients with ATTR CM with a proposed amyloid-depleting mode of action. Expected benefits associated with treatment with NNC6019-0001 include those associated with removal of amyloid in tissues, specifically in the myocardium.
It is expected that all participants will benefit from participation through frequent and close contact with investigators and other site staff who will ensure that the participants are treated to
recommended standard of care for their conditions, including ATTR CM, and disease development and progression will be closely monitored and treated.
Taking into account the measures taken to minimise risk and burden to participants participating in this study, the potential risks identified in association with NNC6019-0001 are justified by the anticipated benefits that may be afforded to participants with ATTR CM

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

• Male or female.
• Age >= 18 to < 85 years at the time of signing informed consent.
• Have an established diagnosis of ATTR CM with either wild-type TTR or hereditary TTR
genotype as per local standards.
• Expected to be on stable doses of cardiovascular medical therapy 6 weeks prior to the
randomisation visit.
• Known end-diastolic interventricular septal wall thickness >= 12 mm.
• Presently classified as New York Heart Association (NYHA) Class II-III.
• NT-proBNP concentration >=650 pg/mL in sinus cardiac rhythm and >1000 pg/mL in atrial fibrillation

at screening.
• Completed >=150 meters to <=450 meters on the 6-MWT at screening.
• Estimated glomerular filtration rate (eGFR) >=25 mL/min/1.73 m2 at screening.

Exclusion criteria

• Cardiomyopathy not primarily caused by ATTR CM, for example, cardiomyopathy due to hypertension, valvular heart disease, or ischemic heart disease
• A prior solid organ transplant
• Planned solid organ transplant during the study
• Presence or history of malignant neoplasm (other than basal or squamous cell skin cancer, in-situ carcinomas of the cervix, or in-situ/high grade prostatic intraepithelial neoplasia (PIN) or low-grade prostate cancer) within 5 years before screening
• Current treatment with calcium channel blockers with conduction system effects (e.g., verapamil, diltiazem). The use of dihydropyridine calcium channel blockers is allowed. The use of digoxin will only be allowed if required for management of atrial fibrillation with rapid ventricular response
• Acute coronary syndrome, unstable angina, stroke, transient ischemic attack (TIA), coronary revascularization, cardiac valve repair, or major surgery within 3 months of screening
• Body weight >120 kg (264.6 lb) at screening
• History of contrast allergy or adverse reactions to gadolinium-containing agents

Study design

Design

Study phase:	2
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):	16-11-2023
Enrollment:	9
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	nog niet bekend
Generic name:	NNC6019-0001

Ethics review

Approved WMO Date:	27-06-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-08-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-10-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	CTIS2023-506824-96-00
EudraCT	EUCTR2021-006226-49-NL
CCMO	NL80998.056.22
Other	UTN: U1111-1271-3861