Effect of Semaglutide 2.4 mg once-weekly on function and symptoms in subjects with obesity-related heart failure with preserved ejection fraction, and type 2 diabetes

Published: 03-03-2021
Last updated: 04-04-2024

Primary objectiveTo investigate the effects of semaglutide s.c. 2.4 mg once-weekly on physical function, symptoms and body weight compared with placebo, both added to standard of care, in subjects with obesity-related HFpEF and T2D.Secondary…

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

Summary

ID

NL-OMON51963

Source
ToetsingOnline

Brief title
STEP HFpEF DM

Condition

- Other condition
- Heart failures
- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
hartfailure, obesity

Health condition

obesitas

Research involving
Human

Sponsors and support

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

Intervention

Keyword: heartfailure, obesity, semaglutide 2.4 mg, type 2 diabetes

Outcome measures

Primary outcome

The primary endpoints are change in KCCQ (clinical summary score) and change in body weight from baseline to end of treatment.

Secondary outcome

The secondary endpoints are change in C-Reactive Protein (CRP) and change in six-minute walking distance from baseline to endof treatment.

Hierarchical composite of:

- Time to all-cause death, number of heart failure events requiring hospitalisation or urgent heart failure visit,

- time to first heart failure event requiring hospitalisation or urgent heart failure visit,

- difference at least 15 in KCCQ clinical summary score change from baseline to 52 weeks,

- difference at least 10 in KCCQ clinical summary score change from baseline to 52 weeks,

- difference at least 5 in KCCQ clinical summary score change from baseline to

52 weeks,

- difference at least 30 metres in sixminute walking distance change from

baseline to 52 weeks

(assessed by the win ratio).

Study description

Background summary

Heart Failure with Preserved Ejection Fraction
Heart failure (HF) is a haemodynamic disorder where the heart fails to keep up with the circulatory demands of the body (HFrEF), or does so at the expense of raised left ventricular filling pressures (HFpEF). HFpEF is a clinical syndrome of heart failure symptoms combined with normal or near-to- normal LVEF and increased left ventricular filling pressures. The increased pressure can be measured by cardiac catheterization or estimated by echocardiography. Other echocardiographic findings include both structural and functional changes as part of diagnosing HFpEF, and left ventricular diastolic dysfunction (abnormal relaxation) is a key defining feature of HFpEF. The increased pressure generally leads to elevation of NT-proBNP and BNP due to increased ventricular wall tension, but levels of NT-proBNP are inversely related to body weight in both the general population and in the HFpEF patient population. The prevalence of HFpEF has increased during the last decades and is now more frequent than HFrEF. HF, including HFpEF, remains to be a leading
cause of morbidity and mortality. To date, no pharmacological interventions to address HFpEF have been approved, and the current HF therapies do not directly target the fundamental metabolic derangements, thus making it one of the greatest unmet needs in cardiology today.

Obesity-related HFpEF
Obesity, a chronic disease resulting in decreased health-related quality of life and 5-10 years reduced life expectancy, has been identified as a major risk factor for the development of HFpEF. The impact of obesity on HFpEF is probably due to a combination of mechanical mechanisms, volume overload, endocrine-, metabolic- and cellular signalling together with an altered inflammatory status. The aggregate of these factors ultimately leads to cardiomyocyte dysfunction and impaired diastolic function of the heart, while contractility is preserved. More than 83% of patients with HFpEF are found to have either overweight or obesity.
Obesity is associated with systemic inflammation and with increased risk of a variety of comorbidities including T2D, hypertension, dyslipidaemia,

cardiovascular diseases, and risk of early death. A study of elderly subjects with HFpEF and obesity has indicated that a weight loss of 3-7 kg increases exercise tolerance and improvement in HF-specific health-related quality of life as assessed by the KCCQ.
Lifestyle intervention in the form of diet and exercise is first line treatment for obesity, but most people with obesity struggle to achieve and maintain their weight loss without pharmacotherapy. Consequently, semaglutide may serve as a valuable adjunct to lifestyle intervention for individuals with obesity-related HFpEF in order to achieve and sustain a clinically relevant weight loss, to improve complications and health-related quality of life.

Study objective

Primary objective
To investigate the effects of semaglutide s.c. 2.4 mg once-weekly on physical function, symptoms and body weight compared with placebo, both added to standard of care, in subjects with obesity-related HFpEF and T2D.

Secondary objectives
To investigate the effects of semaglutide s.c. 2.4 mg once-weekly on walking distance, biomarker of inflammation, disease specific aspects, social limitation, change in body composition and health-related quality of life, and glycaemic control and hypoglycaemia compared with placebo, both added to standard of care, in subjects with obesity-related HFpEF and T2D.

Study design

This is a 52-week, randomised, placebo-controlled, double blind, multi-centre clinical trial
comparing semaglutide s.c. 2.4 mg with placebo in subjects with obesity related HFpEF and T2D.
Eligible subjects will be randomised in a 1:1 manner to receive either semaglutide s.c. 2.4 mg or placebo once weekly as add-on to standard of care. The trial includes a screening visit to assess the subject*s eligibility followed by a randomisation visit. A period of 16 weeks of dose escalation is planned to minimise potential gastrointestinal adverse events with a dose increase every 4th week. Hereafter a visit will take place every 8th week until end of treatment (week 52). Follow-up period is 5 weeks after end of treatment.
A subset of 240 randomised subjects will undergo echocardiography at randomisation to ensure at least 180 subjects undergoing echocardiography at the end of treatment. Measures of diastolic dysfunction will be evaluated as exploratory endpoints in order to gain mechanistic insights associated with weight loss on semaglutide treatment.
Randomisation will be stratified by BMI into two subgroups (BMI <35.0 and BMI >=35.0).To ensure sufficient statistical power for subgroup analyses according to BMI, a maximum of 50% of subjects will be included in the lower BMI

subgroup.

Intervention

Once weekly semaglutide/placebo subcuteneous injection, dose 2.4 mg.

Study burden and risks

Necessary precautions have been implemented in the design and planned conduct of the trial in order to minimize the risks and inconveniences of participation in the trial. The safety profile for semaglutide generated from the clinical and non-clinical development programme has not revealed any safety issues that would prohibit administration of semaglutide 2.4 mg. The results of the phase 3a weight management programme (NN9536, STEP) indicate that semaglutide provides a clinically meaningful weight loss that will provide benefit and is expected to relieve symptoms and improve physical function. The anticipated benefits from healthy lifestyle counselling will include all subjects participating in this trial.
Considering the measures taken to minimise risk to subjects participating in this trial, the potential risks identified in association with semaglutide are justified by the anticipated benefits that may be afforded to subjects with obesity-related HFpEF and T2D.

Contacts

Public
Novo Nordisk

Flemingweg 8
Alphen aan den Rijn 2408AV
NL
Scientific
Novo Nordisk

Flemingweg 8
Alphen aan den Rijn 2408AV
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

• Male or female, age above or equal to 18 years at the time of signing informed consent.
• Body mass index (BMI) >= 30.0 kg/m2
• New York Heart Association (NYHA) Class II-IV
• Left ventricular ejection fraction (LVEF) >= 45% at screening
• Diagnosed with T2D >= 90 days prior to the day of screening
• HbA1c of <= 10.0% as measured at the screening visit

Exclusion criteria

• A self-reported change in body weight > 5 kg (11 lbs) within 90 days before screening
irrespective of medical records
• Uncontrolled and potentially unstable diabetic retinopathy or maculopathy. Verified by a fundus
examination performed within 90 days prior to screening or in the period between screening and
randomisation. Pharmacological pupil-dilation is a requirement unless using a digital fundus
photography camera specified for non-dilated examination.

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:	Recruitment stopped
Start date (anticipated):	24-08-2021
Enrollment:	25
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	nog niet bekend
Generic name:	semaglutide
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	03-03-2021
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	10-06-2021
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	10-07-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-08-2021

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-10-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	09-11-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	04-02-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	25-02-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	31-08-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	10-11-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	13-11-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	29-12-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	19-07-2023

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-09-2023
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	EUCTR2020-004170-22-NL
CCMO	NL76450.042.21