Efficacy and safety of oral semaglutide versus placebo both in combination with metformin and/or basal insulin in children and adolescents with type 2 diabetes

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This study has been transitioned to CTIS with ID 2023-506923-27-00 check the CTIS register for the current data. Primary objectiveTo confirm superiority of oral semaglutide at the maximum tolerated dose* (3 mg, 7 mg or 14 mg) versus placebo on...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Glucose metabolism disorders (incl diabetes mellitus)
Study type	Interventional

Summary

ID

NL-OMON54032

Source
ToetsingOnline

Brief title
PIONEER TEENS

Condition

- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
diabetes, Diabetes mellitus type 2

Research involving
Human

Sponsors and support

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

Intervention

Keyword: adolescents, children, Oral semaglutide, Type 2 diabetes

Outcome measures

Primary outcome

Change from baseline (week 0) to week 26 in glycosylated haemoglobin (HbA1c)

(%-point and mmol/mol)

Secondary outcome

Confirmatory secondary endpoints

Change from baseline (week 0) to week 26 in:

• Fasting plasma glucose (FPG) (mmol/L)

• Body mass index (BMI) standard deviation score (SDS)

Supportive secondary efficacy endpoints

Change from baseline (week 0) to week 26 and to week 52 in:

• HbA1c, FPG , Body weight , Waist circumference, BMI, Systolic and

diastolic blood pressure

Time to event:

• Time to additional anti-diabetic medication

• Time to rescue medication

Supportive secondary safety endpoints

Number of treatment-emergent adverse events

Hypoglycaemic episodes:

• Number of treatment-emergent severe or blood glucose confirmed symptomatic hypoglycaemic episodes

Change from baseline to week 26 and week 52 in:

• Biochemistry

• amylase (U/L)

• lipase (U/L)

• Biomarkers

• insulin-like growth factor 1 (IGF-1) (ng/mL)

• insulin-like growth factor binding protein 3 (IGFBP 3) (ng/mL)

• Hormones

• calcitonin (pmol/L)

• estradiol (for girls) (pmol/L)

• testosterone (for boys) (nmol/L)

• prolactin (mIU/L)

• thyroid stimulating hormone (TSH/thyrotropin) (mIU/L)

• follicle stimulating hormone (FSH) (mIU/mL)

• luteinizing hormone (LH) (mIU/mL)

• dehydroepiandrosterone sulfate (DHEAS) (µmol/L)

Study description

Background summary

Despite the increased prevalence and the potential short-term and long-term risks associated with early onset of T2D, optimal regimens to treat children and adolescents with T2D are not established. Treatment approaches are often extrapolated from those used for adults. For many years, metformin was the only globally approved non-insulin treatment for children and adolescents with T2D.

There is an unmet medical need for effective therapies that preserve or sustainably improve beta-cell function in young patients with T2D.
Insulins are approved for the treatment of paediatric T2D; however, insulins are associated with hypoglycaemia and weight gain and are therefore subject to considerable clinical inertia, i.e. the failure to in a timely manner initiate insulin or intensify the dose.

GLP-1 RAs have therefore been suggested as another treatment option when glycaemic control is not achieved with metformin and insulin alone.
Recently, the GLP-1 RA liraglutide (Victoza®) was approved in the US and EU for use in patients 10 years and older with T2D. To date, no studies in children or adolescents with T2D have evaluated whether improvements in beta-cell function (and other parameters central to the pathophysiology of diabetes) gained while on treatment with GLP-1 RAs in clinical trials persist after treatment cessation.

Study objective

This study has been transitioned to CTIS with ID 2023-506923-27-00 check the CTIS register for the current data.

Primary objective
To confirm superiority of oral semaglutide at the maximum tolerated dose* (3 mg, 7 mg or 14 mg) versus placebo on glycaemic control in children and adolescents (age 10 to <18 years) with type 2 diabetes on a background treatment of metformin or basal insulin or both.

Secondary objectives
To assess and compare the efficacy of oral semaglutide at the maximum tolerated dose (3 mg, 7 mg or 14 mg) versus placebo on a background treatment of metformin or basal insulin or both on:
• Other parameters of glycaemic control
• Parameters of body composition
• Growth parameters
• Cardio-metabolic parameters
To assess and compare the safety and tolerability of oral semaglutide at the maximum tolerated dose (3 mg, 7 mg or 14 mg) versus placebo on a background

treatment of metformin or basal insulin or both.

Study design

This is a randomised, double-blind, placebo-controlled, parallel-group, multi-national, and multi-centre clinical trial that includes a 52-week treatment period followed by a 12-week off-trial product follow-up period in subjects aged 10 to <18 years (at randomisation) with T2D diagnosed according to the most recent ADA criteria1. Subjects will be randomised in a 1:1 manner to receive either oral semaglutide or oral semaglutide placebo (hereafter referred to as placebo) once daily in addition to background treatment with metformin or basal insulin or both, in addition to diet and exercise for 52 weeks. Randomisation will be stratified by sex (male or female) and by age (<14 years of age or >=14 years of age). The stratification is done to ensure an even distribution of males vs. females and age groups across treatment groups.

The trial consists of a 2-week screening period during which time all screening parameters must be assessed. If eligible according to the inclusion and exclusion criteria, subjects are to be randomised to either oral semaglutide or placebo treatment for 52 weeks. All subjects will be dose-escalated to an individual maximum tolerated dose. For the duration of the trial, subjects should be on stable background treatment with either metformin, basal insulin or a combination of both, all in addition to diet and exercise. After the 52-week treatment period, all subjects will continue in a 12-week follow-up period with visits at week 57 and week 64 (end-of-trial visit). The maximum duration of the trial including the 2-week screening and the 12-week follow-up period will be up to 66 weeks (2+52+12 weeks), with an additional 2 weeks if the visit window is fully used.

Intervention

Subjects will, after a 2-week screening period, be randomised in a 1:1 manner to receive either oral semaglutide or placebo. All subjects will follow a dose escalation regimen to an individualised maximum tolerated dose.

As a safety precaution, dose-escalation in the paediatric subjects will be approached cautiously depending on pre-defined criteria for glycaemic control and the subjects' tolerability to trial product. Subjects will receive a starting dose of 3 mg for 4 weeks and then the dose will be escalated with minimum 4-week intervals to 7 mg and then to 14 mg.

The dose will only be escalated if the pre-defined criteria for glycaemic control are met: mean of three fasting self-measured plasma glucose (SMPG) measurements > 6.1 mmol/L [>110 mg/dL] taken on three consecutive days prior the visit and the individual subject*s tolerability for the trial product.

The end-of-treatment visit will be at week 52. After the 52-week treatment period, all subjects will continue a 12-week off-trial product follow-up period with visits at week 57 and week 64 (end-of-trial visit).

Study burden and risks

Data from the oral semaglutide clinical development programme in adults with T2D has not revealed any safety issues that outweigh the benefits.

As the trial population will consist of children and adolescents with T2D, an external independent Data Monitoring Committee (DMC) will monitor unblinded subject safety data on an ongoing basis.

Assessment of diabetes control and adherence to standard of care treatment will be provided throughout the trial. It is therefore concluded that the potential benefits from participating in the trial outweigh the risks for oral semaglutide as well as placebo treated subjects.

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
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

- Informed consent from parent(s) or legally acceptable representative (LAR) and child assent from the subject obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial.
- Male or female, aged 10 to less than18 years at the day of randomisation.
- Glycosylated haemoglobin (HbA1c) 6.5*11.0 percent (47*97 mmol/mol) (both inclusive).
- Diagnosed with type 2 diabetes mellitus according to the American Diabetes Association criteria and treated with:
- stable metformin dose* or
- stable metformin dose* and a stable dose of basal insulin** or
- stable dose of basal insulin**
*stable metformin dose is defined as at least 1000 mg daily or the maximum tolerated dose for 56 days or longer prior to screening.
**stable dose of basal insulin is defined as basal insulin treatment more than or equal to 30 days prior to screening, compared to the dose at screening, dose adjustments of plus or minus 25 percent are allowed.

Exclusion criteria

- Diagnosis of type 1 diabetes.
- Maturity onset diabetes of the young (MODY).
- Positive insulinoma associated-protein 2 (IA-2) antibodies or anti-glutamic acid decarboxylase (anti-GAD) antibodies.
-C-peptide <0.6 ng/mL and ALT >=3 times the UNL and bilirubin >=1.5 times the UNL

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):	02-07-2021
Enrollment:	3
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Rybelsus
Generic name:	oral semaglutide
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	22-09-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-10-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-08-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	24-08-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-03-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-03-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-08-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-08-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-06-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl
Approved WMO Date:	19-07-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214

	Postbus 22660
	1100 DD Amsterdam
	020 566 7389
	mecamc@amsterdamumc.nl
Approved WMO Date:	25-07-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam)
	Kamer G4-214
	Postbus 22660
	1100 DD Amsterdam
	020 566 7389
	mecamc@amsterdamumc.nl
Approved WMO Date:	10-10-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam)
	Kamer G4-214
	Postbus 22660
	1100 DD Amsterdam
	020 566 7389
	mecamc@amsterdamumc.nl
Approved WMO Date:	14-11-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam)
	Kamer G4-214

Postbus 22660

1100 DD Amsterdam

020 566 7389

mecamc@amsterdamumc.nl

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	CTIS2023-506923-27-00
EudraCT	EUCTR2018-002952-34-NL
CCMO	NL74631.018.20