Effect of liraglutide for weight management in paediatric subjects with Prader-Willi Syndrome.
A randomised, placebo controlled, parallel group, multi-centre, multinational trial with a 16-week double-blind period and 36-week open-label period.

Published: 17-08-2015
Last updated: 20-04-2024

Primary objective- To compare the efficacy of liraglutide versus placebo on weight loss in obese paediatric subjects with PWS at 16 weeks and versus no treatment at 52 weeks.Secondary objectives - To compare the efficacy of liraglutide versus...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Appetite and general nutritional disorders
Study type	Interventional

Summary

ID

NL-OMON47321

Source
ToetsingOnline

Brief title
NN8022-4179 (Prader-Willi Syndrome)

Condition

- Appetite and general nutritional disorders

Synonym
Obesity, weight management

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Liraglutide, Obesity, Prader-Willi Syndrome, Weight management

Outcome measures

Primary outcome

There are two co-primary endpoints:

- Change in body mass index (BMI) standard deviation score (SDS) from baseline

to 16 weeks

- Change in body mass index (BMI) standard deviation score (SDS) from baseline

to 52 weeks

Secondary outcome

Supportive secondary endpoints

- Percent of subjects achieving * 5% reduction in baseline BMI at weeks 16 and

52*

- Percent of subjects achieving * 10% reduction in baseline BMI at weeks 16 and

52*

Change from baseline to 16 and 52 weeks in:

- BMI

- Body weight (kilogram (kg), pounds (lb) and percent (%))

- Hyperphagia score:

* total score and

* hyperphagic behaviour, drive and severity score

- Systolic and diastolic blood pressure

- Glucose metabolism

Study description

Background summary

Prader-Willi syndrome (PWS) is a genetic disorder characterised by hypotonia with poor sucking reflex, feeding difficulties, and poor weight gain during infancy, hypogonadism, growth hormone insufficiency causing short stature, mild to moderate mental retardation, early childhood-onset hyperphagia and obesity.

Obesity typically manifests in early childhood and is a major cause of morbidity and mortality and is strongly associated with multiple comorbid conditions, including cardiopulmonary compromise, type 2 diabetes mellitus (T2DM), hypertension, etc. Food-seeking behaviour is common in patients with PWS. Left unchecked and untreated, lack of appetite control can lead to morbid obesity. Therefore improvement in weight control remains the most important goal of any PWS treatment programme.
For treatment and prevention of obesity in PWS, low calorie and well-balanced diets with rigorous supervision and restriction of food access combined with regularly scheduled meals and physical activities are recommended. The treatment of obesity in PWS is difficult and requires a comprehensive multidisciplinary approach with establishment of rigid structures to limit food intake and promote supervised physical activity. Bariatric surgery is not recommended for children with PWS.

The role of pharmacotherapy in PWS is uncertain. No medication has shown long-term effectiveness in controlling appetite.
Liraglutide is a once-daily glucagon-like peptide-1 (GLP-1) analogue. Liraglutide has unique therapeutic potential for the treatment of obesity, due to its combined effects not only on body weight but also on glycaemic control and other weight-related comorbidities. Liraglutide regulates appetite by increasing feelings of fullness and satiety, while lowering feelings of hunger and prospective food consumption.

Currently, there are no approved weight management pharmacotherapies for children and adolescents within Europe, and in the US the only medication approved by the FDA for children * 12 years of age is orlistat. Therefore there is an unmet medical need for anti-obesity medication as an adjunct to lifestyle interventions in this patient population.

Study objective

Primary objective
- To compare the efficacy of liraglutide versus placebo on weight loss in obese paediatric subjects with PWS at 16 weeks and versus no treatment at 52 weeks.

Secondary objectives
- To compare the efficacy of liraglutide versus placebo on glycaemic control in obese children and adolescents with PWS at 16 weeks and versus no treatment at 52 weeks.
- To estimate the liraglutide steady state exposure in obese children and adolescents with PWS after 16 weeks of treatment.
- To compare the safety of liraglutide versus placebo in obese children and adolescents with PWS at 16 weeks and versus no treatment at 52 weeks.

Study design

This is a multi-centre, multi-national, randomised, parallel group, placebo-controlled trial with a 16 week double-blind period and a 36-week open-label period. This trial consists of a part A and a part B. Part A of the trial is conducted in obese adolescents (* 12 and < 18 years, Tanner stage 2*5) with PWS. Part B of the trial is conducted in obese children (* 6 and * 12 years, Tanner stage 1) with PWS. Entry into part A and part B of the trial will be sequential. After all subjects in part A have completed the 16-week double-blind period, an independent external Data Monitoring Committee (DMC) will review the PK data and safety data from part A. Based on result of the safety and PK data of NN8022-4181 and part A of NN8022-4179, the recommendation for part B - PWS children (aged 6 to < 12 years) with obesity is to initiate treatment with liraglutide/placebo based on weight.
Subjects will be randomised 2:1 to receive liraglutide or liraglutide placebo.
Part A has four strata as subjects are stratified according to Tanner stage 2*3 and 4*5 and by presence/absence of dysglycaemia. Part B includes subjects with Tanner 1 development and has two strata for presence/absence of dysglycaemia, see section 11.
Dysglycaemia is defined as pre-diabetes with FPG * 5.6 * 6.9 mmol/L (* 100-125 mg/dl) and/or HbA1c 5.7 * 6.4 % (both inclusive). The HbA1c and FPG results from V2 must be used.
At least 30% of subjects will be from areas with lifestyle and nutrition comparable to that in the European Union (EU). All subjects and/or their legally acceptable representative (LAR) will undergo counselling for weight

loss and must be prescribed a structured programme for diet and physical activity throughout the trial (from randomisation to the end of the trial).
Placebo injections will be stopped at week 16, at the end of the double-blind period.
Subjects treated with growth hormone therapy may enter the trial and will have no change in treatment plan with growth hormone from randomisation to the end of the open-label period (subjects on growth hormone will stay on, and subjects off growth hormone will stay off during this period. Adjustments to doses of growth hormone are permitted).

Intervention

Liraglutide or liraglutide placebo will be administered by once-daily subcutaneous (s.c.) injections either in the abdomen, thigh, or upper arm. During the 16-week double-blind period, subjects randomised to receive liraglutide placebo will receive placebo s.c. injections with injection volumes equivalent to the corresponding liraglutide dose. Injections can be administered at any time of day irrespective of meals. It is recommended that the time of injection is consistent throughout the trial. At the end-of the double-blind period, subjects randomised to receive placebo will stop injections once the investigator and subject are un-blinded to treatment allocation. During the 36-week open-label period, subjects in the liraglutide group will continue to receive liraglutide treatment. The maximum duration of treatment of a single subject, from first trial product administration to last trial product administration will be 52 weeks, and the maximum dose will be 3.0 mg/day in part A and 2.4 or 3.0 mg/day in part B.

Dose escalation will be based on tolerability as assessed by the investigator. In part A and in part B for children with a body weight * 45 kg, treatment is planned to be initiated with liraglutide/placebo 0.6 mg daily for one week and increase in weekly steps of 0.6 mg until a maximum tolerated dose (MTD) (as judged by the investigator) or a dose of 3.0 mg liraglutide/placebo is reached. For children with a body weight < 45 kg in part B, dosing will be initiated with liraglutide/placebo 0.3 mg daily for one week and increased to 0.6 mg after the first week, thereafter the dose is increased in weekly steps of 0.6 mg until a MTD (as judged by the investigator) or a dose of 2.4 mg liraglutide/placebo is reached.

The trial product dose will be escalated only if the current dose is tolerated. If a subject has tolerability issues with the higher dose level (as judged by the investigator), it is allowed to lower to the previous dose level.
If a trial product dose is poorly tolerated, subjects are allowed to remain at a dose level for a maximum of 2 weeks. This extended time of one additional week is allowed at each dose level, i.e. the dose escalation process may take up to 8 weeks in total. It is at the discretion of the investigator to judge

when the subject has reached MTD

Study burden and risks

The trial consists of 20 visits in 54 weeks, 10 during the screening and double blind period of 16 weeks, 9 during the open label period of 36 weeks and one follow-up visit after an additional 2 weeks.
At 5 visits a physical exam will be performed.
During the trial a diary consisting of a dosing diary, hypoglycaemia diary and a menstrual calendar needs to be completed by the patient or parent/legal representative.
At 3 visits questionnaires/interviews (hyperphagia, PHQ-9 and C-SSRS; PHQ and C-SSRS only applicable for part A) need to be completed.
Since liraglutide is a blood glucose lowering agent (blood glucose-dependent) for safety reasons patients will be instructed in the use of a blood glucose meter (will be provided to them).
As with all medication side-effects can occur (gastro-intestinal side effects, pancreatitis, dehydration and decrease kidney function, gallstone disease, injection site reactions, allergic reactions, hypoglycaemia, increased heart rate, dizziness, decrease in appetite, changed sense of taste and feeling weak or tired). These have been described extensively in the patient information.

There might also be some discomfort due to a more frequent blood testing during the trial. At 12 visits blood samples will be collected (approximately 150 mL in total). Laboratory blood sampling may cause bruising and infection but the risk of this occurring in the trial is not higher than for normal laboratory blood sampling.

Contacts

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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 obtained before any trial-related activities.
- Confirmed diagnosis of PWS (by genetic testing)
- Male or female, age at the time of signing informed consent:
Part A: * 12 and < 18 years
Part B: * 6 and < 12 years
- Tanner stage 2*5 pubertal development for part A, and Tanner stage 1 for part B
- BMI corresponding to * 30 kg/m2 for adults by international cut-off points1 and * the 95th percentile for age and sex (for diagnosis of obesity)
- Stable body weight during the previous 90 days before screening (< 10 kg self-reported weight change)
- Testing has been performed to evaluate for adrenal insufficiency and documented in medical record

Exclusion criteria

- Type 1 diabetes mellitus (T1DM)
- Type 2 diabetes mellitus (T2DM)
- Calcitonin * 50 ng/L
- No change in treatment plan with growth hormone from randomisation to the end of the open label period (patients on GH to stay on, patients off GH to stay off during this period. Adjustments in doses of growth hormone will be permitted)
- Family or personal history of Multiple Endocrine Neoplasia Type 2 (MEN2) or Medullary Thyroids Carcinoma (MTC)
- History of pancreatitis (acute or chronic)
- Treatment with any medication prescribed for weight loss within 90 days before screening (e.g. orlistat, zonisamide, topiramate/phentermine, lorcaserin, phentermine,

bupropion/naltrexone, liraglutide, metformin)
- Untreated adrenal insufficiency
- Suggestive history of, or significant risk of gastroparesis (e.g. marked abdominal bloating post meal, history of vomiting, severe constipation), as judged by the Investigator

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	22-06-2016
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Saxenda
Generic name:	Liraglutide
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	17-08-2015

Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-10-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-03-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-02-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-02-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-02-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-06-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-06-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	09-04-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2014-004415-37-NL
CCMO	NL54145.078.15
Other	U1111-1162-7884