The efficacy and safety of liraglutide as adjunct therapy to insulin in the treatment of type 1 diabetes; A 52-week randomised, treat-to-target, placebo-controlled, double-blinded, parallelgroup, multinational, multi-centre trial

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

Summary

ID

NL-OMON38605

Source
ToetsingOnline

Brief title
ADJUNCT ONE*

Condition

- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
diabetes

Research involving
Human

Sponsors and support

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

Intervention

Keyword: GLP-1 analogue, liraglutide, type 1 diabetes

Outcome measures

Primary outcome

* Change from baseline in HbA1c after 52 weeks of treatment

* Change from baseline in body weight after 52 weeks of treatment

* Change from baseline in total daily insulin dose after 52 weeks of treatment

Secondary outcome

* Number of confirmed treatment -emergent hypoglycaemic episodes .

Study description

Background summary

Glycaemic control in subjects with type 1 diabetes is often suboptimal.
Liraglutide is an analogue of the naturally occurring human hormone GLP-1, and is suitable for once daily administration.
Small scale studies and case reports in subjects with type 1 diabetes indicate that treatment with a GLP-1 receptor agonist, such as liraglutide as adjunct to insulin, may result in:
a) improvement in glycaemic control through reduction in fasting and postprandial hyperglycaemia,
in part due to inhibition of postprandial hyperglucagonaemia,
b) reduction in glucose excursions,
c) reduction in episodes of hypoglycaemia,
d) reduction in insulin requirements and
e) a weight benefit
The clinical circumstances of insulin treatment in type 1 diabetes not being

optimal imply that new efforts to improve treatment for type 1 diabetes subjects are needed. The rationale for this trial in type 1 diabetes is to investigate liraglutide therapy as adjunct to insulin therapy in subjects, where current insulin treatment does not provide adequate and satisfactory glycaemic control, and where subjects due to fear of hypoglycaemia and/or weight gain refrain from optimising their insulin treatment.

For more detailed information please refer to chapter 3 of the trial protocol (p 23-28)

Study objective

To confirm the efficacy of liraglutide as adjunct to insulin treatment on glycaemic control, and to
confirm the superiority of liraglutide treatment compared to placebo, both adjunct to insulin
treatment, with regard to reduction in daily insulin dose and body weight loss, after 52 weeks of
treatment in subjects with established type 1 diabetes with inappropriate glycaemic control.

Study design

The trial is a randomised, placebo-controlled, double-blinded, parallel-group, multinational, multicentre
trial designed for evaluation of the efficacy and safety of adding liraglutide (0.6 mg, or 1.2
mg or 1.8 mg liraglutide) versus placebo to insulin treatment in subjects with type 1 diabetes during
52 weeks of treatment, in a treat-to-target (T-T-T) design.
After 2 weeks of screening, subjects will be randomised in a 3:3:3:1:1:1 manner to liraglutide
treatment (0.6 mg, 1.2 mg or 1.8 mg), or liraglutide placebo both adjunct to insulin treatment.
The total trial duration per subject is approximately 58 weeks and consists of a 2-week screening
period, a treatment period after randomisation with a dose initiation and dose escalation period of 2 to 4 weeks (dependent on randomised dose of liraglutide/ liraglutide placebo adjunct to insulin
treatment), a maintenance period 48-52 weeks (dependent on randomised dose of liraglutide/
liraglutide placebo adjunct to insulin treatment), and 4-week follow-up period.
Subjects will be in close and frequent contact, both by phone and site visits to the clinic during the
dose escalation part of the trial. During the maintenance part of the trial the subjects will have site

visits every four to six weeks.

Intervention

During the trial the subjects will follow their regular insulin treatment.

For this trial the following trial products will be provided:
* Liraglutide 6.0 mg/mL, in a 3 mL pre-filled pen injector for subcutaneous (s.c.) injection
* Liraglutide placebo 3 mL in a pre-filled pen injector for s.c. injection

All subjects will initiate liraglutide/ liraglutide placebo treatment at 0.6 mg on the day of
randomisation (Visit 2).
Subjects randomised to the 0.6 mg arms will remain on this dose throughout the study (52 weeks).
Subjects randomised to the 1.2 mg and 1.8 mg arms will increase the dose to 1.2 mg after 2 weeks.
Subjects randomised to the 1.2 mg arms will remain on this dose for 50 weeks.
Subjects randomised to the 1.8 mg dose group will increase the dose to 1.8 mg 4 weeks after
randomisation and remain on this dose for 48 weeks.

Study burden and risks

Subjects are requested to visit the trial site 15 times and attend telephonecalls with the site staff 17-23 times . This could be perceived as a burden.
Bloodsampling is part of standard diabetes care. Due to the higher frequency the subjects may perceive some inconvenience.
12 x venapunction, of which 5x fasting
4-point bloodglucoseprofile (27x)
7-point bloodglucoseprofile on day of start and dose increase trialmedication and the following 3 days (4 to 12x, depending on randomisation).
9-point bloodglucoseprofile (total 4x)
Hypoglycamia could occur. Therefore the subject is closely followed at start of treatment and at dose increase, in order to adjust the insulin dose to the subjects individual needs.
There have been few reported events of acute pancreatitis. Subjects will be informed of the characteristic symptoms and lipase, amylase and calcitonine will be monitored closely during the trial.
In the early part of treatment gastrointestinal adverse events may occur. This may induce loss of body fluid and could lead to dehydration. Subjects are requested explicitly to take in plenty of fluids.
Physical examination, pregnancy test and funduscopy at trial start and end.
Subjects are requested to complete questionnaires on quality of life 3 times

during the trial and are requested to complete diaries (concerning self measured plasmaglucose, insuline dose, comcomittant illness and medication).

Contacts

Public
Novo Nordisk

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Informed consent obtained
- Type 1 diabetes mellitus* 12 months
- Male or female, aged 18 * 75 years
- Basal bolus or CSII (Continuous Subcutaneous Insulin Infusion, insulin pump) treatment * 6 months
- Stable insulin treatment for the last 3 month prior to Screening, as judged and documented by the investigator
- HbA1c 7.0-10% (Diabetes Control and Complications Trial (DCCT)), both inclusive

- Ability and willingness to comply with all protocol procedures e.g. correct handling of trial product, complete trial related questionnaires, diaries, self-monitoring of plasma glucose, selftitration of insulin and attend all scheduled visits

Exclusion criteria

- Prior use of glucagon-like peptide-1 (GLP-1) receptor agonist or dipeptidyl peptidase IV (DPP-4) inhibitors
- Use of any medication, which in the investigator*s opinion could interfere with the glycaemic control or affect the subject*s safety
- Known proliferative retinopathy or maculopathy requiring treatment
- Severe neuropathy, in particular autonomic neuropathy, i.e. gastroparesis, as judged by the investigator
- Uncontrolled/ untreated blood pressure at screening >160 mmHg for systolic or >100 mmHg for diastolic
- History of acute or chronic pancreatitis
- Screening calcitonin value * 50 ng/L
- Personal or family history of medullary thyroid carcinoma or Multiple Endocrine Neoplasia type 2 (MEN2)
- Diagnosis of malignant neoplasm in the previous 5 years (except basal cell skin cancer or squamous cell skin cancer)

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	06-12-2013

Enrollment:	50
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	25-04-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-07-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-09-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-09-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-10-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-03-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO Date:	18-03-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-11-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2012-003580-21-NL
CCMO	NL44136.018.13