Clinical trial results:
The impact of liraglutide on glucose tolerance and the risk of type 2 diabetes in women with previous gestational diabetes mellitus

Summary

EudraCT number	2012-001371-37
Trial protocol	DK
Global end of trial date	04 September 2019

Results information

Result version number	v1 (current)
This version publication date	25 June 2021
First version publication date	25 June 2021

Trial information

Trial identification

Sponsor protocol code	GDM-TREAT

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Steno Diabetes Center Copenhagen
Sponsor organisation address	Gentofte Hospitalsvej 1, Hellerup, Denmark, 2900
Public contact	Center for diabetesforskning, Gentofte Hospital, University of Copenhagen, 45 38672461, emilie.skytte.andersen@regionh.dk
Scientific contact	Center for diabetesforskning, Gentofte Hospital, University of Copenhagen, 61685006 38672461, emilie.skytte.andersen@regionh.dk
Sponsor organisation name	Steno Diabetes Center Copenhagen
Sponsor organisation address	Gentofte Hospitalsvej 1, Hellerup, Denmark, 2900
Public contact	Tina Vilsbøll, Steno Diabetes Center Copenhagen, 0045 40940825, tina.vilsboell.01@regionh.dk
Scientific contact	Tina Vilsbøll, Steno Diabetes Center Copenhagen, 0045 40940825, tina.vilsboell.01@regionh.dk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	19 May 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 September 2019
Global end of trial reached?	Yes
Global end of trial date	04 September 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the effect of the glucagon-like peptide-1 receptor agonist liraglutide on patophysiological characteristics and the risk of type 2 diabetes mellitus in women with previous gestational diabetes mellitus (GDM).

Protection of trial subjects:

This study is not considered as having any ethical problems. The treatment is associated with minimal discomfort for the participating patients comprising blood sample collection, daily injection of liraglutide (Victoza®) or placebo in the subcutis of the abdomen, in the thigh or the upper arm. Common adverse events are mild to moderate transient gastrointestinal symptoms (nausea, vomiting and diarrhoea) affecting around 10-15% of treated patients and headache. The injection is practically pain-free but may leave a small haemorrhage. This will resolve on its own. Less commonly, the patients may experience stomach pain, constipation, fever, reflux, gastritis, dizziness, tiredness and upper airway infection. Uncommon adverse events comprise struma (in patients with existing thyroid adenoma) and angioedema (very uncommon 0.05%).

When collecting blood, some patients may experience minor discomfort when the needle penetrates the skin and rarely a small bleeding occurs. The amount of blood collected during the entire study period is a maximum of 1800 ml (during 5 years) and only patients with a normal blood percent will be included. Severe systemic AEs are not expected.

Dexa scanning will be performed three times during the study with the object of determining the distribution of bone and adipose tissue. Such an examination results in a modest radiation dosis (approximately equivalent to 2-3 times the dose received from a dental X-ray). Dexa scanning takes 15 minutes and is a painless procedure with no expected side effects.

The patients will receive thorough verbal and written information about the risk of developing the mentioned AEs. Verbal and written informed consent will be obtained from patients prior to participation in accordance with current rules. It will be emphasized in the declaration of consent that participation in the project is voluntary and that patients may withdraw their consent to participate at any time without providing a reason and wit

Background therapy:

Liraglutide (Victoza®) is supplied in pens for injection containing 18 mg of the GLP-1 agonist liraglutide in 3 ml sterile water with disodiumphosphate and propylenglycol, and phenol for conservation (pH 8.15). Commercial pens will be used and the information given in the packaging will be applicable. The initial daily dose will be 0.6 mg for one week, thereafter, the dose will be titrated once-weekly (by 0.6 mg) up to 1.8 mg (after 2 weeks) for the remaining treatment period. Patients who do not tolerate injections of liraglutide 1.8 mg will be allowed to continue on the maximally tolerated dose. The injection is administered once daily in the morning. The maximal plasma concentration is reached 8-12 hours after s.c. injection (21). The half-life in plasma is approximately 13 hours and the duration of effect is 24 hours. The placebo pens contain the same as the Victoza® pens except from the GLP-1 analogue and are administered in the same way and volume as liraglutide. The placebo pens are specially prepared for this study and will be used in the study only.

Evidence for comparator: -

Actual start date of recruitment	01 August 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 105
Worldwide total number of subjects	105
EEA total number of subjects	105

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	105
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Women with previous gestational diabetes mellitus were invited to participate in the study (n=2418). They were recruited from the three major obstetric departmens in the Capital region of Denmark. All eligible women (n=121) were screened between september 2012 and august 2014 and 105 women were randomised.

Pre-assignment

Screening details:

The women were fasting (10 hours) including water, coffea, medication and tobacco. We meassured height, waist, hip-circumference, weight, Blodd pressure, urine , basic blood sampling and medical history was obtained.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Women with previous GDM randomised to recieve placebo injection with saline during the first double-blinded year of the study. The placebo pens was specially prepared for this study and was only used in the study.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	s
Pharmaceutical forms	Dispersion for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Plascebo injections with saline in 1.8 mg

Arm title	Liraglutide

Arm description:

Overweight women with previous gestational diabetes mellitus taken injections with active liraglutide 1.8 mg .
Liraglutide (Victoza®) is supplied in pens for injection containing 18 mg of the GLP-1 agonist liraglutide in 3 ml sterile water with disodiumphosphate and propylenglycol, and phenol for conservation (pH 8.15). Commercial pens will be used and the information given in the packaging will be applicable. The initial daily dose will be 0.6 mg for one week, thereafter, the dose will be titrated once-weekly (by 0.6 mg) up to 1.8 mg (after 2 weeks) for the remaining treatment period. Patients who do not tolerate injections of liraglutide 1.8 mg will be allowed to continue on the maximally tolerated dose. The injection is administered once daily in the morning. The maximal plasma concentration is reached 8-12 hours after s.c. injection. The half-life in plasma is approximately 13 hours and the duration of effect is 24 hours.

Arm type	Active comparator
Investigational medicinal product name	Victoza
Investigational medicinal product code	
Other name	s
Pharmaceutical forms	Dispersion for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Liraglutide (Victoza®) is supplied in pens for injection containing 18 mg of the GLP-1 agonist liraglutide in 3 ml sterile water with disodiumphosphate and propylenglycol, and phenol for conservation (pH 8.15). Commercial pens will be used and the information given in the packaging will be applicable. The initial daily dose will be 0.6 mg for one week, thereafter, the dose will be titrated once-weekly (by 0.6 mg) up to 1.8 mg (after 2 weeks) for the remaining treatment period. Patients who do not tolerate injections of liraglutide 1.8 mg will be allowed to continue on the maximally tolerated dose. The injection is administered once daily in the morning. The maximal plasma concentration is reached 8-12 hours after s.c. injection. The half-life in plasma is approximately 13 hours and the duration of effect is 24 hours.

Number of subjects in period 1	Placebo	Liraglutide
Started	55	50
Completed	40	28
Not completed	15	22
fear of adverse events	-	1
Adverse event, non-fatal	-	2
Other diseases	2	-
Unknown	2	-
Pregnancy	-	3
type 2 diabetes	1	-
unknown reason	-	5
diseases not related to study drug	-	7
Lack of compliance	2	-
Lost to follow-up	3	1
Personal issues	5	3

Period 2

Period 2 title	5 year follow-up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

the double-blinding stopped after one year after randomisation. the following 4 years have been open-labelled and unblinded.

Arms

Are arms mutually exclusive?	Yes

Arm title	Placebo
Arm description: -	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	s
Pharmaceutical forms	Dispersion for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Plascebo injections with saline in 1.8 mg

Arm title	Liraglutide
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Victoza
Investigational medicinal product code	
Other name	s
Pharmaceutical forms	Dispersion for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Liraglutide (Victoza®) is supplied in pens for injection containing 18 mg of the GLP-1 agonist liraglutide in 3 ml sterile water with disodiumphosphate and propylenglycol, and phenol for conservation (pH 8.15). Commercial pens will be used and the information given in the packaging will be applicable. The initial daily dose will be 0.6 mg for one week, thereafter, the dose will be titrated once-weekly (by 0.6 mg) up to 1.8 mg (after 2 weeks) for the remaining treatment period. Patients who do not tolerate injections of liraglutide 1.8 mg will be allowed to continue on the maximally tolerated dose. The injection is administered once daily in the morning. The maximal plasma concentration is reached 8-12 hours after s.c. injection. The half-life in plasma is approximately 13 hours and the duration of effect is 24 hours.

Number of subjects in period 2	Placebo	Liraglutide
Started	40	28
Completed	40	28

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Women with previous GDM randomised to recieve placebo injection with saline during the first double-blinded year of the study. The placebo pens was specially prepared for this study and was only used in the study.	
Reporting group title	Liraglutide
Reporting group description:	
Overweight women with previous gestational diabetes mellitus taken injections with active liraglutide 1.8 mg . Liraglutide (Victoza®) is supplied in pens for injection containing 18 mg of the GLP-1 agonist liraglutide in 3 ml sterile water with disodiumphosphate and propylenglycol, and phenol for conservation (pH 8.15). Commercial pens will be used and the information given in the packaging will be applicable. The initial daily dose will be 0.6 mg for one week, thereafter, the dose will be titrated once-weekly (by 0.6 mg) up to 1.8 mg (after 2 weeks) for the remaining treatment period. Patients who do not tolerate injections of liraglutide 1.8 mg will be allowed to continue on the maximally tolerated dose. The injection is administered once daily in the morning. The maximal plasma concentration is reached 8-12 hours after s.c. injection. The half-life in plasma is approximately 13 hours and the duration of effect is 24 hours.	

Reporting group values	Placebo	Liraglutide	Total
Number of subjects	55	50	105
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	55	50	105
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	38.3	38.5	
standard deviation	± 4.9	± 4.9	-
Gender categorical Units: Subjects			
Female	55	50	105
Male	0	0	0
Weight Units: Kg			
arithmetic mean	86.2	90.5	
standard deviation	± 10.6	± 19.1	-

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Women with previous GDM randomised to recieve placebo injection with saline during the first double-blinded year of the study. The placebo pens was specially prepared for this study and was only used in the study.

Reporting group title	Liraglutide

Reporting group description:

Overweight women with previous gestational diabetes mellitus taken injections with active liraglutide 1.8 mg .
Liraglutide (Victoza®) is supplied in pens for injection containing 18 mg of the GLP-1 agonist liraglutide in 3 ml sterile water with disodiumphosphate and propylenglycol, and phenol for conservation (pH 8.15). Commercial pens will be used and the information given in the packaging will be applicable. The initial daily dose will be 0.6 mg for one week, thereafter, the dose will be titrated once-weekly (by 0.6 mg) up to 1.8 mg (after 2 weeks) for the remaining treatment period. Patients who do not tolerate injections of liraglutide 1.8 mg will be allowed to continue on the maximally tolerated dose. The injection is administered once daily in the morning. The maximal plasma concentration is reached 8-12 hours after s.c. injection. The half-life in plasma is approximately 13 hours and the duration of effect is 24 hours.

Reporting group title	Placebo

Reporting group description: -

Reporting group title	Liraglutide

Reporting group description: -

Primary: Glucose tolerance

End point title	Glucose tolerance

End point description:

End point type	Primary

End point timeframe:

Glucose tolerance meassured as Area unde the curve for the 75g oral glucose tolerance test. We calculated the between group difference from baseline to 5-year to evaluate the effect from treatment with liraglutide and reported as differences from baseline

End point values	Placebo	Liraglutide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	28		
Units: mmol/L*min				
arithmetic mean (confidence interval 95%)				
glucose tolerance	123 (46.6 to 199)	-69.2 (-160 to 21.6)		

Statistical analyses

Statistical analysis title	Constrained liniar mixed model
Comparison groups	Placebo v Liraglutide
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	≤ 0.05
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Secondary: Body weight

End point title	Body weight

End point description:

End point type	Secondary

End point timeframe:

Body weight was assesed at baseline and at five years follow-up. We calculated the between group difference from baseline to 5-year to evaluate the effect from treatment with liraglutide and reported as differences from baseline

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

We assesed adverse events throughout the complete study period, beeing from beginning of the randomisation to end of trial for each individual.

Assessment type	Systematic

Dictionary used

Dictionary name	No dictionary
Dictionary version	0

Reporting groups

Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Liraglutide

Reporting group description: -

Serious adverse events	Placebo	Liraglutide	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 55 (0.00%)	0 / 50 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Placebo	Liraglutide	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 55 (45.45%)	40 / 50 (80.00%)	
Nervous system disorders			
Fatigue			
subjects affected / exposed	0 / 55 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Dizziness			
subjects affected / exposed	0 / 55 (0.00%)	4 / 50 (8.00%)	
occurrences (all)	0	4	
Headache			
subjects affected / exposed	4 / 55 (7.27%)	4 / 50 (8.00%)	
occurrences (all)	4	4	
General disorders and administration site conditions			

Marks on injection site			
subjects affected / exposed	15 / 55 (27.27%)	9 / 50 (18.00%)	
occurrences (all)	15	9	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	9 / 55 (16.36%)	23 / 50 (46.00%)	
occurrences (all)	9	23	
Vomiting			
subjects affected / exposed	0 / 55 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Decreased appetite			
subjects affected / exposed	3 / 55 (5.45%)	6 / 50 (12.00%)	
occurrences (all)	3	6	
Obstipation			
subjects affected / exposed	2 / 55 (3.64%)	8 / 50 (16.00%)	
occurrences (all)	2	8	
Diarrhoea			
subjects affected / exposed	5 / 55 (9.09%)	5 / 50 (10.00%)	
occurrences (all)	5	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The dropout rate is a limitation.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/33036179

http://www.ncbi.nlm.nih.gov/pubmed/28364253

http://www.ncbi.nlm.nih.gov/pubmed/27810989

http://www.ncbi.nlm.nih.gov/pubmed/24176797