Clinical trial results:
A randomized, double-blinded placebo-controlled, paralleled designed, investigator sponsored study of the effect of the GLP-1 receptor agonist liraglutide on beta-cell function in C-peptide positive type 1 diabetic patients.

Summary

EudraCT number	2014-005174-11
Trial protocol	SE
Global end of trial date	01 September 2020

Results information

Result version number	v1 (current)
This version publication date	20 October 2022
First version publication date	20 October 2022

Trial information

Trial identification

Sponsor protocol code	U1111-1166-6923

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02617654
WHO universal trial number (UTN)	U1111-1166-6923

Notes:

Sponsors

Sponsor organisation name	Uppsala University Hospital
Sponsor organisation address	Sjukhusvägen, Uppsala, Sweden, 751 85
Public contact	Department of Special Medicine. Unit of Endocrinology & Diabetology, Uppsala University Hospital, +46 186110000, mms@akademiska.se
Scientific contact	Department of Special Medicine. Unit of Endocrinology & Diabetology, Uppsala University Hospital, +46 186110000, mms@akademiska.se

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	16 December 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 June 2020
Global end of trial reached?	Yes
Global end of trial date	01 September 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the effect of 52 weeks of treatment with liraglutide 1.8 mg/day, compared to placebo, on stimulated C-peptide concentrations in patients with long-standing type 1 diabetes (T1D) and residual insulin production.

Protection of trial subjects:

At each visit a full safety profile was obtained by asking for discomfort and side effects combined with laboratory safety assessments. Study personnel was available to be contacted by study subjects between study visits if necessary.

Before each of the study procedures were carried out, the study personnel explained the procedure to the study subject as to make the subject aware of the procedure. When necessary, topical anesthetics were used prior to blood sampling as per clinical practice, in order to minimize discomfort related to the procedure.

Besides, patients participating in the study were covered by the Swedish Patient Insurance and the Swedish Pharmaceutical Insurance.

Background therapy:

Insulin treatment by either pump or multiple daily injection regimen as per clinical practice (standard of care for patients with Type1 diabetes) was allowed in both arms during the study. Concomitant medication which may interfere with glucose regulation other than insulin treatment was not allowed during the study, leading to study subject withdrawal.

Evidence for comparator:

Glucagon-like peptide 1 (GLP-1) plays a key role in limiting postprandial glucose excursions by stimulating insulin secretion, inhibiting glucagon release and delaying gastric emptying. Other putative effects of GLP-1 are increased insulin sensitivity and, at least in rodents, trophic effects on beta-cells.

GLP-1 receptor analogs (GLP-1RA) are today successfully used for treatment of type 2 diabetes (T2D). These drugs have also been tested in clinical trials on C-peptide negative T1D patients, showing a decrease in glycaemic excursions, exogenous insulin doses and HbA1c.

GLP-1RA stimulates beta-cell neogenesis in rodents and specifically liraglutide has shown some potency for human beta-cell regeneration in vitro. In contrast to its rodent counterparts, human beta-cell regeneration in adults has been hard to achieve. However, there is a clear age-dependent responsiveness in the capacity of human beta-cell mass to expand, with beta-cells of younger individuals still having plasticity up to approximately 30 years of age. Clinically, GLP-1RAs are commonly used in the treatment of adults with T2D in the elderly, thereby having a less plastic beta-cell population as part of the disease pathogenesis. Noteworthy, in head-to-head clinical trials in T2D patients liraglutide treatment has been superior or equal to other GLP-1RAs with regard to efficacy to decrease HbA1c.

Recently it has been shown that many patients have remaining beta-cells with residual measurable C-peptide concentrations in blood even several decades after diagnosis. This implies that some beta-cells may be resistant to destruction, that the immune attack has stopped or that beta-cell regeneration continues.

To our knowledge, the long-term effect of liraglutide on C-peptide positive T1D patients has not yet been studied. We aim to investigate the possibility to expand beta-cell mass in young individuals with T1D and remaining beta- cell mass function by liraglutide.

Actual start date of recruitment	01 October 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 18
Worldwide total number of subjects	18
EEA total number of subjects	18

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)	18
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited from the population of T1D patients at Uppsala University Hospital (Sweden) or referral hospitals. All subjects received both oral and written information and signed informed consent prior to study-specific screening procedures. The trial was initiated on 15-11-2015 and the first patient (FPFV) was included on 08-02-2016.

Pre-assignment

Screening details:

Female and male adults between 18-30 years of age with clinical diagnose of T1D for 5 or more years and hb1c between 45 and 75 mmol/mol and fasting plasma C-peptide >1.5 pmol/L.
88 patients screened and 70 excluded. 66 patients did not meet inclusion criteria, 4 declined to participate. Main reason was c-peptide (49) or hba1c (13) out of range.

Pre-assignment period milestones

Number of subjects started	18
Number of subjects completed	18

Period 1

Period 1 title	On-treatment week 0-52
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

After randomization, a patient identification number was assigned to each study subjects in consecutive order. This identification number corresponds to specific batch of study drug, either liraglutide and placebo. Batch number were blinded by the MAH.

Double-blinding was achieved as both liraglutide and placebo were labelled and packed identically by the MAH. The injection pens were identical and the study subjects were instructed to inject the same volume of active substance or placebo.

Arms

Are arms mutually exclusive?	Yes
Arm title	Liraglutide Arm

Arm description:

Treatment with IMP liraglutide during 52 weeks. Initial titration phase 6 weeks.

Arm type	Experimental
Investigational medicinal product name	Victoza (liraglutide)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Solution for injection , Subcutaneous use

Dosage and administration details:

Subjects will initiate treatment with a dose of 0.6 mg during 2 weeks, increase to a dose of 1.2 mg for 2 weeks and then finally increase to 1.8 mg for 48 weeks.

Arm title	Placebo

Arm description:

Treatment with placebo during 52 weeks. Initial titration phase 6 weeks.

Arm type	Placebo

Investigational medicinal product name	Liraglutide-Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Solution for injection , Subcutaneous use

Dosage and administration details:

Subjects initiated treatment with a dose of 0.6 mg during 2 weeks, increase to a dose of 1.2 mg for 2 weeks and then finally increase to 1.8 mg for 48 weeks, same dose as for Liraglutide.

Number of subjects in period 1	Liraglutide Arm	Placebo
Started	10	8
Completed	8	8
Not completed	2	0
Adverse event, non-fatal	2	-

Period 2

Period 2 title	Follow-up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

See period 2

Arms

Are arms mutually exclusive?	Yes
Arm title	Liraglutide-Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Liraglutide-Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Solution for injection , Subcutaneous use

Dosage and administration details:

Subjects will initiate treatment with a dose of 0.6 mg during 2 weeks, increase to a dose of 1.2 mg for 2 weeks and then finally increase to 1.8 mg for 48 weeks.

Arm title	Liraglutide

Arm description: -

Arm type	Experimental

Investigational medicinal product name	Victoza (liraglutide)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Solution for injection , Subcutaneous use

Dosage and administration details:

Subjects will initiate treatment with a dose of 0.6 mg during 2 weeks, increase to a dose of 1.2 mg for 2 weeks and then finally increase to 1.8 mg for 48 weeks.

Number of subjects in period 2	Liraglutide-Placebo	Liraglutide
Started	8	8
Completed	8	8

Baseline characteristics

Reporting groups	
Reporting group title	Liraglutide Arm
Reporting group description:	
Treatment with IMP liraglutide during 52 weeks. Initial titration phase 6 weeks.	
Reporting group title	Placebo
Reporting group description:	
Treatment with placebo during 52 weeks. Initial titration phase 6 weeks.	

Reporting group values	Liraglutide Arm	Placebo	Total
Number of subjects	10	8	18
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)	10	8	18
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	24.0	24.6	
standard deviation	± 3.5	± 3.4	-
Gender categorical			
Units: Subjects			
Female	2	3	5
Male	8	5	13
Insulin treatment at baseline			
Insulin treatment modality at baseline as per clinical practice. MDI (multiple daily injection) and subcutaneous insulin pump.			
Units: Subjects			
MDI	9	4	13
Insulin Pump	1	4	5
Retinopathy			
Diabetes retinopathy status at baseline			
Units: Subjects			
Yes	2	2	4
No	8	6	14
GAD			
GAD antibody status at baseline			
Units: Subjects			
Positive	6	5	11
Negative	4	2	6
Not Recorded	0	1	1

IA-2			
IA-2 antibody status at baseline			
Units: Subjects			
Positive	7	5	12
Negative	3	3	6
Not Recorded	0	0	0
HbA1c			
Glycated haemoglobin at baseline			
Units: mol/L			
arithmetic mean	54.3	59.9	
standard deviation	± 7.4	± 8.1	-
Weight			
Weight at baseline			
Units: Kg			
arithmetic mean	75.9	76.7	
standard deviation	± 7.5	± 15.3	-
BMI			
Body Mass Index at baseline			
Units: kg/m2			
arithmetic mean	24.4	25.7	
standard deviation	± 2.8	± 3.7	-
Fasting C-peptide			
Fasting C-peptide concentration at baseline			
Units: pmol/L			
arithmetic mean	48.1	25.3	
standard deviation	± 37.9	± 45.8	-
Insulin dose at baseline			
Units: U/kg			
arithmetic mean	0.57	0.66	
standard deviation	± 0.14	± 0.22	-
Age at onset of diabetes			
Units: years			
arithmetic mean	14.0	15.6	
standard deviation	± 2.4	± 4.7	-
Duration of T1D			
Units: years			
arithmetic mean	10.0	9.0	
standard deviation	± 4.8	± 3.5	-

End points

End points reporting groups

Reporting group title	Liraglutide Arm
Reporting group description:	
Treatment with IMP liraglutide during 52 weeks. Initial titration phase 6 weeks.	
Reporting group title	Placebo
Reporting group description:	
Treatment with placebo during 52 weeks. Initial titration phase 6 weeks.	
Reporting group title	Liraglutide-Placebo
Reporting group description: -	
Reporting group title	Liraglutide
Reporting group description: -	

Primary: Δ-change in C-peptide AUC after 52 weeks

End point title	Δ-change in C-peptide AUC after 52 weeks
End point description:	
The Area Under the Curve (AUC) change in plasma C-peptide concentration in response to a standardized mixed meal tolerance test (MMTT) after completion of one year of treatment with liraglutide.	
End point type	Primary
End point timeframe:	
Week 0 (start of treatment) Week 52 (treatment stop)	

End point values	Liraglutide Arm	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8[1]	8		
Units: pmol/l x min				
arithmetic mean (standard deviation)	-1103 (± 4194)	-283 (± 4423)		

Notes:

[1] - 2 subjects discontinued during the titration phase due to adverse events.

Attachments (see zip file)	Delta C-peptide AUC w52-w0.pdf

Statistical analyses

Statistical analysis title	T-test of change in C-peptide AUC w52-w0
Statistical analysis description:	
Student’s unpaired two-tailed t-test	
Comparison groups	Liraglutide Arm v Placebo

Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7091
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-820.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5442
upper limit	3801
Variability estimate	Standard error of the mean
Dispersion value	2155

Secondary: Δ- change in C-peptide AUC w52-w6

End point title	Δ- change in C-peptide AUC w52-w6

End point description:

The Area Under the Curve (AUC) change in plasma C-peptide concentration in response to a standardized mixed meal tolerance test (MMTT) comparing week 52 and week 6, after the titration period.

End point type	Secondary

End point timeframe:

week 6 (end of IMP titration)
week 52 (end of treatment)

End point values	Liraglutide Arm	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	8		
Units: pmol/l x min				
arithmetic mean (standard deviation)	-4548 (± 7682)	1479 (± 4861)		

Attachments (see zip file)	Delta C-peptide AUC w52-w6.pdf

Statistical analyses

Statistical analysis title	Unpaired t-test

Statistical analysis description:

Secondary endpoints will be evaluated as Δ-changes using Student’s unpaired two-tailed t-test

Comparison groups	Liraglutide Arm v Placebo

Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0818
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-6027
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12920
upper limit	866.9
Variability estimate	Standard error of the mean
Dispersion value	3214

Secondary: Δ-change in C-peptide AUC w65-w0

End point title	Δ-change in C-peptide AUC w65-w0
End point description:	
Δ-change in C-peptide AUC between the MMTT three months after cessation of treatment and that after the run-in period	
End point type	Secondary
End point timeframe:	
Week 65 (end of follow-up) Week 0 (treatment start)	

End point values	Liraglutide Arm	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	8		
Units: pmol/l x min				
arithmetic mean (standard deviation)	-4447 (± 5545)	-796 (± 2399)		

Attachments (see zip file)	Delta C-peptide AUC w65-w0.pdf

Statistical analyses

Statistical analysis title	T-test Δ-change in C-peptide AUC w65-w0
Statistical analysis description:	
Secondary endpoints were evaluated as Δ-changes using Student’s unpaired two-tailed t-test.	
Comparison groups	Liraglutide Arm v Placebo

Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1094
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-3651
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8233
upper limit	929.8
Variability estimate	Standard error of the mean
Dispersion value	2136

Secondary: Δ- change in HbA1c w52-w0

End point title	Δ- change in HbA1c w52-w0

End point description:

End point type	Secondary

End point timeframe:

week 52 (treatment stop)
week 0 (start of treatment)

End point values	Liraglutide Arm	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	8		
Units: mmol/mol				
arithmetic mean (standard deviation)	0.25 (± 5.092)	0.5 (± 6.047)		

Attachments (see zip file)	Delta HbA1c w52-w0.pdf

Statistical analyses

Statistical analysis title	T-test Δ- change in HbA1c w52-w0

Statistical analysis description:

Secondary endpoints were evaluated as Δ-changes using Student’s unpaired two-tailed t-test.

Comparison groups	Placebo v Liraglutide Arm

Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.93
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.245
upper limit	5.745
Variability estimate	Standard error of the mean
Dispersion value	2.795

Secondary: Δ- change in HbA1c w52-w6

End point title	Δ- change in HbA1c w52-w6

End point description:

Δ- change in HbA1c between after one year and after 6 weeks of treatment

End point type	Secondary

End point timeframe:

week 52 (treatment stop)
week 6 (end of titration period)

End point values	Liraglutide Arm	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	8		
Units: mmol/mol				
arithmetic mean (standard deviation)	3.50 (± 4.44)	4.625 (± 4.627)		

Attachments (see zip file)	Delta HbA1c w52-w6.pdf

Statistical analyses

Statistical analysis title	T-test Δ- change in HbA1c w52-w6

Statistical analysis description:

Δ- change in HbA1c between after one year and after 6 weeks of treatment

Comparison groups	Liraglutide Arm v Placebo

Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6275
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-1.125
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.988
upper limit	3.738
Variability estimate	Standard error of the mean
Dispersion value	2.267

Secondary: Δ- change in HbA1c w65-w0

End point title	Δ- change in HbA1c w65-w0
End point description:	
Δ- change in HbA1c between three months after the cessation of treatment and after the run-in period	
End point type	Secondary
End point timeframe:	
week 65 (end of follow-up) week 0 (treatment start)	

End point values	Liraglutide Arm	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	8		
Units: mmol/mol				
arithmetic mean (standard deviation)	2.875 (± 7.754)	2.125 (± 6.312)		

Attachments (see zip file)	Delta HbA1c w65-w0.pdf

Statistical analyses

Statistical analysis title	T-test Δ- change in HbA1c w65-w0
Statistical analysis description:	
Δ- change in HbA1c between three months after the cessation of treatment and after the run-in period	
Comparison groups	Liraglutide Arm v Placebo

Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.835
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.832
upper limit	8.332
Variability estimate	Standard error of the mean
Dispersion value	3.535

Secondary: Δ- change in insulin dose w52-w0

End point title	Δ- change in insulin dose w52-w0
End point description:	
Δ- change in exogenous insulin doses between after one year and after the run-in period	
End point type	Secondary
End point timeframe:	
week 52 (treatment stop) week 0 (start of treatment)	

End point values	Liraglutide Arm	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	7[2]		
Units: U/kg/24h				
arithmetic mean (standard deviation)	-0.025 (± 0.057)	-0.054 (± 0.104)		

Notes:

[2] - w52 measurement missing in one subject

Attachments (see zip file)	Delta Insulin dose w52-w0.pdf

Statistical analyses

Statistical analysis title	T-test Δ- change in insulin dose w52-w0
Statistical analysis description:	
Secondary endpoints were evaluated as Δ-changes using Student’s unpaired two-tailed t-test.	
Comparison groups	Liraglutide Arm v Placebo

Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.506
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.029
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.063
upper limit	0.121
Variability estimate	Standard error of the mean
Dispersion value	0.042

Secondary: Δ- change in insulin dose w52-w6

End point title	Δ- change in insulin dose w52-w6
End point description:	
Δ- change in exogenous insulin doses between after one year and after 6 weeks of treatment	
End point type	Secondary
End point timeframe:	
week 52 (end of treatment) week 6 (end of titration period)	

End point values	Liraglutide Arm	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	7[3]		
Units: U/kg/24h				
arithmetic mean (standard deviation)	0.147 (± 0.084)	-0.094 (± 0.089)		

Notes:

[3] - Week 52 measurement missing in one patient

Attachments (see zip file)	Delta Insulin dose w52-w6.pdf

Statistical analyses

Statistical analysis title	T-test Δ- change in insulin dose w52-w6
Comparison groups	Liraglutide Arm v Placebo
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.241

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.145
upper limit	0.338
Variability estimate	Standard error of the mean
Dispersion value	0.044

Secondary: Δ- change in insulin dose w65-w0

End point title	Δ- change in insulin dose w65-w0

End point description:

Δ- change in exogenous insulin doses between three months after the cessation of treatment and after the run-in period.

End point type	Secondary

End point timeframe:

week 65 (end of follow-up)
week 0 (treatment start)

End point values	Liraglutide Arm	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7[4]	8		
Units: U/kg/24h				
arithmetic mean (standard deviation)	0.0357 (± 0.102)	-0.046 (± 0.138)		

Notes:

[4] - Measurement at week 65 missing for 1 patient

Attachments (see zip file)	Delta Insulin dose w65-w0.pdf

Statistical analyses

Statistical analysis title	T-test Δ- change in insulin dose w65-w0

Statistical analysis description:

Secondary endpoints were evaluated as Δ-changes using Student’s unpaired two-tailed t-test

Comparison groups	Liraglutide Arm v Placebo
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.22
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.081

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.055
upper limit	0.219
Variability estimate	Standard error of the mean
Dispersion value	0.063

Secondary: Δ- change in glucose variability w52-w0

End point title	Δ- change in glucose variability w52-w0
End point description:	
Δ- change in glucose variability between after one year and after the run-in period	
End point type	Secondary
End point timeframe:	
week 52 (end of treatment) week 0 (treatment start)	

End point values	Liraglutide Arm	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	7		
Units: mmol/l				
arithmetic mean (standard deviation)	0.525 (± 0.573)	-0.034 (± 0.913)		

Attachments (see zip file)	Delta Glucose Variability w52-w0.pdf

Statistical analyses

Statistical analysis title	T-test Δ- change in glucose varibility w52-w0
Statistical analysis description:	
Secondary endpoints were evaluated as Δ-changes using Student’s unpaired two-tailed t-test	
Comparison groups	Liraglutide Arm v Placebo
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1947
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.328
upper limit	1.448

Variability estimate	Standard error of the mean
Dispersion value	0.407

Secondary: Δ- change in glucose varibility w52-w6

End point title	Δ- change in glucose varibility w52-w6

End point description:

Δ- change in glucose variability between after one year and after 6 weeks of treatment

End point type	Secondary

End point timeframe:

week 52 (end of treatment)
week 6 (end of titration period)

End point values	Liraglutide Arm	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	8		
Units: mmol/l				
arithmetic mean (standard deviation)	0.701 (± 0.749)	-0.366 (± 1.105)		

Attachments (see zip file)	Delta Glucose Variability w52-w6.pdf

Statistical analyses

Statistical analysis title	T-test Δ- change in glucose varibility w52-w6

Statistical analysis description:

Secondary endpoints were evaluated as Δ-changes using Student’s unpaired two-tailed t-test.

Comparison groups	Liraglutide Arm v Placebo
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0402
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	1.068
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.055
upper limit	2.08
Variability estimate	Standard error of the mean
Dispersion value	0.472

Secondary: Δ- change in glucose varibility w65-w0

End point title	Δ- change in glucose varibility w65-w0
End point description:	
Δ- change in glucose variability between three months after the cessation of treatment and after the run-in period.	
End point type	Secondary
End point timeframe:	
week 65 (end of follow-up) week 0 (start of treatment)	

End point values	Liraglutide Arm	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	7		
Units: mmol/l				
arithmetic mean (standard deviation)	0.440 (± 0.587)	0.12 (± 1.063)		

Attachments (see zip file)	Delta Glucose Variability w65-W0.pdf

Statistical analyses

Statistical analysis title	T-test Δ- change in glucose varibility w65-w0
Statistical analysis description:	
Secondary endpoints were evaluated as Δ-changes using Student’s unpaired two-tailed t-test.	
Comparison groups	Liraglutide Arm v Placebo
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4989
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.679
upper limit	1.32
Variability estimate	Standard error of the mean
Dispersion value	0.458

Secondary: Δ- change in QoL (DTSQ) week 0-52

End point title	Δ- change in QoL (DTSQ) week 0-52

End point description:

Δ- change in assessment of QoL between after one year of treatment and after the run-in period. Assessment was done by means of the DTSQ test (Diabetes treatment satisfaction questionnaire)

End point type	Secondary

End point timeframe:

week 0 (treatment start)
week 52 (end of treatment)

End point values	Liraglutide Arm	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	8		
Units: points				
arithmetic mean (standard deviation)	2.875 (± 5.768)	-0.1250 (± 4.051)		

Attachments (see zip file)	Delta DTSQ w52-w0.pdf

Statistical analyses

Statistical analysis title	T-test Δ- change in QoL (DTSQ) week 0-52
Comparison groups	Liraglutide Arm v Placebo
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2486
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.345
upper limit	8.345
Variability estimate	Standard error of the mean
Dispersion value	2.492

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On-treatment: week 0 (start of treatment) through week 52 (end of treatment)

Adverse event reporting additional description:

Assessment of adverse events by a study nurse or physician was done at each study visit under the treatment period. Study subjects received a diary and were instructed to document adverse events and other happenings during the study period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18

Reporting groups

Reporting group title	Liraglutide Arm

Reporting group description:

Treatment with IMP liraglutide during 52 weeks. Initial titration phase 6 weeks.

Reporting group title	Placebo

Reporting group description:

Treatment with placebo during 52 weeks. Initial titration phase 6 weeks.

Serious adverse events	Liraglutide Arm	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Liraglutide Arm	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 8 (87.50%)	7 / 8 (87.50%)	
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	7 / 8 (87.50%)	7 / 8 (87.50%)	
occurrences (all)	24	24	

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 trial planned to randomize 50 patients. 88 patients were assessed for eligibility but 70 did not meet inclusion criteria. Thus, the sponsor took the decision to discontinue further subject recruitment after the inclusion of 18 patients.

Notes: