



Clinical trial results:

A randomized, double blind, two-period cross-over trial investigating the effect of liraglutide as add on to intensive insulin treatment on the endogenous glucose production in subjects with C-peptide positive type 1 diabetes mellitus

Summary

EudraCT number	2014-001381-96
Trial protocol	AT
Global end of trial date	04 May 2016

Results information

Result version number	v1 (current)
This version publication date	13 November 2020
First version publication date	13 November 2020

Trial information

Trial identification

Sponsor protocol code	LG_T1_EGP
-----------------------	-----------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02408705
WHO universal trial number (UTN)	U1111-1151-3332

Notes:

Sponsors

Sponsor organisation name	Medical University Graz, Univ. Prof. Thomas Pieber, Department of Internal Medicine, Division of Endocrinology and Metabolism
Sponsor organisation address	Auenbruggerplatz 15, Graz, Austria, 8036
Public contact	Zentrum f. Med. Grundlagenforschung, Medizinische Universität Graz / Endokrinologie und Stoffwechsel, +43 316385 72833, sabine.zenz@medunigraz.at
Scientific contact	Zentrum f. Med. Grundlagenforschung, Medizinische Universität Graz / Endokrinologie und Stoffwechsel, +43 316385 72833, sabine.zenz@medunigraz.at

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	20 January 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 May 2016
Global end of trial reached?	Yes
Global end of trial date	04 May 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the effect of liraglutide as add on to intensive insulin treatment on the change of EGP during a hypoglycaemic clamp in C-peptide positive subjects with type 1 diabetes mellitus

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki and ICH Good Clinical Practice. All study participants were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 February 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	Austria: 14
Worldwide total number of subjects	14
EEA total number of subjects	14

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)	14
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Single-Center Study - 1 Site in Austria - 14 Subjects

For recruitment, we used an electronic diabetes database and contacted hospitals in the region. The recruitment lasted 9 months, and 14 type 1 diabetes patients were enrolled and randomized to the study.

Pre-assignment

Screening details:

33 Patients have been screened and a total 14 randomizations were performed. 14 subjects completed the study.

Period 1

Period 1 title	Overall Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Subject, Data analyst

Blinding implementation details:

Liraglutide and placebo were supplied in similar 3 mL pre-filled injection pens and were visually identical, and packed and labelled to fulfil the requirements for double-blind procedures. Equal volumes of liraglutide and placebo were administered. Blinding was maintained for the whole study period.

Arms

Are arms mutually exclusive?	No
Arm title	Liraglutide

Arm description:

Liraglutide was administered once daily by subcutaneous injection at 10:00 pm. Starting dose of liraglutide was 0.3 mg and the dose was increased weekly by 0.3 mg to reach a dose of 1.2 mg after 4 weeks. This final dose was then kept stable for 8 weeks. Insulin-treatment was adjusted depending on the treatment dose and the patient's demand. Patients had to document the daily study product administration and each hypoglycaemic event during the study.

Each randomized subject was allocated to one of the two treatment sequences (liraglutide/placebo or placebo/liraglutide) adjunct to intensive insulin treatment for 12 weeks. A wash-out period of 4 weeks between the two periods was carried out

Arm type	Experimental
Investigational medicinal product name	Liraglutide, 6 mg/mL, 3 mL pre-filled pen
Investigational medicinal product code	
Other name	Victoza
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Liraglutide, 6.0 mg/mL in a 3 mL pre-filled pen was administered once daily by subcutaneous injection at 10:00 pm.

Arm title	Placebo
------------------	---------

Arm description:

Placebo was administered once daily by subcutaneous injection at 10:00 pm. Starting dose of placebo was 0.3 mg and the dose was increased weekly by 0.3 mg to reach a dose of 1.2 mg after 4 weeks. This final dose was then kept stable for 8 weeks. Insulin-treatment was adjusted depending on the treatment dose and the patient's demand. Patients had to document the daily study product administration and each hypoglycaemic event during the study.

Each randomized subject was allocated to one of the two treatment sequences (liraglutide/placebo or placebo/liraglutide) adjunct to intensive insulin treatment for 12 weeks. A wash-out period of 4 weeks between the two periods was carried out.

Arm type	Placebo
----------	---------

Investigational medicinal product name	Liraglutide placebo, 3 mL
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Liraglutide placebo was administered once daily by subcutaneous injection at 10:00 pm.

Number of subjects in period 1	Liraglutide	Placebo
Started	14	14
Completed	14	14

Baseline characteristics

Reporting groups

Reporting group title	Overall Period
Reporting group description: -	

Reporting group values	Overall Period	Total	
Number of subjects	14	14	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	14	14	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	33.6		
standard deviation	± 12.1	-	
Gender categorical			
Units: Subjects			
Female	7	7	
Male	7	7	
Fasting C-Peptide			
Baseline characteristics for Fasting C-peptide			
Units: nmol/l			
arithmetic mean	0.23		
standard deviation	± 0.12	-	
HbA1c			
Baseline characteristics HbA1c			
Units: mmol/mol			
arithmetic mean	50.3		
standard deviation	± 7.2	-	
Diabetes duration			
Units: years			
arithmetic mean	3.43		
standard deviation	± 2.44	-	
Weight			
Units: kg			
arithmetic mean	70.5		
standard deviation	± 12.8	-	

End points

End points reporting groups

Reporting group title	Liraglutide
Reporting group description: Liraglutide was administered once daily by subcutaneous injection at 10:00 pm. Starting dose of liraglutide was 0.3 mg and the dose was increased weekly by 0.3 mg to reach a dose of 1.2 mg after 4 weeks. This final dose was then kept stable for 8 weeks. Insulin-treatment was adjusted depending on the treatment dose and the patient's demand. Patients had to document the daily study product administration and each hypoglycaemic event during the study. Each randomized subject was allocated to one of the two treatment sequences (liraglutide/placebo or placebo/liraglutide) adjunct to intensive insulin treatment for 12 weeks. A wash-out period of 4 weeks between the two periods was carried out	
Reporting group title	Placebo
Reporting group description: Placebo was administered once daily by subcutaneous injection at 10:00 pm. Starting dose of placebo was 0.3 mg and the dose was increased weekly by 0.3 mg to reach a dose of 1.2 mg after 4 weeks. This final dose was then kept stable for 8 weeks. Insulin-treatment was adjusted depending on the treatment dose and the patient's demand. Patients had to document the daily study product administration and each hypoglycaemic event during the study. Each randomized subject was allocated to one of the two treatment sequences (liraglutide/placebo or placebo/liraglutide) adjunct to intensive insulin treatment for 12 weeks. A wash-out period of 4 weeks between the two periods was carried out.	

Primary: Area under the curve of endogenous glucose production

End point title	Area under the curve of endogenous glucose production
End point description: The primary endpoint was defined based on results from a previously performed study as comparison between the AUC values for EGP (AUCEGP) from begin of the 5.5 mmol/l plateau until the end of recovery period (3.9 mmol/l) of the liraglutide-treatment group and those of the placebo-treatment group.	
End point type	Primary
End point timeframe: During hypoglycemic clamp - comparison liraglutide vs placebo	

End point values	Liraglutide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: mg/kg				
arithmetic mean (standard deviation)				
Liraglutide/Placebo sequence	45.12 (± 15.36)	37.62 (± 14.96)		
Placebo/Liraglutide sequence	43.99 (± 15.64)	36.86 (± 18.06)		

Attachments (see zip file)	Study design and Hypoglycaemic design.PNG EGP.PNG
-----------------------------------	--

Statistical analyses

Statistical analysis title	Mixed effects model
Statistical analysis description: Hypoglycaemic levels were compared with a Kruskal-Wallis test and in case of a statistically significant Kruskal-Wallis test, a pairwise Wilcoxon signed rank tests was performed.	
Comparison groups	Liraglutide v Placebo
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Mixed models analysis

Secondary: Treatment effect on Glucose, C-peptide, Glucagon and Gastric emptying (from the paracetamol concentrations) 0-240 min (change after treatment vs. pre-treatment)

End point title	Treatment effect on Glucose, C-peptide, Glucagon and Gastric emptying (from the paracetamol concentrations) 0-240 min (change after treatment vs. pre-treatment)
-----------------	--

End point description:

- Area under the C-peptide concentration curve (AUC C-peptide) from time point 0 until 240 min during MMTT
- Area under the glucose curve above the average baseline glucose value (average of the -5 and 0 min values) from time point 0 until 240 min during MMTT (AUCglu)
- Area under the glucagon curve above the average baseline glucagon value (average of the -5 and 0 min values) from time point 0 until 240 min during MMTT (AUCglucagon)
- Gastric emptying calculated from the paracetamol concentrations as the area under the paracetamol concentration curve from time point 0 until 240 min (AUCpara240).

End point type	Secondary
----------------	-----------

End point timeframe:

During MMTT - comparison liraglutide vs placebo

End point values	Liraglutide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: nmol/l				
arithmetic mean (standard deviation)				
Delta AUC C-peptide 240 min	7.79 (± 116.19)	-9.76 (± 216.73)		
Delta AUCglu 240 min	-2582.84 (± 17368.70)	-358.13 (± 12154.58)		
Delta AUCglucagon 240 min	-240.71 (± 1417.45)	-82.33 (± 1557.94)		
Delta AUCpara 240 min	16.58 (± 453.41)	-13.21 (± 585.60)		

Statistical analyses

No statistical analyses for this end point

Secondary: EGP during Hypoglycaemic clamp

End point title EGP during Hypoglycaemic clamp

End point description:

End point type Secondary

End point timeframe:

During hypoglycemic clamp - comparison liraglutide vs placebo

End point values	Liraglutide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: mg/kg/min				
arithmetic mean (standard deviation)				
5.5 mmol/L	0.65 (± 0.57)	0.45 (± 0.22)		
3.5 mmol/L	0.58 (± 0.38)	0.41 (± 0.30)		
2.5 mmol/L	1.03 (± 0.54)	0.93 (± 0.54)		
4.0 mmol/L	2.19 (± 0.73)	1.93 (± 0.81)		

Statistical analyses

No statistical analyses for this end point

Secondary: PGU during Hypoglycaemic clamp

End point title PGU during Hypoglycaemic clamp

End point description:

End point type Secondary

End point timeframe:

During hypoglycemic clamp - comparison liraglutide vs placebo

End point values	Liraglutide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: mg/kg/min				
arithmetic mean (standard deviation)				
5.5 mmol/L	9.33 (± 4.14)	9.06 (± 3.85)		
3.5 mmol/L	6.11 (± 2.16)	6.70 (± 2.92)		
2.5 mmol/L	4.08 (± 1.62)	4.38 (± 2.11)		
4.0 mmol/L	4.63 (± 2.08)	3.96 (± 1.27)		

Statistical analyses

No statistical analyses for this end point

Secondary: Glucagon during Hypoglycaemic clamp

End point title	Glucagon during Hypoglycaemic clamp
End point description:	
End point type	Secondary
End point timeframe:	
During hypoglycemic clamp - comparison liraglutide vs placebo	

End point values	Liraglutide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: pmol/l				
arithmetic mean (standard deviation)				
5.5 mmol/L	1.79 (± 2.16)	3.37 (± 2.67)		
3.5 mmol/L	4.58 (± 5.31)	5.20 (± 4.62)		
2.5 mmol/L	17.40 (± 16.47)	14.77 (± 15.91)		
4.0 mmol/L	12.11 (± 10.24)	11.88 (± 9.03)		

Attachments (see zip file)	Glucagon.PNG
-----------------------------------	--------------

Statistical analyses

No statistical analyses for this end point

Secondary: C-Peptide during Hypoglycaemic clamp

End point title	C-Peptide during Hypoglycaemic clamp
-----------------	--------------------------------------

End point description:

End point type	Secondary
----------------	-----------

End point timeframe:

During hypoglycemic clamp - comparison liraglutide vs placebo

End point values	Liraglutide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: nmol/l				
arithmetic mean (standard deviation)				
5.5 mmol/L	0.38 (± 0.44)	0.17 (± 0.16)		
3.5 mmol/L	0.22 (± 0.20)	0.10 (± 0.10)		
2.5 mmol/L	0.11 (± 0.14)	0.05 (± 0.06)		
4.0 mmol/L	0.09 (± 0.13)	0.06 (± 0.07)		

Attachments (see zip file)	C-Peptide.PNG
-----------------------------------	---------------

Statistical analyses

No statistical analyses for this end point

Secondary: Epinephrine during Hypoglycaemic clamp

End point title	Epinephrine during Hypoglycaemic clamp
-----------------	--

End point description:

End point type	Secondary
----------------	-----------

End point timeframe:

During hypoglycemic clamp - comparison liraglutide vs placebo

End point values	Liraglutide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: pg/ml				
arithmetic mean (standard deviation)				
5.5 mmol/L	46.07 (± 52.82)	46.46 (± 46.25)		
3.5 mmol/L	61.57 (± 65.97)	64.08 (± 68.25)		
2.5 mmol/L	406.00 (± 285.76)	401.07 (± 346.98)		
4.0 mmol/L	229.79 (± 216.95)	219.86 (± 293.71)		

Attachments (see zip file)	Epinephrine.PNG
-----------------------------------	-----------------

Statistical analyses

No statistical analyses for this end point

Secondary: Norepinephrine during Hypoglycaemic clamp

End point title	Norepinephrine during Hypoglycaemic clamp
-----------------	---

End point description:

End point type	Secondary
----------------	-----------

End point timeframe:

During hypoglycemic clamp - comparison liraglutide vs placebo

End point values	Liraglutide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: pg/ml				
arithmetic mean (standard deviation)				
5.5 mmol/L	114.57 (± 38.41)	108.86 (± 59.38)		
3.5 mmol/L	129.14 (± 66.84)	128.36 (± 101.98)		
2.5 mmol/L	231.00 (± 119.22)	226.93 (± 152.72)		
4.0 mmol/L	218.00 (± 117.15)	191.86 (± 127.17)		

Attachments (see zip file)	Norepinephrine.PNG
-----------------------------------	--------------------

Statistical analyses

No statistical analyses for this end point

Secondary: Growth hormone during Hypoglycaemic clamp

End point title	Growth hormone during Hypoglycaemic clamp
-----------------	---

End point description:

End point type	Secondary
----------------	-----------

End point timeframe:

During hypoglycemic clamp - comparison liraglutide vs placebo

End point values	Liraglutide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: ng/ml				
arithmetic mean (standard deviation)				
5.5 mmol/L	2.73 (± 5.37)	1.81 (± 2.14)		
3.5 mmol/L	3.29 (± 9.31)	3.89 (± 6.09)		
2.5 mmol/L	8.43 (± 7.19)	11.63 (± 11.44)		
4.0 mmol/L	10.61 (± 7.93)	8.90 (± 7.34)		

Attachments (see zip file)	Growth hormone.PNG
-----------------------------------	--------------------

Statistical analyses

No statistical analyses for this end point

Secondary: Cotisol during Hypoglycaemic clamp

End point title	Cotisol during Hypoglycaemic clamp
End point description:	
End point type	Secondary
End point timeframe:	
During hypoglycemic clamp - comparison liraglutide vs placebo	

End point values	Liraglutide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: ng/ml				
arithmetic mean (standard deviation)				
5.5 mmol/L	110.38 (± 53.17)	95.27 (± 29.08)		
3.5 mmol/L	95.74 (± 38.94)	101.26 (± 37.48)		
2.5 mmol/L	131.00 (± 55.04)	142.66 (± 48.43)		
4.0 mmol/L	194.35 (± 62.36)	196 (± 69.80)		

Attachments (see zip file)	Cortisol.PNG
-----------------------------------	--------------

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AEs) were collected from signature of the informed consent form up to the final visit regardless of seriousness or relationship to investigational product.

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
Dictionary version	23

Reporting groups

Reporting group title	Liraglutide
-----------------------	-------------

Reporting group description: -

Reporting group title	Placebo
-----------------------	---------

Reporting group description: -

Serious adverse events	Liraglutide	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Liraglutide	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 14 (57.14%)	7 / 14 (50.00%)	
Vascular disorders			
Anal thrombose			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	
occurrences (all)	1	1	
Graves Disease			

subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 14 (0.00%) 1	
Hematuria subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 14 (0.00%) 1	
Reflux subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 14 (0.00%) 1	
Reproductive system and breast disorders Uterus Prolaps subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 1	1 / 14 (7.14%) 1	
Respiratory, thoracic and mediastinal disorders Rhinitis subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 1	1 / 14 (7.14%) 1	
Right shoulder pain subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 14 (0.00%) 1	
Injury, poisoning and procedural complications Lower back injury subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 14 (0.00%) 1	
Small ankle fracture right foot subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 1	1 / 14 (7.14%) 1	
Phlebitis vena intermedia cubita left subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 1	1 / 14 (7.14%) 1	
Cardiac disorders Sinus tachycardia subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 1	1 / 14 (7.14%) 1	
Supraventricular ectopic rhythmus			

subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 1	1 / 14 (7.14%) 1	
Common cold subjects affected / exposed occurrences (all)	6 / 14 (42.86%) 13	4 / 14 (28.57%) 13	
Tachycardia subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 14 (0.00%) 1	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 5	2 / 14 (14.29%) 5	
Numb left arm subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 1	1 / 14 (7.14%) 1	
Blood and lymphatic system disorders Right eye bruising subjects affected / exposed occurrences (all)	Additional description: Right eye bruising after bicycle		
	0 / 14 (0.00%) 1	1 / 14 (7.14%) 1	
Ear and labyrinth disorders Emesis subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 14 (0.00%) 1	
Eye disorders Fever Blister subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 2	1 / 14 (7.14%) 2	
Gastrointestinal disorders Diarrhea subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 3	2 / 14 (14.29%) 3	
Nausea subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 3	1 / 14 (7.14%) 3	
Constipation subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 2	0 / 14 (0.00%) 2	

Vomiting subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 14 (0.00%) 1	
Abdomen pain subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 14 (0.00%) 1	
Renal and urinary disorders Urinary tract infection subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 3	1 / 14 (7.14%) 3	
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 1	1 / 14 (7.14%) 1	
Infections and infestations Paronychia subjects affected / exposed occurrences (all) Genital infection subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 2 0 / 14 (0.00%) 1	1 / 14 (7.14%) 2 1 / 14 (7.14%) 1	
Metabolism and nutrition disorders Iron deficiencies subjects affected / exposed occurrences (all) Muscle Pain subjects affected / exposed occurrences (all) Hyperglycemia subjects affected / exposed occurrences (all) Loss of appetite subjects affected / exposed occurrences (all) Hypokalemia	3 / 14 (21.43%) 8 1 / 14 (7.14%) 3 1 / 14 (7.14%) 1 1 / 14 (7.14%) 1 1	4 / 14 (28.57%) 8 1 / 14 (7.14%) 3 0 / 14 (0.00%) 1 0 / 14 (0.00%) 1 1	

subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	
occurrences (all)	1	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 September 2014	I) The study protocol was amended regarding: 1) The timetable 2) Secondary objectives and Secondary Endpoints 3) Inclusion criterion of the BMI in this study was between 20.0 - 25.0 kg/m ² and not as initial stated (28.0 kg/m ²) 5) Table overview 6) Additional information added regarding blood analysis, blood sample of glucagon and deut. glucose, 7) Randomization information 7) The chapter Data analysis has been update II) The Patient Information and consent form has been updated regarding the total amount of blood drawn in one treatment period
06 March 2015	I) The Protocol has been amended regarding: 1) The timetable 2) The HbA1c range 3) The Body mass index range has been wided 4) The Amylase blood values has been changed from "outside normal range" to "above normal range" 5) The time for the intake of thyroid hormones has been changed f 6) The timeline for the intake of thyroid hormones has been changed 7) An additional laboratory examination of TSH has been added 8) Timepoint for blood sampling for the TSH examination has been added

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported