Clinical trial results:
Meal-time Administration of exenatide for Glycaemic control in type 1 diabetic Cases: A randomised, placebo-controlled trial

Summary

EudraCT number	2016-001365-92
Trial protocol	DK
Global end of trial date	19 June 2019

Results information

Result version number	v1 (current)
This version publication date	01 May 2020
First version publication date	01 May 2020

Trial information

Trial identification

Sponsor protocol code	Eudract-nr.: 2016-001365-92

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03017352
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Center for Clinical Metabolic Research, Gentofte Hospital
Sponsor organisation address	Gentofte Hospitalsvej 7, 3rd floor, Gentofte, Denmark, DK-2820
Public contact	Filip Krag Knop, Center for Clinical Metabolic Research, 0045 26830161, filipknop@dadlnet.dk
Scientific contact	Filip Krag Knop, Center for Clinical Metabolic Research, 0045 26830161, filipknop@dadlnet.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	10 July 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 June 2019
Global end of trial reached?	Yes
Global end of trial date	19 June 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The present project aims to evaluate the safety and therapeutic effect of the short-acting GLP-1RA exenatide administered three times daily (at meal-times) as add-on therapy to standard basal-plus-prandial insulin regimen in patients with T1D.

Protection of trial subjects:

This study contributed with important information about short-acting GLP-1 receptor agonists as adjunct to insulin treatment in patients with type 1 diabetes. The risk of side effects when participating in this study was expected to be modest. The injection of arginine is a well-validated and safe method, but potentially associated with transient mild flushing, nausea and a metallic taste. Exenatide is approved for the treatment of type 2 diabetes by the European Medicines Agency, and prior studies have shown limited side effects. Among these are nausea, vomiting, hypoglycaemia and headache. Nausea and vomiting are usually seen in the first three weeks after initiation of treatment and are generally temporary; in this study, the risk of side effects was minimised amongst participant by gradual dose titration. The risk of hypoglycaemia was reduced by reducing insulin doses at study start and instructing the patients in carefully monitoring their blood glucose and report any problems to the investigators. Few cases of acute pancreatitis have been reported in patients with type 2 diabetes using exenatide, but the incidence was not different from that in the background population with type 2 diabetes. No cases of acute pancreatitis happened in the present trial. Performing vein puncture could inflict a short pain and a risk of a small haematoma and there was a minimal risk of infection at the puncture site. At the two DXA scans, the participants were exposed to weak X-ray radiation (less than 1 mSv in total). For comparison, the background radiation in Denmark is about 3 mSv per year. With regard to all other planned study procedures, the risk of complications or adverse events was negligible.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	04 January 2017
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	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)	85
From 65 to 84 years	20
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

At screening, information on demography, medical history, smoking/drinking status and concomitant medication was obtained. Further, a physical assessment was made including heart rate, blood pressure, body weight, hip/waist ratio and electrocardiography together with blood samples and urine tests.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Exenatide

Arm description:

Short-acting exenatide 10 microgram three times daily within one hour of breakfast, lunch and dinner

Arm type	Experimental
Investigational medicinal product name	Exenatide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Exenatide solution for injection (manufacturer AstraZeneca) in 5 µg and 10 µg doses. The medication exenatide, comes in 3.0 ml, 0.25 mg/mL cartridges, which are inserted into a reusable pen, Ypsopen™, for subcutaneous injection. Exenatide will be introduced at a dose of 5 µg three times daily (with every main meal) and increased to 10 µg three times daily (with every main meal) after two weeks or gradually in the case of side effects.

Arm title	Placebo

Arm description:

Placebo

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo solution for injection (manufacturer AstraZeneca) in 5 µg and 10 µg doses. The medication , comes in 3.0 ml, 0.25 mg/mL cartridges, which are inserted into a reusable pen, Ypsopen™, for subcutaneous injection. Placebo will be introduced at a dose of 5 µg three times daily (with every main meal) and increased to 10 µg three times daily (with every main meal) after two weeks or gradually in the case of side effects.

Number of subjects in period 1	Exenatide	Placebo
Started	52	53
Completed	35	47
Not completed	17	6
Consent withdrawn by subject	3	3
Physician decision	1	-
Adverse event, non-fatal	10	-
Protocol deviation	3	3

Baseline characteristics

Reporting groups	
Reporting group title	Exenatide
Reporting group description:	
Short-acting exenatide 10 microgram three times daily within one hour of breakfast, lunch and dinner	
Reporting group title	Placebo
Reporting group description:	
Placebo	

Reporting group values	Exenatide	Placebo	Total
Number of subjects	52	53	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)	43	43	86
From 65-84 years	9	10	19
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	50.1	50.4	
standard deviation	± 14.2	± 14.0	-
Gender categorical Units: Subjects			
Female	13	16	29
Male	39	37	76
Caucasian ethnicity Units: Subjects			
Number	52	53	105
Diabetes duration Units: Years			
arithmetic mean	21.2	21	
standard deviation	± 11.3	± 12.9	-
HbA1c Units: mmol/mol			
arithmetic mean	66.8	65.9	
standard deviation	± 7.9	± 6.5	-
Weight Units: kg			
arithmetic mean	89.7	85.8	
standard deviation	± 14.4	± 14.3	-
BMI			

Body mass index			
Units: kg/m^2			
arithmetic mean	29.0	27.7	
standard deviation	± 4.8	± 4.1	-
C-peptide fasting			
Units: pmol/L			
arithmetic mean	24.6	23.2	
standard deviation	± 53.2	± 64.2	-
Insulin dose, basal			
Units: Units/day			
arithmetic mean	31.2	29.7	
standard deviation	± 11.1	± 13.7	-
Insulin dose, bolus (IU/day)			
Units: Units/day			
arithmetic mean	30.2	29.6	
standard deviation	± 13.7	± 19.6	-
Insulin dose, breakfast			
Units: Units/day			
arithmetic mean	8.9	9.3	
standard deviation	± 4.8	± 6.6	-
Insulin dose, lunch			
Units: Units/day			
arithmetic mean	8.9	9.3	
standard deviation	± 4.8	± 6.6	-
Insulin dose, dinner			
Units: Units/day			
arithmetic mean	11.7	11.6	
standard deviation	± 6.0	± 7.6	-
Fasting plasma glucose			
Units: mmol/l			
arithmetic mean	9.2	9.4	
standard deviation	± 2.2	± 2.9	-
Postprandial plasma glucose			
Units: mmol/l			
arithmetic mean	9.4	8.9	
standard deviation	± 2.0	± 1.7	-
Mean glucose			
Continous glucose monitoring			
Units: mmol/l			
arithmetic mean	10.3	10.2	
standard deviation	± 1.8	± 1.8	-
Standard deviation			
Continous glucose monitoring			
Units: mmol/l			
arithmetic mean	4.0	4.0	
standard deviation	± 0.9	± 0.8	-
Target glycaemia (4-10 mmol/l)			
Continous glucose monitoring			
Units: Percentage of 24 hours			
arithmetic mean	48.4	48.7	
standard deviation	± 15.0	± 13.9	-
Hyperglycaemia (>10 mmol/l)			

Continous glucose monitoring			
Units: Percentage of 24 hours			
arithmetic mean	47.5	46.6	
standard deviation	± 15.9	± 15.7	-
Hypoglycaemia level 1 (3.0-3.9 mmol/l)			
Continous glucose monitoring			
Units: Percentage of 24 hours			
arithmetic mean	2.8	3.3	
standard deviation	± 2.8	± 3.4	-
Hypoglycaemia level 2 (<3.0 mmol/l)			
Continous glucose monitoring			
Units: Percentage of 24 hours			
arithmetic mean	1.3	1.4	
standard deviation	± 2.2	± 2.6	-
Ketones			
Units: mmol/l			
arithmetic mean	0.23	0.29	
standard deviation	± 0.23	± 0.27	-
Amylase			
Units: Units/l			
arithmetic mean	15.4	16.4	
standard deviation	± 5.8	± 7.5	-
Lipase			
Units: Units/l			
arithmetic mean	21.2	22.5	
standard deviation	± 10.9	± 9.6	-
Blood pressure, systolic			
Units: mmHg			
arithmetic mean	129.0	129.0	
standard deviation	± 13.1	± 15.7	-
Blood pressure, diastolic			
Units: mmHg			
arithmetic mean	82.0	82.5	
standard deviation	± 8.3	± 9.5	-
Heart rate			
Units: beats/minute			
arithmetic mean	69.8	69.8	
standard deviation	± 10.4	± 11.3	-
Cholesterol, total			
Units: mmol/L			
arithmetic mean	4.15	4.05	
standard deviation	± 0.87	± 0.89	-
Cholesterol, high-density lipoprotein			
Units: mmol/l			
arithmetic mean	1.37	1.34	
standard deviation	± 0.37	± 0.36	-
Cholesterol, low-density lipoprotein			
Units: Mmol/l			
arithmetic mean	2.38	2.34	
standard deviation	± 0.73	± 0.83	-
Cholesterol, very low-density lipoprotein			
Units: Mmol/l			

arithmetic mean	0.40	0.37	
standard deviation	± 0.19	± 0.19	-
Triglycerides			
Units: Mmol/l			
arithmetic mean	0.87	0.83	
standard deviation	± 0.39	± 0.42	-

End points

End points reporting groups

Reporting group title	Exenatide
Reporting group description:	
Short-acting exenatide 10 microgram three times daily within one hour of breakfast, lunch and dinner	
Reporting group title	Placebo
Reporting group description:	
Placebo	

Primary: HbA1c

End point title	HbA1c
End point description:	
End point type	Primary
End point timeframe:	
26 weeks (end-of-treatment values)	

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: Mmol/mol				
arithmetic mean (confidence interval 95%)	63.2 (61.1 to 65.2)	64.2 (62.4 to 66.1)		

Statistical analyses

Statistical analysis title	Linear mixed model (primary)
Statistical analysis description:	
Incorporating maximum likelihood estimation for missing data substitution (equivalent to multiple imputation).	
Comparison groups	Exenatide v Placebo
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard error of the mean

Secondary: Weight

End point title	Weight

End point description:

End point type	Secondary

End point timeframe:

26 weeks (end-of-treatment values)

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: Kg				
arithmetic mean (confidence interval 95%)	83.6 (80.8 to 86.5)	88.0 (85.2 to 90.8)		

Statistical analyses

Statistical analysis title	Linear mixed model (secondary)

Statistical analysis description:

Incorporating maximum likelihood estimation for missing data substitution (equivalent to multiple imputation). This model was used for all secondary endpoints unless stated otherwise at the specific endpoint.

Comparison groups	Exenatide v Placebo
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05 [1]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard error of the mean

Notes:

[1] - Secondary endpoints are adjusted for multiple testing via the 'False discovery rate' method

Secondary: Insulin, total

End point title	Insulin, total

End point description:

End point type	Secondary

End point timeframe:

26 weeks (end-of-treatment values)

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: Units/day				
arithmetic mean (confidence interval 95%)	53.3 (48.0 to 58.7)	62.3 (57.0 to 67.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Insulin, basal

End point title	Insulin, basal

End point description:

End point type	Secondary

End point timeframe:

26 weeks (end-of-treatment values)

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: Units/day				
arithmetic mean (confidence interval 95%)	31.6 (29.1 to 34.2)	32.2 (29.6 to 34.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Insulin prandial (total)

End point title	Insulin prandial (total)

End point description:

End point type	Secondary

End point timeframe:

26 weeks (end-of-treatment values)

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: Units/day				
arithmetic mean (confidence interval 95%)	21.7 (18.2 to 25.2)	30.1 (26.8 to 33.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Insulin, prandial (breakfast)

End point title	Insulin, prandial (breakfast)

End point description:

End point type	Secondary

End point timeframe:

26 weeks (end-of-treatment values)

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: Units/day				
arithmetic mean (confidence interval 95%)	6.4 (5.1 to 7.7)	9.2 (7.9 to 10.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Insulin, prandial (lunch)

End point title	Insulin, prandial (lunch)

End point description:

End point type	Secondary

End point timeframe:

26 weeks (end-of-treatment values)

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: Units/day				
arithmetic mean (confidence interval 95%)	6.9 (5.7 to 8.0)	9.1 (8.0 to 10.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Insulin, prandial (dinner)

End point title	Insulin, prandial (dinner)

End point description:

End point type	Secondary

End point timeframe:

26 weeks (end-of-treatment values)

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: Units/day				
arithmetic mean (confidence interval 95%)	8.4 (7.0 to 9.8)	11.8 (10.5 to 13.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean glucose

End point title	Mean glucose

End point description:

Based on seven-point self-monitoring of blood glucose profiles.

End point type	Secondary

End point timeframe:

26 weeks (end-of-treatment values)

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: mmol/l				
arithmetic mean (confidence interval 95%)	9.0 (8.4 to 9.5)	9.4 (8.9 to 9.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Fasting plasma glucose

End point title	Fasting plasma glucose
End point description:	
Based on seven-point self-monitoring of blood glucose profiles.	
End point type	Secondary
End point timeframe:	
26 weeks (end-of-treatment values)	

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: Mmol/l				
arithmetic mean (confidence interval 95%)	9.7 (8.7 to 10.6)	9.1 (8.2 to 10.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Postprandial plasma glucose (average)

End point title	Postprandial plasma glucose (average)
End point description:	
Based on seven-point self-monitoring of blood glucose profiles.	
End point type	Secondary
End point timeframe:	
26 weeks (end-of-treatment values)	

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: Mmol/l				
arithmetic mean (confidence interval 95%)	8.7 (8.0 to 9.5)	9.7 (9.1 to 10.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Postprandial plasma glucose (breakfast)

End point title	Postprandial plasma glucose (breakfast)
End point description:	
Based on seven-point self-monitoring of blood glucose profiles.	
End point type	Secondary
End point timeframe:	
26 weeks (end-of-treatment values)	

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: mmol/l				
arithmetic mean (confidence interval 95%)	8.7 (7.6 to 9.9)	9.9 (8.9 to 10.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Postprandial plasma glucose (lunch)

End point title	Postprandial plasma glucose (lunch)
End point description:	
Based on seven-point self-monitoring of blood glucose profiles.	
End point type	Secondary
End point timeframe:	
26 weeks (end-of-treatment values)	

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: mmol/l				
arithmetic mean (confidence interval 95%)	8.9 (7.7 to 10.1)	8.6 (7.6 to 9.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Postprandial plasma glucose (dinner)

End point title	Postprandial plasma glucose (dinner)
End point description:	
Based on seven-point self-monitoring of blood glucose profiles.	
End point type	Secondary
End point timeframe:	
26 weeks (end-of-treatment values)	

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: Mmol/l				
arithmetic mean (confidence interval 95%)	8.1 (6.9 to 9.4)	9.7 (8.8 to 10.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Postprandial plasma glucose (incremental)

End point title	Postprandial plasma glucose (incremental)
End point description:	
Based on seven-point self-monitoring of blood glucose profiles.	
End point type	Secondary
End point timeframe:	
26 weeks (end-of-treatment values)	

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: Mmol/l				
arithmetic mean (confidence interval 95%)	0.4 (-0.6 to 1.4)	0.5 (-0.3 to 1.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Self-reported hypoglycaemia level 1 (3.0–3.9 mmol/L)

End point title	Self-reported hypoglycaemia level 1 (3.0–3.9 mmol/L)

End point description:

End point type	Secondary

End point timeframe:

26 weeks (end-of-treatment values)

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: incidence rate				
arithmetic mean (confidence interval 95%)	0.9 (0.7 to 1.1)	0.7 (0.6 to 0.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Self-reported hypoglycaemia level 2 (<3.0 mmol/L)

End point title	Self-reported hypoglycaemia level 2 (<3.0 mmol/L)

End point description:

End point type	Secondary

End point timeframe:

26 weeks (end-of-treatment values)

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: Incidence rate				
arithmetic mean (confidence interval 95%)	0.3 (0.2 to 0.4)	0.2 (0.1 to 0.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Self-reported hypoglycaemia daytime (6:00 a.m.–midnight)

End point title	Self-reported hypoglycaemia daytime (6:00 a.m.–midnight)

End point description:

End point type	Secondary

End point timeframe:

26 weeks (end-of-treatment values)

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: Incidence rate				
arithmetic mean (confidence interval 95%)	1.1 (0.8 to 1.5)	0.8 (0.6 to 1.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Self-reported hypoglycaemia nighttime (midnight–6:00 a.m.)

End point title	Self-reported hypoglycaemia nighttime (midnight–6:00 a.m.)

End point description:

End point type	Secondary

End point timeframe:

26 weeks (end-of-treatment values)

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: Incidence rate				
arithmetic mean (confidence interval 95%)	0.1 (0.0 to 0.1)	0.1 (0.0 to 0.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Heart rate

End point title	Heart rate

End point description:

End point type	Secondary

End point timeframe:

26 weeks (end-of-treatment values)

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: Beats/minute				
arithmetic mean (confidence interval 95%)	74.4 (71.5 to 77.3)	70.6 (67.9 to 73.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Blood pressure, systole

End point title	Blood pressure, systole

End point description:

End point type	Secondary

End point timeframe:

26 weeks (end-of-treatment values)

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: mmHg				
arithmetic mean (confidence interval 95%)	129.4 (125.3 to 133.5)	128.1 (124.4 to 131.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Blood pressure, diastole

End point title	Blood pressure, diastole

End point description:

End point type	Secondary

End point timeframe:

26 weeks (end-of-treatment values)

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: mmHg				
arithmetic mean (confidence interval 95%)	80.6 (78.0 to 83.1)	79.0 (76.8 to 81.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Ketones

End point title	Ketones

End point description:

End point type	Secondary

End point timeframe:

26 weeks (end-of-treatment values)

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: Mmol/l				
arithmetic mean (confidence interval 95%)	0.24 (0.18 to 0.30)	0.23 (0.18 to 0.29)		

Statistical analyses

No statistical analyses for this end point

Secondary: Amylase

End point title	Amylase

End point description:

End point type	Secondary

End point timeframe:

26 weeks (end-of-treatment values)

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: Units/l				
arithmetic mean (confidence interval 95%)	19.4 (16.7 to 22.2)	15.6 (13.2 to 18.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Lipase

End point title	Lipase

End point description:

End point type	Secondary

End point timeframe:

26 weeks (end-of-treatment values)

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: Units/l				
arithmetic mean (confidence interval 95%)	32.4 (27.3 to 37.5)	23.0 (18.4 to 27.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Total cholesterol

End point title	Total cholesterol

End point description:

End point type	Secondary

End point timeframe:

26 weeks (end-of-treatment values)

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: mmol/l				
arithmetic mean (confidence interval 95%)	4.05 (3.80 to 4.30)	4.23 (4.01 to 4.46)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cholesterol, high-density lipoprotein

End point title	Cholesterol, high-density lipoprotein

End point description:

End point type	Secondary

End point timeframe:

26 weeks (end-of-treatment values)

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: Mmol/l				
arithmetic mean (confidence interval 95%)	1.34 (1.24 to 1.43)	1.42 (1.34 to 1.51)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cholesterol, low-density lipoprotein

End point title	Cholesterol, low-density lipoprotein

End point description:

End point type	Secondary

End point timeframe:

26 weeks (end-of-treatment values)

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: Mmol/l				
arithmetic mean (confidence interval 95%)	2.34 (2.13 to 2.54)	2.35 (2.16 to 2.54)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cholesterol, very low-density lipoprotein

End point title	Cholesterol, very low-density lipoprotein

End point description:

End point type	Secondary

End point timeframe:

26 weeks (end-of-treatment values)

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: Mmol/l				
arithmetic mean (confidence interval 95%)	0.38 (0.32 to 0.43)	0.40 (0.35 to 0.45)		

Statistical analyses

No statistical analyses for this end point

Secondary: Triglycerides

End point title	Triglycerides

End point description:

End point type	Secondary

End point timeframe:

26 weeks (end-of-treatment values)

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: Mmol/l				
arithmetic mean (confidence interval 95%)	0.82 (0.71 to 0.94)	0.83 (0.72 to 0.94)		

Statistical analyses

No statistical analyses for this end point

Secondary: Urinary albumin creatinin ratio

End point title	Urinary albumin creatinin ratio

End point description:

End point type	Secondary

End point timeframe:

26 weeks (end-of-treatment values)

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: mg/g				
arithmetic mean (confidence interval 95%)	16.6 (5.3 to 28.0)	10.0 (-0.5 to 20.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Prepandial plasma glucose (lunch)

End point title	Prepandial plasma glucose (lunch)
End point description:	
Based on seven-point self-monitoring of blood glucose profiles.	
End point type	Secondary
End point timeframe:	
26 weeks (end-of-treatment values)	

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: mmol/l				
arithmetic mean (confidence interval 95%)	7.7 (6.7 to 8.7)	8.2 (7.3 to 9.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Preprandial plasma glucose (dinner)

End point title	Preprandial plasma glucose (dinner)
End point description:	
Based on seven-point self-monitoring of blood glucose profiles.	
End point type	Secondary
End point timeframe:	
26 weeks (end-of-treatment values)	

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: mmol/l				
arithmetic mean (confidence interval 95%)	9.2 (8.1 to 10.2)	9.4 (8.4 to 10.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Bedtime plasma glucose

End point title	Bedtime plasma glucose
End point description:	
Based on seven-point self-monitoring of blood glucose profiles.	
End point type	Secondary
End point timeframe:	
26 weeks (end-of-treatment values)	

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: mmol/l				
arithmetic mean (confidence interval 95%)	9.0 (7.9 to 10.1)	10.3 (9.4 to 11.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Continuous glucose monitoring: mean glucose

End point title	Continuous glucose monitoring: mean glucose
End point description:	
End point type	Secondary
End point timeframe:	
26 weeks (end-of-treatment values)	

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: mmol/l				
arithmetic mean (confidence interval 95%)	10.0 (9.5 to 10.5)	9.9 (9.5 to 10.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Continuous glucose monitoring: standard deviation

End point title	Continuous glucose monitoring: standard deviation

End point description:

End point type	Secondary

End point timeframe:

26 weeks (end-of-treatment values)

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: mmol/l				
arithmetic mean (confidence interval 95%)	4.0 (3.7 to 4.3)	3.9 (3.6 to 4.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Continuous glucose monitoring: coefficient of variance

End point title	Continuous glucose monitoring: coefficient of variance

End point description:

End point type	Secondary

End point timeframe:

26 weeks (end-of-treatment values)

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: no unit				
arithmetic mean (confidence interval 95%)	0.40 (0.38 to 0.42)	0.39 (0.37 to 0.41)		

Statistical analyses

No statistical analyses for this end point

Secondary: Continuous glucose monitoring: hypoglycaemia level 1 (3.0 to 3.9 mmol/l)

End point title	Continuous glucose monitoring: hypoglycaemia level 1 (3.0 to 3.9 mmol/l)

End point description:

End point type	Secondary

End point timeframe:

26 weeks (end-of-treatment values)

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: percentage of 24 hours				
arithmetic mean (confidence interval 95%)	4.0 (3.0 to 5.1)	3.4 (2.5 to 4.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Continuous glucose monitoring: hypoglycaemia level 2 (>3.0 mmol/l)

End point title	Continuous glucose monitoring: hypoglycaemia level 2 (>3.0 mmol/l)

End point description:

End point type	Secondary

End point timeframe:

26 weeks (end-of-treatment values)

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: percentage of 24 hours				
arithmetic mean (confidence interval 95%)	1.5 (0.7 to 2.3)	1.3 (0.6 to 2.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Continuous glucose monitoring: Target glycaemia (4 to 10 mmol/l)

End point title	Continuous glucose monitoring: Target glycaemia (4 to 10 mmol/l)

End point description:

End point type	Secondary

End point timeframe:

26 weeks (end-of-treatment values)

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: Percentage of 24 hours				
arithmetic mean (confidence interval 95%)	50.0 (45.6 to 54.4)	52.3 (48.4 to 56.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Continuous glucose monitoring: hyperglycaemia level 1 (> 10.0 mmol/l)

End point title	Continuous glucose monitoring: hyperglycaemia level 1 (> 10.0 mmol/l)

End point description:

End point type	Secondary

End point timeframe:

26 weeks (end-of-treatment values)

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: mmol/l				
arithmetic mean (confidence interval 95%)	44.4 (39.6 to 49.3)	43.0 (38.7 to 47.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Continuous glucose monitoring: hyperglycaemia level 2 (> 13.9 mmol/)

End point title	Continuous glucose monitoring: hyperglycaemia level 2 (> 13.9 mmol/)

End point description:

End point type	Secondary

End point timeframe:

26 weeks (end-of-treatment values)

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: Mmol/l				
arithmetic mean (confidence interval 95%)	18.7 (14.8 to 22.6)	18.1 (14.6 to 21.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Continuous glucose monitoring: mean amplitude of glycaemic excursion

End point title	Continuous glucose monitoring: mean amplitude of glycaemic excursion

End point description:

End point type	Secondary

End point timeframe:

26 weeks (end-of-treatment values)

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: mmol/l				
arithmetic mean (confidence interval 95%)	8.5 (7.8 to 9.2)	7.9 (7.2 to 8.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Continuous glucose monitoring: continuous overall net glycaemic action

End point title	Continuous glucose monitoring: continuous overall net glycaemic action

End point description:

End point type	Secondary

End point timeframe:

26 weeks (end-of-treatment values)

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: mmol/l				
arithmetic mean (confidence interval 95%)	9.2 (8.7 to 9.7)	9.1 (8.7 to 9.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: C-peptide: area under the curve

End point title	C-peptide: area under the curve

End point description:

Based on arginine stimulation tests.

End point type	Secondary

End point timeframe:

26 weeks (end-of-treatment values)

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: pmol/l				
arithmetic mean (confidence interval 95%)	925.8 (362.2 to 1489.5)	1168.2 (638.1 to 1698.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: C-peptide: peak value

End point title	C-peptide: peak value
End point description:	
Based on arginine stimulation tests.	
End point type	Secondary
End point timeframe:	
26 weeks (end-of-treatment values)	

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: pmol/l				
arithmetic mean (confidence interval 95%)	41.8 (14.3 to 69.3)	56.9 (31.1 to 82.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: C-peptide: peak time

End point title	C-peptide: peak time
End point description:	
Based on arginine stimulation tests.	
End point type	Secondary
End point timeframe:	
26 weeks (end-of-treatment values)	

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: minutes				
arithmetic mean (confidence interval 95%)	2.4 (1.6 to 3.3)	2.3 (1.4 to 3.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: C-peptide: fasting level

End point title	C-peptide: fasting level
End point description:	
Based on arginine stimulation tests.	
End point type	Secondary
End point timeframe:	
26 weeks (end-of-treatment values)	

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: pmol/l				
arithmetic mean (confidence interval 95%)	27.3 (10.7 to 43.8)	33.3 (17.8 to 48.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Glucagon: area under the curve

End point title	Glucagon: area under the curve
End point description:	
Based on arginine stimulation tests.	
End point type	Secondary
End point timeframe:	
26 weeks (end-of-treatment values)	

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: pmol/l				
arithmetic mean (confidence interval 95%)	544.1 (481.9 to 606.4)	533.4 (478.4 to 588.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Glucagon: peak value

End point title	Glucagon: peak value
End point description: Based on arginine stimulation tests.	
End point type	Secondary
End point timeframe: 26 weeks (end-of-treatment values)	

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: pmol/l				
arithmetic mean (confidence interval 95%)	42.3 (37.3 to 47.3)	40.7 (36.3 to 45.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Glucagon: peak time

End point title	Glucagon: peak time
End point description: Based on arginine stimulation tests.	
End point type	Secondary
End point timeframe: 26 weeks (end-of-treatment values)	

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: minutes				
arithmetic mean (confidence interval 95%)	2.6 (2.1 to 3.1)	2.5 (2.1 to 3.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Glucagon: fasting level

End point title	Glucagon: fasting level
End point description:	
Based on arginine stimulation tests.	
End point type	Secondary
End point timeframe:	
26 weeks (end-of-treatment values)	

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: pmol/l				
arithmetic mean (confidence interval 95%)	12.1 (10.3 to 13.9)	10.7 (9.1 to 12.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma glucose: area under the curve

End point title	Plasma glucose: area under the curve
End point description:	
Based on arginine stimulation tests.	
End point type	Secondary
End point timeframe:	
26 weeks (end-of-treatment values)	

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: mmol/l				
arithmetic mean (confidence interval 95%)	352.2 (301.0 to 403.3)	337.5 (293.7 to 381.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma glucose: peak value

End point title	Plasma glucose: peak value
End point description:	
Based on arginine stimulation tests.	
End point type	Secondary
End point timeframe:	
26 weeks (end-of-treatment values)	

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: mmol/l				
arithmetic mean (confidence interval 95%)	12.1 (10.4 to 13.8)	11.5 (10.1 to 13.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma glucose: peak time

End point title	Plasma glucose: peak time
End point description:	
Based on arginine stimulation tests.	
End point type	Secondary
End point timeframe:	
26 weeks (end-of-treatment values)	

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: minutes				
arithmetic mean (confidence interval 95%)	9.4 (6.3 to 12.6)	12.5 (9.8 to 15.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma glucose: fasting level

End point title	Plasma glucose: fasting level
End point description:	
Based on arginine stimulation tests.	
End point type	Secondary
End point timeframe:	
26 weeks (end-of-treatment values)	

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: mmol/l				
arithmetic mean (confidence interval 95%)	11.3 (9.5 to 13.0)	10.8 (9.3 to 12.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: ADDQoL: item 1

End point title	ADDQoL: item 1
End point description:	
Based on the Audit of Diabetes-Dependent Quality of Life questionnaire.	
End point type	Secondary
End point timeframe:	
26 weeks (end-of-treatment values)	

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: no unit				
arithmetic mean (confidence interval 95%)	1.6 (1.3 to 1.8)	1.9 (1.7 to 2.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: ADQoL: item 2

End point title	ADQoL: item 2
End point description:	
Based on the Audit of Diabetes-Dependent Quality of Life questionnaire.	
End point type	Secondary
End point timeframe:	
26 weeks (end-of-treatment values)	

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: no unit				
arithmetic mean (confidence interval 95%)	-0.9 (-1.2 to -0.6)	-0.9 (-1.2 to -0.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: ADDQoL: mean average weighted impact

End point title	ADDQoL: mean average weighted impact
End point description:	
Based on the Audit of Diabetes-Dependent Quality of Life questionnaire.	
End point type	Secondary
End point timeframe:	
26 weeks (end-of-treatment values)	

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: no unit				
arithmetic mean (confidence interval 95%)	-1.0 (-1.3 to -0.8)	-1.2 (-1.4 to -0.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: DTSQs: item 1, 4–8

End point title	DTSQs: item 1, 4–8

End point description:

Based on the Diabetes Treatment Satisfaction Questionnaire status version questionnaire.

End point type	Secondary

End point timeframe:

26 weeks (end-of-treatment values)

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: no unit				
arithmetic mean (confidence interval 95%)	28.8 (27.2 to 30.4)	28.7 (27.2 to 30.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: DTSQs: item 2

End point title	DTSQs: item 2

End point description:

Based on the Diabetes Treatment Satisfaction Questionnaire status version questionnaire.

End point type	Secondary

End point timeframe:

26 weeks (end-of-treatment values)

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: no unit				
arithmetic mean (confidence interval 95%)	2.8 (2.4 to 3.3)	2.8 (2.4 to 3.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: DTSQs: item 3

End point title	DTSQs: item 3

End point description:

Based on the Diabetes Treatment Satisfaction Questionnaire status version questionnaire.

End point type	Secondary

End point timeframe:

26 weeks (end-of-treatment values)

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: no unit				
arithmetic mean (confidence interval 95%)	2.1 (1.7 to 2.5)	2.1 (1.7 to 2.5)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

At week 26 (end-of-treatment)

Adverse event reporting additional description:

Adverse events were subjectively reported events by the participants, as clinically assessed by the investigators (if possible, corroborated by medical records).

Assessment type	Systematic

Dictionary used

Dictionary name	Patient-reported
Dictionary version	1

Reporting groups

Reporting group title	Exenatide

Reporting group description: -

Reporting group title	Placebo

Reporting group description: -

Serious adverse events	Exenatide	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 52 (3.85%)	6 / 53 (11.32%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Alcohol intoxication	Additional description: Placebo group		
subjects affected / exposed	0 / 52 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug intoxication	Additional description: Placebo group, not related to study drug		
subjects affected / exposed	0 / 52 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Suspected acute coronary syndrome	Additional description: Placebo group		
subjects affected / exposed	0 / 52 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Minor stroke	Additional description: Placebo group		

subjects affected / exposed	0 / 52 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Inguinal hernia surgery	Additional description: Exenatide group		
subjects affected / exposed	1 / 52 (1.92%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Resection of residual abscess tissue	Additional description: Exenatide group; follow-up prodecure to surgery prior to randomisation		
subjects affected / exposed	1 / 52 (1.92%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Removal of implantable loop recorder	Additional description: Placebo group		
subjects affected / exposed	0 / 52 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Erysipelas,	Additional description: Placebo group		
subjects affected / exposed	0 / 52 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Exenatide	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	49 / 52 (94.23%)	46 / 53 (86.79%)	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	6 / 52 (11.54%)	2 / 53 (3.77%)	
occurrences (all)	8	2	
Other	Additional description: Other adverse events were uniquely registered events of minor clinical importance and unrelated to study drug (not possible to classify by precise medical terms).		

subjects affected / exposed	42 / 52 (80.77%)	39 / 53 (73.58%)	
occurrences (all)	49	49	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	40 / 52 (76.92%)	9 / 53 (16.98%)	
occurrences (all)	48	9	
Vomiting			
subjects affected / exposed	12 / 52 (23.08%)	0 / 53 (0.00%)	
occurrences (all)	12	0	
Acid reflux or heartburn			
subjects affected / exposed	10 / 52 (19.23%)	0 / 53 (0.00%)	
occurrences (all)	10	0	
Decreased appetite			
subjects affected / exposed	12 / 52 (23.08%)	3 / 53 (5.66%)	
occurrences (all)	14	3	
Constipation			
subjects affected / exposed	3 / 52 (5.77%)	2 / 53 (3.77%)	
occurrences (all)	3	2	
Diarrhoea			
subjects affected / exposed	1 / 52 (1.92%)	6 / 53 (11.32%)	
occurrences (all)	1	7	
Bloating			
subjects affected / exposed	4 / 52 (7.69%)	0 / 53 (0.00%)	
occurrences (all)	4	0	
Endocrine disorders			
Severe hypoglycaemia	Additional description: Not requiring hospital admission		
subjects affected / exposed	3 / 52 (5.77%)	2 / 53 (3.77%)	
occurrences (all)	4	2	
Prolonged hypoglycaemia			
subjects affected / exposed	1 / 52 (1.92%)	1 / 53 (1.89%)	
occurrences (all)	1	1	
Postprandial hypoglycaemia			
subjects affected / exposed	1 / 52 (1.92%)	0 / 53 (0.00%)	
occurrences (all)	1	0	
Lowered hypoglycaemia awareness	Additional description: As perceived and reported by participant		

subjects affected / exposed	1 / 52 (1.92%)	0 / 53 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Minor orthopaedic injuries	Additional description: Not related to hypoglycaemia		
subjects affected / exposed	3 / 52 (5.77%)	14 / 53 (26.42%)	
occurrences (all)	3	16	
Infections and infestations			
Upper-airway infection			
subjects affected / exposed	20 / 52 (38.46%)	15 / 53 (28.30%)	
occurrences (all)	26	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

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/32135138

http://www.ncbi.nlm.nih.gov/pubmed/29950475