Clinical trial results:
A Randomized, Double-blind, Placebo Controlled Trial to Assess Safety/Tolerability, Pharmacokinetics & Pharmacodynamics of Liraglutide in Paediatric (10 – 17 years old) Subjects with Type 2 Diabetes

Summary

EudraCT number	2010-021057-39
Trial protocol	GB SI BE
Global end of trial date	30 September 2011

Results information

Result version number	v1 (current)
This version publication date	15 March 2016
First version publication date	21 July 2015

Trial information

Trial identification

Sponsor protocol code	NN2211-1800

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00943501
WHO universal trial number (UTN)	U1111-1111-9256

Notes:

Sponsors

Sponsor organisation name	Novo Nordisk A/S
Sponsor organisation address	Novo Allè, Bagsvaerd, Denmark, 2880
Public contact	Global Clinical Registry (GCR,1452), Novo Nordisk A/S, clinicaltrials@novonordisk.com
Scientific contact	Global Clinical Registry (GCR,1452), Novo Nordisk A/S, clinicaltrials@novonordisk.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000128-PIP01-07
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	19 March 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 September 2011
Global end of trial reached?	Yes
Global end of trial date	30 September 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the safety and tolerability of 0.3, 0.6, 0.9, 1.2 and 1.8 mg doses of liraglutide in the paediatric population (10 – 17 years of age).

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (59th WMA General Assembly, Seoul, October 2008) and ICH Good Clinical Practice (01-May-1996).

Background therapy:

Subject previously using metformin, the pre-trial treatment regimen was continued unaltered throughout the study as background medication. Some subjects were on diet and exercise only. Pre-trial regimen was continued during the trial.

Evidence for comparator:

Not applicable

Actual start date of recruitment	02 November 2009
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	Slovenia: 2
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	United States: 15
Worldwide total number of subjects	21
EEA total number of subjects	6

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)	3
Adolescents (12-17 years)	18
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

19 sites were activated in 4 countries; 14 sites enrolled study subjects (United States (9 sites –15 subjects), United Kingdom (3 sites –3 subjects), Slovenia (1 site – 2 subjects) and Belgium (1 site – 1 subject))

Pre-assignment

Screening details:

Not applicable

Period 1

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

Blinding implementation details:

This trial is double-blind and placebo controlled.

Arms

Are arms mutually exclusive?	Yes
Arm title	Liraglutide

Arm description:

Subjects randomised to liraglutide treatment received 0.3 mg liraglutide daily (starting on Day 1) during the first week, followed by 0.6 mg daily (starting on Day 8) during the second week, 0.9 mg daily (starting on Day 15) during the third week, 1.2 mg daily (starting on Day 22) during the fourth week, and 1.8 mg daily (starting on Day 29) during the fifth and final treatment week. If a subject did not meet the dose escalation criteria, he/she continued on the highest dose reached.

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

Dosage and administration details:

Liraglutide was administered once-daily by a s.c. FlexPen injection in the abdomen.

Arm title	Placebo

Arm description:

Liraglutide placebo, was administered once-daily by a s.c. FlexPen injection in the abdomen.

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

Dosage and administration details:

Liraglutide placebo, was administered once-daily by a s.c. FlexPen injection in the abdomen.

Number of subjects in period 1	Liraglutide	Placebo
Started	14	7
Completed	13	6
Not completed	1	1
Withdrawal criteria	1	-
Unclassified	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Liraglutide
Reporting group description:	
Subjects randomised to liraglutide treatment received 0.3 mg liraglutide daily (starting on Day 1) during the first week, followed by 0.6 mg daily (starting on Day 8) during the second week, 0.9 mg daily (starting on Day 15) during the third week, 1.2 mg daily (starting on Day 22) during the fourth week, and 1.8 mg daily (starting on Day 29) during the fifth and final treatment week. If a subject did not meet the dose escalation criteria, he/she continued on the highest dose reached.	
Reporting group title	Placebo
Reporting group description:	
Liraglutide placebo, was administered once-daily by a s.c. FlexPen injection in the abdomen.	

Reporting group values	Liraglutide	Placebo	Total
Number of subjects	14	7	21
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)	2	1	3
Adolescents (12-17 years)	12	6	18
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	9	5	14
Male	5	2	7

End points

End points reporting groups

Reporting group title	Liraglutide

Reporting group description:

Subjects randomised to liraglutide treatment received 0.3 mg liraglutide daily (starting on Day 1) during the first week, followed by 0.6 mg daily (starting on Day 8) during the second week, 0.9 mg daily (starting on Day 15) during the third week, 1.2 mg daily (starting on Day 22) during the fourth week, and 1.8 mg daily (starting on Day 29) during the fifth and final treatment week. If a subject did not meet the dose escalation criteria, he/she continued on the highest dose reached.

Reporting group title	Placebo

Reporting group description:

Liraglutide placebo, was administered once-daily by a s.c. FlexPen injection in the abdomen.

Primary: Adverse Events

End point title	Adverse Events[1]

End point description:

All AEs either observed by the investigator or reported spontaneously by the subjects were recorded by the investigator and evaluated. The AEs were collected from randomisation (Visit 2/week 1 day 1) to follow up (Visit 9/week 6 day 5+ 2 days)

End point type	Primary

End point timeframe:

Randomisation (Visit 2/ week 1 day 1) to follow up (Visit 9/ week 6 day 5+ 2 days)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The summary statistics by treatment were the primary mode of statistical presentation of safety data.

End point values	Liraglutide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	7		
Units: Number of Adverse Events	38	18		

Statistical analyses

No statistical analyses for this end point

Primary: Hypoglycaemic episodes

End point title	Hypoglycaemic episodes[2]

End point description:

1) Major-Subject unable to treat himself/herself. 2) Minor-An episode with symptoms consistent with hypoglycaemia with confirmation by plasma glucose <56mg/dL (3.1mmol/L) or full blood glucose<50mg/dL (2.8mmol/L) and which is self-handled by the subject. Any asymptomatic plasma glucose value <56mg/dl (3.1mmol/L) or full blood glucose value <50mg/dL (2.8mmol/L)
ADA Classification- 1) Severe-An episode requiring assistance of another person to actively administer carbohydrate, glucagons or other resuscitative actions. 2) Documented symptomatic- An episode during which typical symptoms of hypoglycaemia are accompanied by a measured plasma glucose concentration of ≤ 70 mg/dL (3.9 mmol/L). 3)Asymptomatic -An episode not accompanied by typical symptoms of hypoglycaemia, but with a measured plasma glucose concentration of ≤ 70 mg/dL (3.9

mmol/L).

End point type	Primary

End point timeframe:

Randomisation (Visit 2/ week 1 day 1) to follow up (Visit 9/ week 6 day 5 + 2 days)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The summary statistics by treatment were the primary mode of statistical presentation of safety data.

End point values	Liraglutide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	7		
Units: Number of hypoglycaemic episodes				
Major	0	0		
Minor	4	0		
ADA severe	0	0		
ADA documented Symptomatic	2	0		
ADA Asymptomatic	9	1		

Statistical analyses

No statistical analyses for this end point

Primary: Anti-Liraglutide Antibodies

End point title	Anti-Liraglutide Antibodies[3]

End point description:

Anti-Liraglutide antibody assessment was a part of safety assessment in this trial.Blood samples for serum antibody against liraglutide were drawn at Visit 2 (randomisation/ week1 day 1) and Visit 9 (follow up/ week 6 day 5 + 2 days) . Blood samples for subjects discontinuing prematurely from the trial treatment (due to withdrawal) were drawn at the withdrawal visit. Antibody-positive samples were to be further characterised for neutralising effect and cross-reactivity.

End point type	Primary

End point timeframe:

Visit 2 (Randomisation/ week 1 day 1) and Visit 9 (follow up/ week 6 day 5 + 2 days)

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The summary statistics by treatment were the primary mode of statistical presentation of safety data.

End point values	Liraglutide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	7		
Units: Number of subjects- negative antibodies	14	7		

Statistical analyses

No statistical analyses for this end point

Primary: Biochemistry- Change from Baseline

End point title	Biochemistry- Change from Baseline[4]

End point description:

Biochemistry parameters were assessed at Screening (Visit 1/week-2 relative to randomisation) and follow up (Visit 9/week 6 day 5+ 2 days).

End point type	Primary

End point timeframe:

Screening (Visit 1/week-2 relative to randomisation) and follow up (Visit 9/week 6 day 5+ 2 days)

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The summary statistics by treatment were the primary mode of statistical presentation of safety data.

End point values	Liraglutide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	7		
Units: U/L,mmol/L,g/L				
arithmetic mean (standard deviation)				
Alanine Aminotransferase (U/L)	-6.79 (± 8.54)	-4.14 (± 10.64)		
Albumin (g/L)	-1.54 (± 2.77)	-0.4 (± 2.24)		
Alkaline Phosphatase (U/L)	-8.21 (± 23.39)	-6.71 (± 12.39)		
Aspartate Aminotransferase (U/L)	-5.86 (± 8.17)	-0.43 (± 7.81)		
Bilirubin Total (umol/L)	-1 (± 2.6)	-0.63 (± 2.13)		
Calcium Total (mmol/L)	0 (± 0.08)	0.07 (± 0.23)		
Creatine Phosphokinase (U/L)	-16.8 (± 47.51)	-3.86 (± 90.23)		
Creatinine (umol/L)	-4.57 (± 3.86)	-2.86 (± 6.47)		
GGT (U/L)	-2 (± 3.88)	3.14 (± 3.89)		
LDH (U/L)	-13.9 (± 25.46)	-15.7 (± 34.44)		
Magnesium (mmol/L)	0 (± 0.05)	0.02 (± 0.06)		
Potassium (mmol/L)	-0.03 (± 0.29)	0.09 (± 0.22)		
Protein (g/L)	-1.12 (± 4.06)	-0.43 (± 3.09)		
Sodium (mmol/L)	-0.57 (± 2.65)	2.43 (± 3.51)		
Urea (mmol/L)	-0.07 (± 1.01)	0.7 (± 0.78)		
Uric Acid (umol/L)	-47.2 (± 70.1)	-41.3 (± 46.45)		

Statistical analyses

No statistical analyses for this end point

Primary: Physical Examination- Change from previous visit.

End point title	Physical Examination- Change from previous visit.[5]

End point description:

Targeted physical examinations were performed at scheduled Visits and at any other time at the

discretion of the Investigator.These results are based on assessments made at the final time point (Visit 8/Week 6 Day 3)

End point type	Primary

End point timeframe:

Visit 2 (Randomisation/ week 1 day 1) to Visit 8 (Week 6 day 3)

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The summary statistics by treatment were the primary mode of statistical presentation of safety data.

End point values	Liraglutide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	7		
Units: Subjects				
Yes (findings)	0	0		
No (No findings)	13	6		
Missing	1	1		

Statistical analyses

No statistical analyses for this end point

Primary: ECG

End point title	ECG[6]

End point description:

A standard 12-lead ECG evaluation was performed by the investigator at screening (Visit 1/ week -2 relative to randomisation) Visit 2 (randomisation /week 1 day 1) and Follow-up (Visit 9/ week 6 day 5 +2 days) and recorded as:
1. Normal
2. Abnormal; not clinically significant
3. Abnormal; clinically significant.
The values presented are overall interpretation for week 6 Day 5. (Follow up/Viist 9)

End point type	Primary

End point timeframe:

Screening (Visit 1/week -2 relative to randomisation) Visit 2 (randomisation /week 1 day 1) and Follow-up (Visit 9/week 6 day 5 +2 days)

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The summary statistics by treatment were the primary mode of statistical presentation of safety data.

End point values	Liraglutide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	7		
Units: Subjects				
Normal	12	7		
Abnormal, NCS	2	0		

Statistical analyses

No statistical analyses for this end point

Primary: Funduscopy

End point title	Funduscopy[7]

End point description:

Funduscopy was a part of safety assessment of the trial. The occurences in both left and right eye at follow up are given below.

End point type	Primary

End point timeframe:

Screening (Visit 1/week-2 relative to randomisation) and follow up (Visit 9/week 6 day 5+ 2 days)

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The summary statistics by treatment were the primary mode of statistical presentation of safety data.

End point values	Liraglutide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	7		
Units: Subjects				
Normal	14	7		
ANCS	0	0		
ACS	0	0		
Mis	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Pulse-Change from baseline

End point title	Pulse-Change from baseline[8]

End point description:

Pulse was measured at all visits as necessary and as scheduled. Pulse was measured after subject has rested for 5 min.

End point type	Primary

End point timeframe:

Screening (Visit 1/week-2 relative to randomisation) to follow up (Visit 9/week 6 day 5+ 2 days)

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The summary statistics by treatment were the primary mode of statistical presentation of safety data.

End point values	Liraglutide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	7		
Units: beats/min				
arithmetic mean (standard deviation)				
Week 6, Day 1	2.4 (± 11.1)	3.3 (± 18)		

Statistical analyses

No statistical analyses for this end point

Primary: Systolic Blood Pressure- Change from baseline

End point title	Systolic Blood Pressure- Change from baseline[9]

End point description:

Systolic blood pressures were measured at all visits as necessary and as scheduled. Blood pressure was measured after the subject has rested for 5 min.

End point type	Primary

End point timeframe:

Screening (Visit 1/week -2 relative to randomisation) to follow up (Visit 9/week 6 Day 5+ 2days)

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The summary statistics by treatment were the primary mode of statistical presentation of safety data.

End point values	Liraglutide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	7		
Units: mmHg				
arithmetic mean (standard deviation)				
Week 6, Day 1	0.6 (± 17.5)	-3 (± 10.7)		

Statistical analyses

No statistical analyses for this end point

Primary: Diastolic Blood Pressure- Change from baseline

End point title	Diastolic Blood Pressure- Change from baseline[10]

End point description:

Diastolic blood pressures was measured at all visits as necessary and as scheduled. Blood pressure was measured after resting for 5 min.

End point type	Primary

End point timeframe:

Screening (Visit 1/week-2 relative to rando misation) to follow up (Visit 9/week 6 day 5+ 2 days)

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The summary statistics by treatment were the primary mode of statistical presentation of

safety data.

End point values	Liraglutide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	7		
Units: mmHg				
arithmetic mean (standard deviation)				
Week 6, Day 1	0.6 (± 8.7)	1.2 (± 4.8)		

Statistical analyses

No statistical analyses for this end point

Primary: Haematology-Change from baseline

End point title	Haematology-Change from baseline[11]

End point description:

Haematology parameters were assessed at screening (Visit 1/week-2 relative to randomisation) and follow up (Visit 9/week 6 day 5+ 2 days)

End point type	Primary

End point timeframe:

Screening (Visit 1/week-2 relative to randomisation) and follow up (Visit 9/week 6 day 5+ 2 days)

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The summary statistics by treatment were the primary mode of statistical presentation of safety data.

End point values	Liraglutide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	7		
Units: 10 ˆ9/L,g/L,%,fL,				
arithmetic mean (standard deviation)				
Basophile_abs (10^9/L)	0.01 (± 0.03)	0.01 (± 0.04)		
Basophils (%)	0 (± 0.39)	0 (± 0)		
Eosinophile_abs (10^9/L)	0.06 (± 0.13)	0.03 (± 0.08)		
Eosinophils (%)	1.07 (± 3.32)	0.29 (± 0.76)		
Erythrocytes (10^12/L)	-0.16 (± 0.22)	-0.08 (± 0.26)		
Haematocrit (ratio)	-0.01 (± 0.02)	0 (± 0.02)		
Haemoglobin (g/L)	-3.36 (± 6.4)	-1.57 (± 5)		
Lymphocytes (%)	0.36 (± 11.95)	-1.29 (± 3.9)		
Lymphocytes_abs (10^9/L)	0.1 (± 0.43)	0.17 (± 0.28)		
MCHC (g/L)	1 (± 7.76)	-1.14 (± 2.79)		
MCV (fL)	0.21 (± 2.08)	1 (± 1.29)		
Monocytes (%)	-0.64 (± 2.1)	0 (± 3.65)		
Monocytes_abs (10^9/L)	-0.03 (± 0.17)	0.04 (± 0.21)		
Neutrophil_abs (10^9/L)	0.39 (± 2.01)	0.9 (± 1.62)		
Neutrophils (%)	-0.71 (± 15.57)	1.29 (± 4.86)		

Reticulocyte (%)	-0.02 (± 1.04)	0.53 (± 0.51)		
Reticulocyte_abs (10^9/L)	-3.62 (± 47.7)	25 (± 29.31)		
Thrombocytes (10^9/L)	1 (± 28.22)	14.43 (± 29.33)		
Total Leucocytes (10^9/L)	0.49 (± 2.08)	1.17 (± 1.7)		

Statistical analyses

No statistical analyses for this end point

Primary: Urinalysis-pH Change from baseline

End point title	Urinalysis-pH Change from baseline[12]

End point description:

The analysis of pH, ketones, protein, blood,leukocyte esterase, nitrite and glucose were perfomed.

End point type	Primary

End point timeframe:

Screening (Visit 1/week-2 relative to randomisation) and follow up (Visit 9/week 6 day 5+ 2 days)

Notes:

[12] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The summary statistics by treatment were the primary mode of statistical presentation of safety data.

End point values	Liraglutide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	7		
Units: pH				
arithmetic mean (standard deviation)	0.08 (± 0.34)	0.14 (± 0.48)		

Statistical analyses

No statistical analyses for this end point

Primary: Fasting Plasma Glucose - Change from baseline

End point title	Fasting Plasma Glucose - Change from baseline

End point description:

FPG (from glucometer) was asessed from screening (Visit 1/week-2 relative to randomisation) to follow up (Visit 9/week 6 day 5+ 2 days). Results presented are for the change from baseline (week 1day1) to the last dose. (after 5 weeks of treatment)

End point type	Primary

End point timeframe:

Screening (Visit 1/week-2 relative to randomisation) to follow up (Visit 9/week 6 day 5+ 2 days)

End point values	Liraglutide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	6		
Units: mmol/L				
least squares mean (standard error)	-1.27 (± 0.56)	0.17 (± 0.86)		

Statistical analyses

Statistical analysis title	FPG-Change from baseline
Comparison groups	Placebo v Liraglutide
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	other[13]
P-value	= 0.1797
Method	ANCOVA
Parameter estimate	Estimated treatmentdifference
Point estimate	-1.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.61
upper limit	0.73

Notes:

[13] - Exploratory

Primary: HbA1c (%) - Change from baseline

End point title	HbA1c (%) - Change from baseline

End point description:

Percentage point change in Glycosylated Haemoglobin A1c (HbA1c). Results presented are for the change from baseline (week1 day1) to the final time point (visit6/week 5 day7)

End point type	Primary

End point timeframe:

Screening (Visit 1/week -2 relative to randomisation) to Visit 6 (Week 5 day 7)

End point values	Liraglutide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	6		
Units: percentage				
least squares mean (standard error)	-0.86 (± 0.12)	0.04 (± 0.18)		

Statistical analyses

Statistical analysis title	HbA1c- Change from baseline
Comparison groups	Liraglutide v Placebo
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0007
Method	ANCOVA
Parameter estimate	Estimated treatment difference
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.36
upper limit	-0.45

Primary: Urinalysis -Glucose

End point title	Urinalysis -Glucose[14]

End point description:

The analysis of pH, ketones, protein, blood,leukocyte esterase, nitrite and glucose were perfomed.

End point type	Primary

End point timeframe:

Screening (Visit 1/week-2 relative to randomisation) and follow up (Visit 9/week 6 day 5+ 2 days)

Notes:

[14] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The summary statistics by treatment were the primary mode of statistical presentation of safety data.

End point values	Liraglutide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	7		
Units: No of subjects				
Negative	9	5		
Positive	4	2		

Statistical analyses

No statistical analyses for this end point

Primary: Urinalysis -Ketones

End point title	Urinalysis -Ketones[15]

End point description:

The analysis of pH, ketones, protein, blood,leukocyte esterase, nitrite and glucose were perfomed.

End point type	Primary

End point timeframe:

Screening (Visit 1/week-2 relative to randomisation) and follow up (Visit 9/week 6 day 5+ 2 days)

Notes:

[15] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The summary statistics by treatment were the primary mode of statistical presentation of safety data.

End point values	Liraglutide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	7		
Units: No of subjects				
Negative	13	7		

Statistical analyses

No statistical analyses for this end point

Primary: Urinalysis-Leucocytes

End point title	Urinalysis-Leucocytes[16]

End point description:

The analysis of pH, ketones, protein, blood,leukocyte esterase, nitrite and glucose were performed.

End point type	Primary

End point timeframe:

Screening (Visit 1/week-2 relative to randomisation) and follow up (Visit 9/week 6 day 5+ 2 days)

Notes:

[16] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The summary statistics by treatment were the primary mode of statistical presentation of safety data.

End point values	Liraglutide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	7		
Units: No of subjects				
Negative	12	6		
Small	1	0		
Moderate	0	1		

Statistical analyses

No statistical analyses for this end point

Primary: Urinalysis- Nitrite

End point title	Urinalysis- Nitrite[17]

End point description:

The analysis of pH, ketones, protein, blood,leukocyte esterase, nitrite and glucose were perfomed.

End point type	Primary

End point timeframe:

Screening (Visit 1/week-2 relative to randomisation) and follow up (Visit 9/week 6 day 5+ 2 days)

Notes:

[17] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The summary statistics by treatment were the primary mode of statistical presentation of safety data.

End point values	Liraglutide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	7		
Units: No of subjects				
Negative	10	7		
Positive	3	0		

Statistical analyses

No statistical analyses for this end point

Primary: Urinalysis-Protein

End point title	Urinalysis-Protein[18]

End point description:

The analysis of pH, ketones, protein, blood,leukocyte esterase, nitrite and glucose were perfomed.

End point type	Primary

End point timeframe:

Screening (Visit 1/week-2 relative to randomisation) and follow up (Visit 9/week 6 day 5+ 2 days)

Notes:

[18] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The summary statistics by treatment were the primary mode of statistical presentation of safety data.

End point values	Liraglutide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	7		
Units: Number of subjects				
Negative	11	6		
30	2	1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from visit 1 to follow-up.Treatment emergent AEs are reported below.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups

Reporting group title	Liraglutide

Reporting group description:

Subjects randomised to liraglutide treatment received 0.3 mg liraglutide daily (starting on Day 1) during the first week, followed by 0.6 mg daily (starting on Day 8) during the second week, 0.9 mg daily (starting on Day 15) during the third week, 1.2 mg daily (starting on Day 22) during the fourth week, and 1.8 mg daily (starting on Day 29) during the fifth and final treatment week. If a subject did not meet the dose escalation criteria, he/she continued on the highest dose until the end of the trial.

Reporting group title	Placebo

Reporting group description:

Liraglutide placebo, was administered once-daily by a s.c. FlexPen injection in the abdomen.

Serious adverse events	Liraglutide	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 14 (0.00%)	0 / 7 (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	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 14 (71.43%)	3 / 7 (42.86%)	
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 14 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Hot flush			
subjects affected / exposed	0 / 14 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
General disorders and administration site conditions			

Chest pain			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Injection site pain			
subjects affected / exposed	0 / 14 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Rhinorrhoea			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Nervousness			
subjects affected / exposed	0 / 14 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Joint sprain			
subjects affected / exposed	2 / 14 (14.29%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Arthropod bite			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Contusion			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Incorrect dose administered			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Muscle strain			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Sunburn			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences (all)	1	0	

Ligament rupture			
subjects affected / exposed	0 / 14 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 14 (21.43%)	1 / 7 (14.29%)	
occurrences (all)	4	2	
Dizziness			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Conjunctivitis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	6 / 14 (42.86%)	1 / 7 (14.29%)	
occurrences (all)	7	1	
Nausea			
subjects affected / exposed	3 / 14 (21.43%)	1 / 7 (14.29%)	
occurrences (all)	4	1	
Vomiting			
subjects affected / exposed	2 / 14 (14.29%)	2 / 7 (28.57%)	
occurrences (all)	2	3	
Abdominal discomfort			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Abdominal pain			
subjects affected / exposed	1 / 14 (7.14%)	1 / 7 (14.29%)	
occurrences (all)	1	2	
Abdominal pain upper			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences (all)	1	0	

Dry mouth			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Rash			
subjects affected / exposed	0 / 14 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 14 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Infections and infestations			
Gastroenteritis viral			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Tonsillitis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 14 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 July 2009	This substantial amendment primarily involves- 1. Addition of a new subject withdrawal criteria related to pancreatitis. 2.Update of one inclusion and two exclusion criteria. 3.Specification of the frequency of Safety Monitoring Board meetings. 4.Addition of new language to the Informed Consent as agreed with USFDA. In addition to the above, a few minor inconsistencies and clarifications are necessary to make the protocol complete, accurate and more informative. Those have also been included.
20 August 2009	This substantial amendment involves the addition of text related to liraglutide toxicology results and results in the addition of approved text to the protocol in order to be aligned with the text previously added to the informed consent as requested by the FDA.
16 July 2010	This substantial amendment primarily involves : 1.Expansion (widening) of the HBA1C inclusion criteria (to ≥ 6.5% and ≤ 11.0%). 2.Expansion (widening) of the FPG randomisation criterion [to 110-240 mg/dL, (6.1-13.3 mmol/L). 3.Altering the language of exclusion criterion involving subjects on prior use of antidiabetic treatment. 4. Altering the pharmacokinetic (blood) sampling schedule. 5. Replacement of measurement of CGRP in this study with CEA. 6.Addition of new and updated language and safety information to the protocol and Informed Consent as agreed with the regulatrory authorities. (or approved product labelling). 7.Allowance for protocol to incorporate an IV/IWRS system for drug distribution. 8. Minor changes, clarifications and corrections to several sections for making the protocol clear for execution.
09 September 2010	In this substantial protocol amendment- 1. It was clarified that a calcitonin level was obtained at Visit 1, Screening, (and not at Visit 2, Randomisation) in order to be avialable for eligibility evaluation, and at Visit 7 in Part I,for paediatric subjects. 2. It was clarified that a calcitonin level was obtained at Visit 1, Screening (and not a Visit 2 Randomisation),to be available for eligibility evaluation and at Visit 6 in part II for paediatric subjects. 3. A calcitonin level for adult subjects will be obtained at Visit 1, Screening (and not at Visit 2 Randomisation) to be available for eligibility evaluation, and at Visit 6 in Part II. 4.The calcitonin level in Exclusion Criteria number 22 was changed from ≥ 100ng/L to ›50 ng/L. 5.A review of withdrawal criteria was added to Visits 7 and 8 in Part I and to Visits 6 and 7 in Part II. 6.A check of vital signs was added to the Flow Chart, Part I day 35, Visit 6. 7.It was clarified that body temperature will be recorded in°F or °C. 8.°F as representing degrees Fahrenheit or °C as representing degrees Celsius were added to the List of Abbreviations.
14 December 2010	This amendment was implemented in order to add Belgium as a participating country in this trial. The language of the protocol and subject informed consent form was modified accordingly. A minor inconsistency was corrected, allowing for greater accuracy.

30 September 2011	The amendment was implemented in order to eliminate the part II of the trial, as per Novo Nordisk's agreement with PDCO on 3 May 2011 (Part II was to evaluate the dose range of 0.6 to 1.8mg liraglutide in paediatric subjects and also included a comparative adult group). In addition , minor inconsistencies were corrected in order to allow for greater accuracy. Justification for the date entered- The amendment date -31Oct 2011 entered showed a validation error , hence the date has been entered as 30 Sep 2011, to surpass the validation error. The date entered here is global end of the trial date. The actual amendment date is 31 Oct 2011.

Notes:

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.

Small number of subjects analysed was the limitation for the trial.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/25036533