Clinical trial results:
Efficacy and safety of liraglutide in combination with metformin versus metformin monotherapy on glycaemic control in children and adolescents with type 2 diabetes

Summary

EudraCT number	2011-002605-29
Trial protocol	GR GB HU DE BE ES DK NO SE PL AT FR PT NL
Global end of trial date	20 May 2020

Results information

Result version number	v3 (current)
This version publication date	04 June 2021
First version publication date	05 December 2018
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	NN2211-3659

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01541215
WHO universal trial number (UTN)	U1111-1121-8743

Notes:

Sponsors

Sponsor organisation name	Novo Nordisk A/S
Sponsor organisation address	Novo Allé, Bagsvaerd, Denmark, 2880
Public contact	Clinical Reporting Anchor and Disclosure (1452), Novo Nordisk A/S, clinicaltrials@novonordisk.com
Scientific contact	Clinical Reporting Anchor and Disclosure (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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 November 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 November 2017
Global end of trial reached?	Yes
Global end of trial date	20 May 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To confirm the superiority of liraglutide at the maximum tolerated dose (0.6 mg, 1.2 mg or 1.8 mg)versus placebo when added to metformin with or without basal insulin treatment in controlling glycaemia in children and adolescents (ages 10–17 years) with type 2 diabetes

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki and ICH Good Clinical Practice, including archiving of essential documents and FDA 21 CFR 312.120.

Background therapy:

Metformin was characterised as background treatment.

Evidence for comparator:

Not applicable

Actual start date of recruitment	13 November 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 1
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Hungary: 3
Country: Number of subjects enrolled	Israel: 13
Country: Number of subjects enrolled	India: 6
Country: Number of subjects enrolled	Lebanon: 3
Country: Number of subjects enrolled	North Macedonia: 6
Country: Number of subjects enrolled	Mexico: 16
Country: Number of subjects enrolled	Malaysia: 2
Country: Number of subjects enrolled	New Zealand: 6
Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	Portugal: 1
Country: Number of subjects enrolled	Russian Federation: 13

Country: Number of subjects enrolled	Thailand: 1
Country: Number of subjects enrolled	Turkey: 5
Country: Number of subjects enrolled	Taiwan: 3
Country: Number of subjects enrolled	United States: 45
Country: Number of subjects enrolled	Morocco: 4
Worldwide total number of subjects	135
EEA total number of subjects	7

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)	16
Adolescents (12-17 years)	119
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 84 sites in 25 countries.

Pre-assignment

Screening details:

Eligible subjects entered an 11- to 12-week run-in period where they were to undergo a 3-4 week titration of metformin to a maximum tolerated dose of metformin (≥1000 mg and ≤2000 mg per day) followed by an 8-week maintenance period.

Period 1

Period 1 title	Treatment period (52 weeks)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

The trial was designed to be double-blind during the first 26 weeks of randomised treatment

Arms

Are arms mutually exclusive?	Yes
Arm title	Liraglutide 1.8 mg

Arm description:

After the run-in period, subjects were randomized to receive liraglutide subcutaneous injections once daily (in combination with metformin with or without basal insulin, on a background of diet and exercise) for 52 weeks (26 weeks double blind treatment period followed by a 26-week open-label extension period). Subjects treated with liraglutide for more than 3 months were asked to return for follow-up visits one and two years after the end of the open label period (after trial drug cessation at week 52).

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

Dosage and administration details:

Liraglutide (6.0 mg/ml solution) was administered once daily by s.c. injections, either in the abdomen, thigh or upper arm. The liraglutide dosing was started at 0.6 mg/day during the first week and escalated in weekly increments of 0.6 mg over the following 2-3 weeks. Dose escalation was based on tolerability, as judged by the investigator and on the average of three fasting plasma glucose (FPG) measurements performed by the subject at home on the 3 consecutive days before the dose escalation visit being >6.1 mmol/L (110 mg/dL). Subjects were treated with doses of 0.6, 1.2 or 1.8 after dose escalation.

Arm title	Placebo

Arm description:

After the run-in period, subjects were randomized to receive placebo (in combination with metformin with or without basal insulin, on a background of diet and exercise) for a 26 weeks double blind treatment period. After 26 weeks, participants discontinued placebo and continued treatment with metformin (with or without basal insulin) during the open-label period.

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 s.c. injections, either in the abdomen, thigh or upper arm. The liraglutide placebo was administered once daily subcutaneously in equivalent volume as liraglutide.

Number of subjects in period 1[1]	Liraglutide 1.8 mg	Placebo
Started	66	68
Completed	56	53
Not completed	10	15
Adverse Event	-	1
Withdrawal criteria	6	7
Non-compliance	4	4
Unclassified	-	3

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: In total, 135 subjects were randomised (66 subjects to liraglutide and 69 subjects to placebo); of these, one subject in the placebo group was not exposed to treatment. Thus, 134 subjects were exposed to either liraglutide or placebo (66 subjects to liraglutide and 68 subjects to placebo).

Period 2

Period 2 title	Follow up 1 (Week 104)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Liraglutide 1.8 mg: Follow-up 1

Arm description:

Subjects treated with liraglutide for more than 3 months during the treatment period; were followed up until week 104 after trial drug cessation at week 52.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2[2]	Liraglutide 1.8 mg: Follow-up 1
Started	52
Completed	50
Not completed	2
Consent withdrawn by subject	1

Lost to follow-up	1

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Subjects who received liraglutide for more than 3 months during the treatment period (week 0-52), were followed-up at week 104.

Period 3

Period 3 title	Follow up 2 (Week 156)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Liraglutide 1.8 mg: Follow-up 2

Arm description:

Subjects treated with liraglutide for more than 3 months during the treatment period; were followed up until week 156 after trial drug cessation at week 52.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 3[3]	Liraglutide 1.8 mg: Follow-up 2
Started	48
Completed	48

Notes:

[3] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Subjects who received liraglutide for more than 3 months during the treatment period (week 0-52), were followed-up at week 156.

Baseline characteristics

Reporting groups	
Reporting group title	Liraglutide 1.8 mg

Reporting group description:

After the run-in period, subjects were randomized to receive liraglutide subcutaneous injections once daily (in combination with metformin with or without basal insulin, on a background of diet and exercise) for 52 weeks (26 weeks double blind treatment period followed by a 26-week open-label extension period). Subjects treated with liraglutide for more than 3 months were asked to return for follow-up visits one and two years after the end of the open label period (after trial drug cessation at week 52).

Reporting group title	Placebo

Reporting group description:

After the run-in period, subjects were randomized to receive placebo (in combination with metformin with or without basal insulin, on a background of diet and exercise) for a 26 weeks double blind treatment period. After 26 weeks, participants discontinued placebo and continued treatment with metformin (with or without basal insulin) during the open-label period.

Reporting group values	Liraglutide 1.8 mg	Placebo	Total
Number of subjects	66	68	134
Age Categorical Units: Subjects			
10-14 years at end of treatment	21	19	40
> 14 years at end of treatment	45	49	94
Age Continuous Units: years			
arithmetic mean	14.57	14.57	
standard deviation	± 1.73	± 1.73	-
Gender Categorical Units: Subjects			
Female	41	42	83
Male	25	26	51
Race Units: Subjects			
American Indian or Alaska Native	2	1	3
Asian	10	8	18
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	9	7	16
White	42	45	87
More than one race	0	0	0
Unknown or Not Reported	3	7	10
Ethnicity Units: Subjects			
Hispanic or Latino	16	23	39
Not Hispanic or Latino	50	45	95
Glycosylated hemoglobin (HbA1c) Units: Percentage of HbA1c			
arithmetic mean	7.87	7.69	
standard deviation	± 1.35	± 1.34	-

End points

End points reporting groups

Reporting group title	Liraglutide 1.8 mg

Reporting group description:

After the run-in period, subjects were randomized to receive liraglutide subcutaneous injections once daily (in combination with metformin with or without basal insulin, on a background of diet and exercise) for 52 weeks (26 weeks double blind treatment period followed by a 26-week open-label extension period). Subjects treated with liraglutide for more than 3 months were asked to return for follow-up visits one and two years after the end of the open label period (after trial drug cessation at week 52).

Reporting group title	Placebo

Reporting group description:

After the run-in period, subjects were randomized to receive placebo (in combination with metformin with or without basal insulin, on a background of diet and exercise) for a 26 weeks double blind treatment period. After 26 weeks, participants discontinued placebo and continued treatment with metformin (with or without basal insulin) during the open-label period.

Reporting group title	Liraglutide 1.8 mg: Follow-up 1

Reporting group description:

Subjects treated with liraglutide for more than 3 months during the treatment period; were followed up until week 104 after trial drug cessation at week 52.

Reporting group title	Liraglutide 1.8 mg: Follow-up 2

Reporting group description:

Subjects treated with liraglutide for more than 3 months during the treatment period; were followed up until week 156 after trial drug cessation at week 52.

Subject analysis set title	Liraglutide 1.8 mg: Follow-up 1 and 2
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects who received liraglutide for more than 3 months during the treatment period (week 0-52), were followed-up at weeks 104 and 156.

Primary: Change in HbA1c - week 26

End point title	Change in HbA1c - week 26

End point description:

Change in HbA1c from baseline to week 26. All available data were used for the primary analysis, including data collected after treatment discontinuation and initiation of rescue medication. Full analysis set (FAS) – included all randomised subjects receiving at least one dose of liraglutide/placebo.

End point type	Primary

End point timeframe:

From baseline to week 26

End point values	Liraglutide 1.8 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	68		
Units: Percentage of HbA1c				
least squares mean (standard error)	-0.643 (± 0.215)	0.415 (± 0.216)		

Statistical analyses

Statistical analysis title	Liraglutide 1.8 mg vs. Placebo

Statistical analysis description:

Analysis using a pattern mixture model of observed data with missing observations imputed from the placebo arm based on multiple (x10.000) imputations. The data for week 26 were then analysed with an ANCOVA model containing treatment, sex and age group as fixed effects and baseline value as covariate. The estimated treatment differences and confidence intervals were combined using Rubins formula.

Comparison groups	Liraglutide 1.8 mg v Placebo
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.001
Method	Pattern Mixture Model
Parameter estimate	Treatment difference
Point estimate	-1.058
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.653
upper limit	-0.464
Variability estimate	Standard error of the mean
Dispersion value	0.304

Notes:

[1] - Stepwise hierarchical testing procedure was applied for confirmatory endpoints:

Step 1: Primary analysis: change from baseline to week 26 in HbA1c

Superiority of liraglutide over placebo was to be concluded if the 95% confidence interval for the treatment difference for change from baseline in HbA1c (%) after 26 weeks of randomised treatment was entirely below 0%, implying that the two sided p-value was less than 5%.

Secondary: Change from baseline in fasting plasma glucose (FPG) - week 26

End point title	Change from baseline in fasting plasma glucose (FPG) - week 26

End point description:

Change in FPG from baseline to week 26. All available data were used for the analysis, including data collected after treatment discontinuation and initiation of rescue medication. Analysis was based on full analysis set.

End point type	Secondary

End point timeframe:

Week 0, week 26

End point values	Liraglutide 1.8 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	68		
Units: mmol/L				
least squares mean (standard error)	-1.076 (± 0.436)	0.801 (± 0.449)		

Statistical analyses

Statistical analysis title	Liraglutide 1.8 mg vs Placebo

Statistical analysis description:

Analysis using a pattern mixture model of observed data with missing observations imputed from the placebo arm based on multiple (x10.000) imputations. The data for weeks 26 were then analysed with an ANCOVA model containing treatment, sex and age group as fixed effects and baseline value as covariate. The estimated treatment differences and confidence intervals were combined using Rubins formula.

Comparison groups	Liraglutide 1.8 mg v Placebo
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.002
Method	Pattern Mixture Model
Parameter estimate	Treatment difference
Point estimate	-1.878
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.093
upper limit	-0.662
Variability estimate	Standard error of the mean
Dispersion value	0.62

Notes:

[2] - Stepwise hierarchical testing procedure was applied for confirmatory endpoints:

Step 2: Change from baseline in FPG after 26 weeks of treatment.

Secondary: Change in FPG - week 52

End point title	Change in FPG - week 52

End point description:

Change in FPG from baseline to week 52. All available data were used for the analysis, including data collected after treatment discontinuation and initiation of rescue medication. Analysis was based on full analysis set. Number of participants analysed=participants with available data.

End point type	Secondary

End point timeframe:

Week 0, week 52

End point values	Liraglutide 1.8 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	53		
Units: mmol/L				
arithmetic mean (standard deviation)	-1.627 (± 2.717)	0.983 (± 3.954)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in body mass index (BMI) standard deviation score (SDS) - week 26

End point title	Change from baseline in body mass index (BMI) standard deviation score (SDS) - week 26

End point description:

Change in BMI SDS from baseline to week 26. BMI SDS was calculated using the following formula: Z=[(value /M)^L - 1] / S*L; where L, M and S are median (M), skewness (L) and variation coefficient (S) of children/adolescents' BMI provided for each sex and age. For each subject, a standard deviation score Z (SDS) was calculated based on age and sex referring to the values L, M and S. The method is described in the world health organisation (WHO) Multicentre Growth Reference, which also contains the values for L, M and S by age and sex. For Z (SDS) scores below −3 and above 3, the score was adjusted as described in the WHO instruction. All available data were used for the analysis including data collected after treatment discontinuation and initiation of rescue medication. Full analysis set. Number of participants analysed=participants with available data.

End point type	Secondary

End point timeframe:

Week 0, week 26

End point values	Liraglutide 1.8 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	68		
Units: SDS score				
least squares mean (standard error)	-0.254 (± 0.039)	-0.208 (± 0.039)		

Statistical analyses

Statistical analysis title	Liraglutide 1.8 mg vs Placebo

Statistical analysis description:

Analysis using a pattern mixture model of observed data with missing observations imputed from the placebo arm based on multiple (x10.000) imputations. The data for weeks 26 were then analysed with an ANCOVA model containing treatment, sex and age group as fixed effects and baseline value as covariate. The estimated treatment differences and confidence intervals were combined using Rubins formula.

Comparison groups	Liraglutide 1.8 mg v Placebo
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.392
Method	Pattern Mixture Model
Parameter estimate	Treatment difference
Point estimate	-0.047
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.153
upper limit	0.06

Variability estimate	Standard error of the mean
Dispersion value	0.055

Notes:

[3] - Stepwise hierarchical testing procedure was applied for confirmatory endpoints:

Step 4: Change from baseline in BMI SDS after 26 weeks of treatment.

Secondary: Change from baseline in BMI standard deviation score (SDS) - week 52

End point title	Change from baseline in BMI standard deviation score (SDS) - week 52

End point description:

Change in BMI SDS from baseline to week 52. BMI SDS was calculated using the following formula: Z=[(value /M)^L - 1] / S*L; where L, M and S are median (M), skewness (L) and variation coefficient (S) of children/adolescents' BMI provided for each sex and age. For each subject, a standard deviation score Z (SDS) was calculated based on age and sex referring to the values L, M and S. The method is described in the WHO Multicentre Growth Reference, which also contains the values for L, M and S by age and sex. For Z (SDS) scores below −3 and above 3, the score was adjusted as described in the WHO instruction. All available data were used for the analysis including data collected after treatment discontinuation and initiation of rescue medication. Analysis was based on full analysis set. Number of participants analysed=participants with available data.

End point type	Secondary

End point timeframe:

Week 0, week 52

End point values	Liraglutide 1.8 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	53		
Units: SDS Score				
arithmetic mean (standard error)	-0.361 (± 0.542)	-0.166 (± 0.330)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects having HbA1c below 7.0% - week 26

End point title	Number of subjects having HbA1c below 7.0% - week 26

End point description:

Estimated percentage of subjects having HbA1c <7.0% at week 26. All available data were used for the analysis including data collected after treatment discontinuation and initiation of rescue medication. Analysis was based on full analysis set.

End point type	Secondary

End point timeframe:

Week 26

End point values	Liraglutide 1.8 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	68		
Units: Percentage of subjects				
number (not applicable)	63.7	36.5		

Statistical analyses

Statistical analysis title	Liraglutide 1.8 mg vs Placebo

Statistical analysis description:

Missing data was imputed using pattern mixture model. For each imputed data set the binary response was analysed in a logistic regression model using a logit link with treatment and stratification group (gender*age group) as fixed factors and baseline HbA1c as covariate.The estimated treatment effects and confidence intervals were combined using Rubin´s formula.

Comparison groups	Liraglutide 1.8 mg v Placebo
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	< 0.001
Method	Logistic Regression Model
Parameter estimate	Treatment odds ratio
Point estimate	5.353
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.105
upper limit	13.615

Notes:

[4] - Stepwise hierarchical testing procedure was applied for confirmatory endpoints:

Step 3: HbA1c < 7.0% after 26 weeks of treatment.

Secondary: Number of subjects having HbA1c below 7.0% - week 52

End point title	Number of subjects having HbA1c below 7.0% - week 52

End point description:

Number of subjects achieving HbA1c <7.0% after 52 weeks. All available data were used for the analysis including data collected after treatment discontinuation and initiation of rescue medication. Full analysis set. Number of participants analysed=participants with available data.

End point type	Secondary

End point timeframe:

Week 52

End point values	Liraglutide 1.8 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	52		
Units: participants				
Yes	27	16		
No	29	36		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects having HbA1c maximum 6.5% - week 26

End point title	Number of subjects having HbA1c maximum 6.5% - week 26

End point description:

Number of subjects achieving HbA1c <=6.5% after 26 weeks. All available data were used for the analysis including data collected after treatment discontinuation and initiation of rescue medication. Full analysis set. Number of participants analysed=participants with available data.

End point type	Secondary

End point timeframe:

Week 26

End point values	Liraglutide 1.8 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	58		
Units: participants				
Yes	28	19		
No	31	39		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects having HbA1c maximum 6.5% - week 52

End point title	Number of subjects having HbA1c maximum 6.5% - week 52

End point description:

Number of subjects achieving HbA1c <=6.5% after 52 weeks. All available data were used for the analysis including data collected after treatment discontinuation and initiation of rescue medication. Full analysis set. Number of participants analysed=participants with available data.

End point type	Secondary

End point timeframe:

Week 52

End point values	Liraglutide 1.8 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	52		
Units: participants				
Yes	25	13		
No	31	39		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects having HbA1c below 7.0% without severe or minor hypoglycaemic episodes - week 26

End point title	Number of subjects having HbA1c below 7.0% without severe or minor hypoglycaemic episodes - week 26

End point description:

Number of subjects achieving HbA1c <7.0% without severe or minor hypoglycaemic episodes after 26 weeks.
Severe hypoglycaemia: An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.
Minor hypoglycaemia was defined as meeting either of the below criteria:
1) an episode with symptoms consistent with hypoglycaemia with confirmation by blood glucose <2.8 mmol/L (50 mg/dL) or plasma glucose <3.1 mmol/L (56 mg/dL), and which was handled by the subject him/herself
2) any asymptomatic blood glucose value <2.8 mmol/L (50 mg/dL) or plasma glucose value <3.1 mmol/L (56 mg/dL)
All available data were used for the analysis including data collected after treatment discontinuation and initiation of rescue medication. Analysis was based on full analysis set. Number of participants analysed=participants with available data.

End point type	Secondary

End point timeframe:

Week 26

End point values	Liraglutide 1.8 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	58		
Units: participants				
Yes	31	21		
No	28	37		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects having HbA1c below 7.0% without severe or minor hypoglycaemic episodes - week 52

End point title	Number of subjects having HbA1c below 7.0% without severe or minor hypoglycaemic episodes - week 52

End point description:

Number of subjects achieving HbA1c <7.0% without severe or minor hypoglycaemic episodes after 52 weeks.
Severe hypoglycaemia: An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.
Minor hypoglycaemia was defined as meeting either of the below criteria:
1) an episode with symptoms consistent with hypoglycaemia with confirmation by blood glucose <2.8 mmol/L (50 mg/dL) or plasma glucose <3.1 mmol/L (56 mg/dL), and which was handled by the subject him/herself
2) any asymptomatic blood glucose value <2.8 mmol/L (50 mg/dL) or plasma glucose value <3.1 mmol/L (56 mg/dL)
All available data were used for the analysis including data collected after treatment discontinuation and initiation of rescue medication. Analysis was based on full analysis set. Number of participants analysed=participants with available data.

End point type	Secondary

End point timeframe:

Week 52

End point values	Liraglutide 1.8 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	52		
Units: participants				
Yes	22	16		
No	34	36		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in mean 7-point self-measured plasma glucose - week 26

End point title	Change in mean 7-point self-measured plasma glucose - week 26

End point description:

Change in mean 7-point self-measured plasma glucose after 26 weeks. Subjects were instructed to measure their plasma glucose at following timepoints: before breakfast, 90 minutes after start of breakfast, before lunch, 90 minutes after start of lunch, before dinner, 90 minutes after start of dinner and at bedtime. Mean 7-point SMPG was defined as the area under the profile (calculated using the trapezoidal method) divided by time. All available data were used for the analysis including data collected after treatment discontinuation and initiation of rescue medication. Analysis was based on full analysis set. Number of participants analysed=participants with available data.

End point type	Secondary

End point timeframe:

Week 0, week 26

End point values	Liraglutide 1.8 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	46		
Units: mmol/L				
arithmetic mean (standard deviation)	-2.384 (± 2.638)	0.198 (± 2.056)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in 7-point self-measured plasma glucose - week 52

End point title	Change from baseline in 7-point self-measured plasma glucose - week 52

End point description:

Change in mean 7-point self-measured plasma glucose after 52 weeks. Subjects were instructed to measure their plasma glucose at following timepoints: before breakfast, 90 minutes after start of breakfast, before lunch, 90 minutes after start of lunch, before dinner, 90 minutes after start of dinner and at bedtime. Mean 7-point SMPG was defined as the area under the profile (calculated using the trapezoidal method) divided by time. All available data were used for the analysis including data collected after treatment discontinuation and initiation of rescue medication. Analysis was based on full analysis set. Number of participants analysed=participants with available data.

End point type	Secondary

End point timeframe:

Week 0, week 52

End point values	Liraglutide 1.8 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	39		
Units: mmol/L				
arithmetic mean (standard deviation)	-2.309 (± 2.968)	-0.748 (± 1.944)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in body weight - week 26

End point title	Change from baseline in body weight - week 26

End point description:

Change from baseline in body weight after 26 weeks. All available data were used for the analysis including data collected after treatment discontinuation and initiation of rescue medication. Analysis was based on full analysis set. Number of participants analysed=participants with available data.

End point type	Secondary

End point timeframe:

Week 0, week 26

End point values	Liraglutide 1.8 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	58		
Units: kg				
arithmetic mean (standard deviation)	-2.48 (± 5.59)	-0.87 (± 3.84)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in body weight - week 52

End point title	Change from baseline in body weight - week 52

End point description:

Change from baseline in body weight after 52 weeks. All available data were used for the analysis including data collected after treatment discontinuation and initiation of rescue medication. Analysis was based on full analysis set. Number of participants analysed=participants with available data.

End point type	Secondary

End point timeframe:

Week 0, week 52

End point values	Liraglutide 1.8 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	53		
Units: kg				
arithmetic mean (standard deviation)	-2.27 (± 8.05)	1.02 (± 4.64)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of adverse events - week 26

End point title	Number of adverse events - week 26

End point description:

Total number of adverse events during 26 weeks. Analysis was based on safety analysis set which included all subjects receiving at least one dose of liraglutide/placebo

End point type	Secondary

End point timeframe:

0-26 weeks

End point values	Liraglutide 1.8 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	68		
Units: events	310	230		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of adverse events - week 52

End point title	Number of adverse events - week 52

End point description:

Total number of adverse events during entire treatment period (during 52 weeks). Analysis was based on the safety analysis set.

End point type	Secondary

End point timeframe:

0-52 weeks

End point values	Liraglutide 1.8 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	68		
Units: events	426	321		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of adverse events- week 104

End point title	Number of adverse events- week 104

End point description:

Total number of adverse events during the follow up 1 period (53 - 104 weeks). Analysis was based on the safety analysis set- Subjects who received liraglutide for more than 3 months during the treatment period (week 0-52) and provided safety follow-up data anytime during week 53-104.

End point type	Secondary

End point timeframe:

1 year after last patient last visit (LPLV)

End point values	Liraglutide 1.8 mg: Follow-up 1			
Subject group type	Reporting group			
Number of subjects analysed	52			
Units: events	30			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of adverse events- week 156

End point title	Number of adverse events- week 156

End point description:

Total number of adverse events during the follow up period (53 - 156 weeks). Analysis was based on the safety analysis set- Subjects who received liraglutide for more than 3 months during the treatment period (week 0-52) and provided safety follow-up data anytime during week 53-156.

End point type	Secondary

End point timeframe:

after 2 years after LPLV

End point values	Liraglutide 1.8 mg: Follow-up 1 and 2			
Subject group type	Subject analysis set			
Number of subjects analysed	52			
Units: events	47			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of serious adverse events - week 26

End point title	Number of serious adverse events - week 26

End point description:

Total number of serious adverse events during 26 weeks. Analysis was based on the safety analysis set.

End point type	Secondary

End point timeframe:

0-26 weeks

End point values	Liraglutide 1.8 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	68		
Units: events	7	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of serious adverse events - week 52

End point title	Number of serious adverse events - week 52

End point description:

0-52 weeks

End point type	Secondary

End point timeframe:

Total number of serious adverse events during entire treatment period (during 52 weeks). Analysis was based on the safety analysis set.

End point values	Liraglutide 1.8 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	68		
Units: events	10	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Nuber of serious adverse events- week 104

End point title	Nuber of serious adverse events- week 104

End point description:

Total number of serious adverse events during the follow up 1 period (53 - 104 weeks). Analysis was based on the safety analysis set- Subjects who received liraglutide for more than 3 months during the treatment period week 0-52 and provided safety follow-up data anytime during week 53-104.

End point type	Secondary

End point timeframe:

1 year after LPLV

End point values	Liraglutide 1.8 mg: Follow-up 1			
Subject group type	Reporting group			
Number of subjects analysed	52			
Units: events	7			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of serious adverse events- week 156

End point title	Number of serious adverse events- week 156

End point description:

Total number of serious adverse events during the follow up period (53 - 156 weeks). Analysis was based on the safety analysis set- Subjects who received liraglutide for more than 3 months during the treatment period week 0-52 and provided safety follow-up data anytime during week 53-156.

End point type	Secondary

End point timeframe:

2 years after LPLV

End point values	Liraglutide 1.8 mg: Follow-up 1 and 2			
Subject group type	Subject analysis set			
Number of subjects analysed	52			
Units: events	9			

Statistical analyses

No statistical analyses for this end point

Secondary: Growth velocity- week 104

End point title	Growth velocity- week 104

End point description:

Growth (i.e., height velocity) is the change in height per year and is measured in cm/year. The height velocity was calculated as the difference between current height and height at week 0 divided by the time (in days) between those measurement time points and multiplied by 365 days. Analysis was based on the safety analysis set- Subjects who received liraglutide for more than 3 months during the treatment period week 0-52 and provided safety follow-up data anytime during week 53-104.

End point type	Secondary

End point timeframe:

1 year after LPLV

End point values	Liraglutide 1.8 mg: Follow-up 1			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: cm/year				
arithmetic mean (standard deviation)	1.149 (± 1.776)			

Statistical analyses

No statistical analyses for this end point

Secondary: Growth velocity- week 156

End point title	Growth velocity- week 156

End point description:

Growth (i.e., height velocity) is the change in height per year and is measured in cm/year. The height velocity was calculated as the difference between current height and height at week 0 divided by the time (in days) between those measurement time points and multiplied by 365 days. Analysis was based on the safety analysis set- Subjects who received liraglutide for more than 3 months during the treatment period week 0-52 and provided safety follow-up data anytime during week 53-156.

End point type	Secondary

End point timeframe:

2 years after LPLV

End point values	Liraglutide 1.8 mg: Follow-up 1 and 2			
Subject group type	Subject analysis set			
Number of subjects analysed	45[5]			
Units: cm/year				
arithmetic mean (standard deviation)	1.100 (± 1.504)			

Notes:

[5] - Number of subjects with available data at week 156.

Statistical analyses

No statistical analyses for this end point

Secondary: Pubertal progression- week 104

End point title	Pubertal progression- week 104

End point description:

Pubertal development was assessed in 3 areas (breast, penis and pubic hair development) by the Tanner staging in accordance with stages I-V, where stage I represents “pre-adoloscent development” and stage V represents “pubertal development equivalent to that of an adult”. The Tanner staging assessment was no longer required to be performed once a subject reached the Tanner stage V, as judged by the investigator. Reported results are number of participants at different Tanner stages at week 104. Analysis was based on the safety analysis set- Subjects who received liraglutide for more than 3 months during the treatment period week 0-52 and provided safety follow-up data anytime during week 53-104.

End point type	Secondary
End point timeframe:	
1 year after LPLV	

End point values	Liraglutide 1.8 mg: Follow-up 1			
Subject group type	Reporting group			
Number of subjects analysed	52			
Units: Subjects				
Female- Breast development: Stage I (n=16)	0			
Female- Breast development: Stage II (n=16)	0			
Female- Breast development: Stage III (n=16)	0			
Female- Breast development: Stage IV (n=16)	5			
Female- Breast development: Stage V (n=16)	11			
Male- Penis development: Stage I (n=14)	0			
Male- Penis development: Stage II (n=14)	1			
Male- Penis development: Stage III (n=14)	0			
Male- Penis development: Stage IV (n=14)	5			
Male- Penis development: Stage V (n=14)	8			
Female- Pubic hair development: Stage I (n=16)	0			
Female- Pubic hair development: Stage II (n=16)	0			
Female- Pubic hair development: Stage III (n=16)	1			
Female- Pubic hair development: Stage IV (n=16)	2			
Female- Pubic hair development: Stage V (n=16)	13			
Male- Pubic hair development: Stage I (n=14)	0			
Male- Pubic hair development: Stage II (n=14)	1			
Male- Pubic hair development: Stage III (n=14)	0			
Male- Pubic hair development: Stage IV (n=14)	4			
Male- Pubic hair development: Stage V (n=14)	9			

Statistical analyses

No statistical analyses for this end point

Secondary: Pubertal progression- week 156

End point title	Pubertal progression- week 156

End point description:

Pubertal development was assessed in 3 areas (breast, penis and pubic hair development) by the Tanner staging in accordance with stages I-V, where stage I represents "pre-adoloscent development" and stage V represents "pubertal development equivalent to that of an adult". The Tanner staging assessment was no longer required to be performed once a subject reached the Tanner stage V, as judged by the investigator. Reported results are number of participants at different Tanner stages at week 156. Analysis was based on the safety analysis set- Subjects who received liraglutide for more than 3 months during the treatment period week 0-52 and provided safety follow-up data anytime during week 53-156.

End point type	Secondary

End point timeframe:

2 years after LPLV

End point values	Liraglutide 1.8 mg: Follow-up 1 and 2			
Subject group type	Subject analysis set			
Number of subjects analysed	27[6]			
Units: subjects				
Female- Breast development: Stage I (n=14)	0			
Female- Breast development: Stage II (n=14)	0			
Female- Breast development: Stage III (n=14)	0			
Female- Breast development: Stage IV (n=14)	3			
Female- Breast development: Stage V (n=14)	11			
Male- Penis development: Stage I (n=13)	0			
Male- Penis development: Stage II (n=13)	0			
Male- Penis development: Stage III (n=13)	1			
Male- Penis development: Stage IV (n=13)	3			
Male- Penis development: Stage V (n=13)	9			
Female- Pubic hair development: Stage I (n=13)	0			
Female- Pubic hair development: Stage II (n=13)	0			
Female- Pubic hair development: Stage III (n=13)	0			
Female- Pubic hair development: Stage IV (n=13)	2			
Female- Pubic hair development: Stage V (n=13)	11			
Male- Pubic hair development: Stage I (n=14)	0			

Male- Pubic hair development: Stage II (n=14)	0			
Male- Pubic hair development: Stage III (n=14)	1			
Male- Pubic hair development: Stage IV (n=14)	3			
Male- Pubic hair development: Stage V (n=14)	10			

Notes:

[6] - Number of subjects with available data at week 156.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Week 0 - 156
All presented AEs are TEAEs. A TEAE was defined as an event that had onset date on or after the first day of exposure to trial product and no later than 7 days after the last day of trial product administration.

Adverse event reporting additional description:

Results are based on SAS: subjects who received at least one dose of liraglutide or placebo for "Liraglutide 1.8 mg- Treatment period" and "Placebo" and who received liraglutide for more than 3 months and provided follow-up data anytime during weeks 53-156.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21

Reporting groups

Reporting group title	Liraglutide 1.8 mg

Reporting group description:

After the run-in period, subjects were randomized to receive liraglutide subcutaneous injections once daily (in combination with metformin with or without basal insulin, on a background of diet and exercise) for 52 weeks (26 weeks double blind treatment period followed by a 26-week open-label extension period). Subjects treated with liraglutide for more than 3 months were asked to return for follow-up visits one and two years after the end of the open label period (after trial drug cessation at week 52).

Reporting group title	Placebo

Reporting group description:

After the run-in period, subjects were randomized to receive placebo (in combination with metformin with or without basal insulin, on a background of diet and exercise) for a 26 weeks double blind treatment period. After 26 weeks, participants discontinued placebo and continued treatment with metformin (with or without basal insulin) during the open-label period.

Reporting group title	Liraglutide 1.8 mg: Follow-up 1

Reporting group description:

Subjects treated with liraglutide for more than 3 months during the treatment period; were followed up until week 104 after trial drug cessation at week 52.

Reporting group title	Liraglutide 1.8 mg: Follow-up 2

Reporting group description:

Subjects treated with liraglutide for more than 3 months during the treatment period; were followed up until week 156 after trial drug cessation at week 52.

Serious adverse events	Liraglutide 1.8 mg	Placebo	Liraglutide 1.8 mg: Follow-up 1
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 66 (13.64%)	4 / 68 (5.88%)	7 / 52 (13.46%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Fibroadenoma of breast			

subjects affected / exposed	1 / 66 (1.52%)	0 / 68 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Glycosylated haemoglobin increased			
subjects affected / exposed	1 / 66 (1.52%)	1 / 68 (1.47%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Fasciotomy			
subjects affected / exposed	0 / 66 (0.00%)	0 / 68 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic surgery			
subjects affected / exposed	0 / 66 (0.00%)	0 / 68 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Nervous system disorder			
subjects affected / exposed	1 / 66 (1.52%)	0 / 68 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 66 (1.52%)	0 / 68 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 66 (1.52%)	0 / 68 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			

subjects affected / exposed	1 / 66 (1.52%)	0 / 68 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 66 (0.00%)	0 / 68 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malocclusion			
subjects affected / exposed	0 / 66 (0.00%)	0 / 68 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depressive symptom			
subjects affected / exposed	0 / 66 (0.00%)	0 / 68 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Scoliosis			
subjects affected / exposed	1 / 66 (1.52%)	0 / 68 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess neck			
subjects affected / exposed	1 / 66 (1.52%)	0 / 68 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis perforated			
subjects affected / exposed	0 / 66 (0.00%)	1 / 68 (1.47%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 66 (0.00%)	1 / 68 (1.47%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Viral infection			
subjects affected / exposed	1 / 66 (1.52%)	0 / 68 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subcutaneous abscess			
subjects affected / exposed	0 / 66 (0.00%)	0 / 68 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 66 (0.00%)	0 / 68 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 66 (0.00%)	1 / 68 (1.47%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	1 / 66 (1.52%)	1 / 68 (1.47%)	2 / 52 (3.85%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Liraglutide 1.8 mg: Follow-up 2		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 48 (4.17%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Fibroadenoma of breast			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
Glycosylated haemoglobin increased			

subjects affected / exposed	0 / 48 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Fasciotomy			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolic surgery			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Nervous system disorder			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Constipation			

subjects affected / exposed	0 / 48 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Malocclusion				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Depressive symptom				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Scoliosis				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Abscess neck				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Appendicitis perforated				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Viral infection				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Subcutaneous abscess			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Appendicitis			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Liraglutide 1.8 mg	Placebo	Liraglutide 1.8 mg: Follow-up 1
Total subjects affected by non-serious adverse events			
subjects affected / exposed	45 / 66 (68.18%)	49 / 68 (72.06%)	7 / 52 (13.46%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 66 (0.00%)	4 / 68 (5.88%)	0 / 52 (0.00%)
occurrences (all)	0	5	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	8 / 66 (12.12%)	2 / 68 (2.94%)	0 / 52 (0.00%)
occurrences (all)	10	4	0
Headache			
subjects affected / exposed	14 / 66 (21.21%)	13 / 68 (19.12%)	0 / 52 (0.00%)
occurrences (all)	27	39	0
General disorders and administration site conditions			

Pyrexia			
subjects affected / exposed	4 / 66 (6.06%)	5 / 68 (7.35%)	0 / 52 (0.00%)
occurrences (all)	5	5	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	11 / 66 (16.67%)	5 / 68 (7.35%)	1 / 52 (1.92%)
occurrences (all)	22	6	1
Abdominal pain upper			
subjects affected / exposed	2 / 66 (3.03%)	8 / 68 (11.76%)	0 / 52 (0.00%)
occurrences (all)	3	9	0
Constipation			
subjects affected / exposed	4 / 66 (6.06%)	1 / 68 (1.47%)	1 / 52 (1.92%)
occurrences (all)	4	1	1
Diarrhoea			
subjects affected / exposed	15 / 66 (22.73%)	11 / 68 (16.18%)	0 / 52 (0.00%)
occurrences (all)	21	13	0
Dyspepsia			
subjects affected / exposed	5 / 66 (7.58%)	1 / 68 (1.47%)	1 / 52 (1.92%)
occurrences (all)	6	1	1
Nausea			
subjects affected / exposed	19 / 66 (28.79%)	9 / 68 (13.24%)	1 / 52 (1.92%)
occurrences (all)	25	12	1
Vomiting			
subjects affected / exposed	17 / 66 (25.76%)	6 / 68 (8.82%)	2 / 52 (3.85%)
occurrences (all)	46	8	2
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	3 / 66 (4.55%)	6 / 68 (8.82%)	0 / 52 (0.00%)
occurrences (all)	10	11	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 66 (6.06%)	4 / 68 (5.88%)	0 / 52 (0.00%)
occurrences (all)	7	5	0
Oropharyngeal pain			
subjects affected / exposed	4 / 66 (6.06%)	6 / 68 (8.82%)	0 / 52 (0.00%)
occurrences (all)	6	10	0

Rhinorrhoea			
subjects affected / exposed	1 / 66 (1.52%)	4 / 68 (5.88%)	0 / 52 (0.00%)
occurrences (all)	2	4	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	4 / 66 (6.06%)	1 / 68 (1.47%)	0 / 52 (0.00%)
occurrences (all)	5	1	0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	7 / 66 (10.61%)	2 / 68 (2.94%)	0 / 52 (0.00%)
occurrences (all)	8	2	0
Influenza			
subjects affected / exposed	4 / 66 (6.06%)	6 / 68 (8.82%)	0 / 52 (0.00%)
occurrences (all)	6	9	0
Nasopharyngitis			
subjects affected / exposed	11 / 66 (16.67%)	19 / 68 (27.94%)	2 / 52 (3.85%)
occurrences (all)	16	28	2
Pharyngitis			
subjects affected / exposed	4 / 66 (6.06%)	4 / 68 (5.88%)	0 / 52 (0.00%)
occurrences (all)	5	6	0
Upper respiratory tract infection			
subjects affected / exposed	6 / 66 (9.09%)	5 / 68 (7.35%)	0 / 52 (0.00%)
occurrences (all)	10	8	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	4 / 66 (6.06%)	3 / 68 (4.41%)	0 / 52 (0.00%)
occurrences (all)	4	3	0
Hyperglycaemia			
subjects affected / exposed	4 / 66 (6.06%)	4 / 68 (5.88%)	1 / 52 (1.92%)
occurrences (all)	4	4	1

Non-serious adverse events	Liraglutide 1.8 mg: Follow-up 2		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 48 (2.08%)		
Investigations			
Alanine aminotransferase increased			

subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all)	 0 / 48 (0.00%) 0 0 / 48 (0.00%) 0		
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	 0 / 48 (0.00%) 0		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Dyspepsia subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	 0 / 48 (0.00%) 0 0 / 48 (0.00%) 0 0 / 48 (0.00%) 0 0 / 48 (0.00%) 0 0 / 48 (0.00%) 0 0 / 48 (0.00%) 0 0 / 48 (0.00%) 0		
Reproductive system and breast disorders			

Dysmenorrhoea subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all) Rhinorrhoea subjects affected / exposed occurrences (all)	 0 / 48 (0.00%) 0 0 / 48 (0.00%) 0 0 / 48 (0.00%) 0		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	 0 / 48 (0.00%) 0		
Infections and infestations Gastroenteritis subjects affected / exposed occurrences (all) Influenza subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Pharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all)	 0 / 48 (0.00%) 0 0 / 48 (0.00%) 0 0 / 48 (0.00%) 0 1 / 48 (2.08%) 1 0 / 48 (0.00%) 0		
Metabolism and nutrition disorders Decreased appetite			

subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Hyperglycaemia			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 August 2012	Protocol changes were primarily driven by the EMA PDCO's acceptance of the request for PIP modification. Some of the changes to the trial design were requested by the FDA. Other minor changes concerned inconsistencies and typos. The key changes involved: - extension of metformin titration period and lowering the lower limit for metformin MTD. - allowing subjects entering the trial on >2000 mg/day of metformin to continue on current dose. - extension of metformin maintenance period during the run-in from 3 to 8 weeks. - extension of liraglutide dose escalation period from 2 to 3 weeks - changing the timing of the anti-liraglutide antibody measurement from week 52 to week 53 - extension of the double-blind treatment period from 14 to 26 weeks - allowing liraglutide dose escalation (to maximum 1.8 mg) as a rescue option - for subjects treated with placebo, allowing the addition of a second anti-diabetic agent as a rescue option - inclusion of testicular volume assessment by trained personnel in the Tanner staging assessment - requirement for the 52-week treatment period completion prior to subject reaching 17 years and 11 months - requirement of 30% of subjects to be aged between 10-14 years - exclusion from the trial of subjects previously treated with liraglutide (new exclusion criterion added) - use of another primary analysis method that does not rely on LOCF for the handling of missing data. A multiple imputation approach was to be used to handle missing data in the new primary analysis.
19 November 2012	Protocol changes were primarily driven by the FDA Paediatric Committee's request to include yearly bone age assessment due to a potential nonclinical safety signal for liraglutide of advancement of puberty. In addition, the text regarding the use of rescue medication was clarified. Other minor corrections and clarifications were implemented. The key changes involved: - inclusion of X-ray of left hand and wrist at randomisation and week 52 (all subjects) and at 1- and 2-year follow-up visits for subjects treated with liraglutide for >3 months - update of withdrawal criterion and rewording of the section on rescue medication
22 June 2013	An additional blood sample was included to ensure that FPG, biochemistry parameters an calcitonin were monitored during the open-label period. In addition, a number of protocol clarifications were implemented. The key changes included: 1. addition of a fasting blood sample at visit 22 (week 42) 2. clarification of age definition of ≤14 years 3. new reporting timelines for MESI

19 March 2015	Significant delays in subject recruitment led to this protocol amendment implemented in order to facilitate recruitment. The key changes included: 1. reducing the required duration of diabetes at screening from 90 to 30 days 2. inclusion of children and adolescents currently treated with basal insulin 3. change in method to evaluate randomisation criterion #1 (FPG measured prior to the randomisation visit (visit 7), must be ≥126 mg/dL (7.0 mmol/L) and ≤220 mg/dL (12.2 mmol/L). The measurement must be based on an average of fasting SMPG values taken on the 3 consecutive days leading up to the randomisation visit (visit 7)) 4. use of basal insulin as initial rescue therapy in both liraglutide and placebo treatment arms 5. elimination of the requirement for randomised treatment unblinding prior to rescue treatment initiation, since subjects in both treatment arms were to receive the same initial rescue treatment (basal insulin) 6. changes to trial completion timeline 7. reduction of sample size from 172 to 150 randomised subjects
18 April 2017	Due to recruitment difficulties, the planned sample size was reduced from 150 to 94 randomised subjects. The primary analysis was changed to a PMM analysis using a multiple imputations approach to account for missing data. Additional revisions and clarifications were also made to the "Statistical Considerations" section of the protocol.

Notes:

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/31034184

http://www.ncbi.nlm.nih.gov/pubmed/33634589