Clinical trial results:
Effect of liraglutide for weight management in pubertal adolescent subjects with obesity. 56-week, double-blind, randomised, parallel-group, placebo-controlled multi-national trial followed by a 26-week period off study-drug

Summary

EudraCT number	2014-004353-14
Trial protocol	SE BE
Global end of trial date	08 August 2019

Results information

Result version number	v1 (current)
This version publication date	21 February 2020
First version publication date	21 February 2020

Trial information

Trial identification

Sponsor protocol code	NN8022-4180

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02918279
WHO universal trial number (UTN)	U1111-1162-7101

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-PIP02-09
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	23 December 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 February 2019
Global end of trial reached?	Yes
Global end of trial date	08 August 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of liraglutide versus placebo on weight loss in adolescent subjects with obesity after 56 weeks of treatment

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (Last amended by the 64th World Medical Association General Assembly, Fortaleza, Brazil. October 2013) and ICH Good Clinical Practice, including archiving of essential documents (E6(R1), Step 4. 10 June 1996) and 21 CFR 312.120.

Background therapy:

Not applicable.

Evidence for comparator:

Not applicable.

Actual start date of recruitment	29 September 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 33
Country: Number of subjects enrolled	Mexico: 46
Country: Number of subjects enrolled	Russian Federation: 68
Country: Number of subjects enrolled	Sweden: 44
Country: Number of subjects enrolled	United States: 60
Worldwide total number of subjects	251
EEA total number of subjects	77

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0

Adolescents (12-17 years)	251
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This trial was conducted at 32 sites in 5 countries: Belgium (6 sites), Sweden (4 sites), Russia (8 sites), Mexico (2 sites) and the United States of America (USA - 12 sites). Additionally, 1 site in the USA was approved by the independent review board, but did not randomise any subject.

Pre-assignment

Screening details:

This trial consisted of a 12-week run-in period, during which participants received counselling on healthy nutrition and physical activity. Completed numbers include participants who completed the trial without prematurely discontinuing the trial product and participants who discontinued the trial product but came for the week 82 follow-up visit.

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	Investigator, Subject

Blinding implementation details:

Liraglutide and placebo injections were visually identical.

Arms

Are arms mutually exclusive?	Yes
Arm title	Liraglutide 3.0 mg

Arm description:

Subjects received liraglutide in a dose escalation manner for 56 weeks: 0.6 mg during week 1, 1.2 mg during week 2, 1.8 mg during week 3, 2.4 mg during week 4 and 3.0 mg from week 5 to week 56. There was a 26-week off-study-drug follow-up period (week 57–82).

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 was administered once daily by subcutaneous (s.c.; under the skin) injection in the abdomen, thigh or upper arm irrespective of the timing of meals.

Arm title	Placebo

Arm description:

Subjects received liraglutide matching placebo for 56 weeks. There was a 26-week off-study-drug follow-up period (week 57–82).

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:

Placebo for liraglutide was administered once daily by s.c. injection in the abdomen, thigh or upper arm irrespective of the timing of meals.

Number of subjects in period 1	Liraglutide 3.0 mg	Placebo
Started	125	126
Full analysis set	125	126
Safety analysis set	125	126
Completed	112	103
Not completed	13	23
Consent withdrawn by subject	5	15
Unspecified	3	1
Lost to follow-up	3	6
Withdrawal by parent/guardian	2	1

Baseline characteristics

Reporting groups	
Reporting group title	Liraglutide 3.0 mg
Reporting group description:	
Subjects received liraglutide in a dose escalation manner for 56 weeks: 0.6 mg during week 1, 1.2 mg during week 2, 1.8 mg during week 3, 2.4 mg during week 4 and 3.0 mg from week 5 to week 56. There was a 26-week off-study-drug follow-up period (week 57–82).	
Reporting group title	Placebo
Reporting group description:	
Subjects received liraglutide matching placebo for 56 weeks. There was a 26-week off-study-drug follow-up period (week 57–82).	

Reporting group values	Liraglutide 3.0 mg	Placebo	Total
Number of subjects	125	126	251
Age Categorical Units: Subjects			
Adolescents (12-17 years)	125	126	251
Age Continuous Units: years			
arithmetic mean	14.6	14.5	
standard deviation	± 1.6	± 1.6	-
Gender Categorical Units: Subjects			
Female	71	78	149
Male	54	48	102

End points

End points reporting groups

Reporting group title	Liraglutide 3.0 mg
Reporting group description:	
Subjects received liraglutide in a dose escalation manner for 56 weeks: 0.6 mg during week 1, 1.2 mg during week 2, 1.8 mg during week 3, 2.4 mg during week 4 and 3.0 mg from week 5 to week 56. There was a 26-week off-study-drug follow-up period (week 57–82).	
Reporting group title	Placebo
Reporting group description:	
Subjects received liraglutide matching placebo for 56 weeks. There was a 26-week off-study-drug follow-up period (week 57–82).	

Primary: Change in body mass index (BMI) standard deviation score (SDS)

End point title	Change in body mass index (BMI) standard deviation score (SDS)
End point description:	
Change from baseline (Wk 0) in BMI SDS was evaluated at Wk 56. 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 SDS Z 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. Results are based on the FAS and included both the participants who completed treatment for 56 weeks and participants who could not complete treatment for 56 weeks, but attended the follow-up visit at week 56.	
End point type	Primary
End point timeframe:	
From baseline (randomisation) to 56 weeks	

End point values	Liraglutide 3.0 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	105		
Units: SDS score				
arithmetic mean (standard deviation)	-0.25 (± 0.51)	-0.02 (± 0.54)		

Statistical analyses

Statistical analysis title	Liraglutide 3.0 mg – Placebo
Statistical analysis description:	
Analysis of in-trial data with missing observations was imputed from the placebo arm based on a jump to reference multiple (x100) imputation approach. Responses at week 56 were analysed using an analysis of covariance model with treatment, sex, region, baseline glycaemic category, stratification factor for Tanner stage and interaction between baseline glycaemic category and stratification factor for Tanner stage as fixed effects, baseline BMI SDS, age as covariates.	
Comparison groups	Placebo v Liraglutide 3.0 mg

Number of subjects included in analysis	218
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.0022
Method	ANCOVA
Parameter estimate	Treatment difference
Point estimate	-0.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.37
upper limit	-0.08

Notes:

[1] - The "number of subjects included in analysis" is being erroneously displayed as 218. Actual "number of subjects included in analysis" is 251.

Secondary: Percent of subjects achieving ≥5% reduction in baseline BMI

End point title	Percent of subjects achieving ≥5% reduction in baseline BMI

End point description:

Participants achieving more than or equal to 5% reduction in their baseline (week 0) body mass index (BMI) was evaluated at weeks 56. Results are based on the FAS and included both participants who completed the 56-week trial period and participants who could not complete the 56-week trial period, but attended the follow-up visit at week 56. The FAS included all randomised participants who had received at least one dose of trial product and had any post-randomisation data (according to the intention-to-treat [ITT] principle).

End point type	Secondary

End point timeframe:

At week 56

End point values	Liraglutide 3.0 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	105		
Units: Percentage of participants				
number (not applicable)				
Yes	45.1	19.0		
No	54.9	81.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of subjects achieving ≥10% reduction in baseline BMI

End point title	Percent of subjects achieving ≥10% reduction in baseline BMI

End point description:

Participants achieving more than or equal to 10% reduction in their baseline (week 0) BMI was evaluated at weeks 56. Results are based on the FAS and included both participants who completed the 56-week trial period and participants who could not complete the 56-week trial period, but attended the follow-up visit at week 56. The FAS included all randomised participants who had received at least one

dose of trial product and had any post-randomisation data (according to the ITT principle).

End point type	Secondary

End point timeframe:

At week 56

End point values	Liraglutide 3.0 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	105		
Units: Percentage of participants				
number (not applicable)				
Yes	29.2	8.6		
No	70.8	91.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in BMI from baseline to 56 weeks

End point title	Change in BMI from baseline to 56 weeks

End point description:

Change in BMI was evaluated from baseline (week 0) to weeks 56. Results are based on the FAS and included both participants who completed the 56-week trial period and participants who could not complete the 56-week trial period, but attended the follow-up visit at week 56. The FAS included all randomised participants who had received at least one dose of trial product and had any post-randomisation data (according to the ITT principle).

End point type	Secondary

End point timeframe:

From baseline to 56 weeks

End point values	Liraglutide 3.0 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	105		
Units: kg/m^2				
arithmetic mean (standard deviation)	-1.6 (± 3.1)	0.1 (± 3.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in body weight (kilogram [kg]) from baseline to 56 weeks

End point title	Change in body weight (kilogram [kg]) from baseline to 56

	weeks

End point description:

Change in body weight (kg) was evaluated from baseline (week 0) to weeks 56. Results are based on the FAS and included both participants who completed the 56-week trial period and participants who could not complete the 56-week trial period, but attended the follow-up visit at week 56. The FAS included all randomised participants who had received at least one dose of trial product and had any post-randomisation data (according to the ITT principle).

End point type	Secondary

End point timeframe:

From baseline to 56 weeks

End point values	Liraglutide 3.0 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	105		
Units: kg				
arithmetic mean (standard deviation)	-2.7 (± 9.1)	2.1 (± 10.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in body weight (pounds [lb]) from baseline to 56 weeks

End point title	Change in body weight (pounds [lb]) from baseline to 56 weeks

End point description:

Body weight was not analysed in pounds (lb). It was analysed for standard unit, ‘kg’ only.

End point type	Secondary

End point timeframe:

From baseline to 56 weeks

End point values	Liraglutide 3.0 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	0[3]		
Units: lb				
arithmetic mean (standard deviation)	()	()		

Notes:

[2] - Body weight was not analysed in pounds (lb). It was analysed for standard unit, ‘kg’ only.

[3] - Body weight was not analysed in pounds (lb). It was analysed for standard unit, ‘kg’ only.

Statistical analyses

No statistical analyses for this end point

Secondary: Change in body weight (percent [%]) from baseline to 56 weeks

End point title	Change in body weight (percent [%]) from baseline to 56 weeks

End point description:

Relative change in body weight (kg) was evaluated from baseline (week 0) to weeks 56. Results are based on the FAS and included both participants who completed the 56-week trial period and participants who could not complete the 56-week trial period, but attended the follow-up visit at week 56. The FAS included all randomised participants who had received at least one dose of trial product and had any post-randomisation data (according to the ITT principle).

End point type	Secondary

End point timeframe:

From baseline to 56 weeks

End point values	Liraglutide 3.0 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	105		
Units: Percentage change				
arithmetic mean (standard deviation)	-3.2 (± 9.4)	2.2 (± 9.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in systolic and diastolic blood pressure

End point title	Change in systolic and diastolic blood pressure

End point description:

Change in systolic blood pressure (SBP) and diastolic blood pressure (DBP) was evaluated from baseline (week 0) to weeks 56. Results are based on the FAS and included participants who completed the 56-week trial period. The FAS included all randomised participants who had received at least one dose of trial product and had any post-randomisation data (according to the ITT principle).

End point type	Secondary

End point timeframe:

From baseline to 56 weeks

End point values	Liraglutide 3.0 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102	101		
Units: mmHg				
arithmetic mean (standard deviation)				
SBP	-2 (± 10)	1 (± 10)		
DBP	1 (± 9)	-1 (± 9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in glycosylated haemoglobin (HbA1c)

End point title	Change in glycosylated haemoglobin (HbA1c)

End point description:

Change in HbA1c was evaluated from baseline (week 0) to weeks 56. Results are based on the FAS and included participants who completed the 56-week trial period. The FAS included all randomised participants who had received at least one dose of trial product and had any post-randomisation data (according to the ITT principle).

End point type	Secondary

End point timeframe:

From baseline to 56 weeks

End point values	Liraglutide 3.0 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	101		
Units: Percentage of HbA1c				
arithmetic mean (standard deviation)	-0.1 (± 0.3)	-0.0 (± 0.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in fasting plasma glucose

End point title	Change in fasting plasma glucose

End point description:

Change in fasting plasma glucose (FPG) was evaluated from baseline (week 0) to weeks 56. Results are based on the FAS and included participants who completed the 56-week trial period. The FAS included all randomised participants who had received at least one dose of trial product and had any post-randomisation data (according to the ITT principle).

End point type	Secondary

End point timeframe:

From baseline to 56 weeks

End point values	Liraglutide 3.0 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	100		
Units: mmol/L				
arithmetic mean (standard deviation)	-0.1 (± 0.5)	-0.0 (± 0.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of treatment emergent adverse events

End point title	Number of treatment emergent adverse events

End point description:

A treatment emergent adverse event (TEAE) was defined as an event that occurred in the "on-treatment" period. 'On-treatment' period: Events with onset date between the first day of trial product administration and any of the following date, whichever came first: 1) 14 days after the last day on trial product, or 2) follow-up visit (week 58) for participants who discontinued trial product, or 3) last study visit (participants withdrawn without follow-up visit). Results are based on the SAS which included all randomised participants exposed to at least one dose of trial product.

End point type	Secondary

End point timeframe:

Week 0–56 + 14 days

End point values	Liraglutide 3.0 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	126		
Units: Events	777	627		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Week 0–56 + 14 days.

Adverse event reporting additional description:

Results are based on the SAS which included all randomised participants exposed to at least one dose of trial product. All presented adverse events are TEAEs.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22

Reporting groups

Reporting group title	Liraglutide 3.0 mg

Reporting group description:

Subjects received liraglutide in a dose escalation manner for 56 weeks: 0.6 mg during week 1, 1.2 mg during week 2, 1.8 mg during week 3, 2.4 mg during week 4 and 3.0 mg from week 5 to week 56. There was a 26-week off-study-drug follow-up period (week 57–82).

Reporting group title	Placebo

Reporting group description:

Subjects received liraglutide matching placebo for 56 weeks. There was a 26-week off-study-drug follow-up period (week 57–82).

Serious adverse events	Liraglutide 3.0 mg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 125 (2.40%)	5 / 126 (3.97%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Post procedural haemorrhage			
subjects affected / exposed	1 / 125 (0.80%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Thrombophlebitis			
subjects affected / exposed	0 / 125 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Haemorrhagic ovarian cyst			

subjects affected / exposed	0 / 125 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 125 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 125 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	1 / 125 (0.80%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Musculoskeletal and connective tissue disorders			
Myositis			
subjects affected / exposed	1 / 125 (0.80%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 125 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 125 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Liraglutide 3.0 mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	100 / 125 (80.00%)	84 / 126 (66.67%)	
Nervous system disorders			
Dizziness			
subjects affected / exposed	13 / 125 (10.40%)	4 / 126 (3.17%)	
occurrences (all)	15	5	
Headache			
subjects affected / exposed	29 / 125 (23.20%)	35 / 126 (27.78%)	
occurrences (all)	43	53	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	10 / 125 (8.00%)	9 / 126 (7.14%)	
occurrences (all)	11	11	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	10 / 125 (8.00%)	11 / 126 (8.73%)	
occurrences (all)	15	15	
Abdominal pain upper			
subjects affected / exposed	17 / 125 (13.60%)	17 / 126 (13.49%)	
occurrences (all)	25	23	
Diarrhoea			
subjects affected / exposed	28 / 125 (22.40%)	18 / 126 (14.29%)	
occurrences (all)	44	29	
Nausea			
subjects affected / exposed	53 / 125 (42.40%)	18 / 126 (14.29%)	
occurrences (all)	101	25	
Vomiting			
subjects affected / exposed	43 / 125 (34.40%)	5 / 126 (3.97%)	
occurrences (all)	85	8	
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	4 / 125 (3.20%)	8 / 126 (6.35%)	
occurrences (all)	5	16	
Respiratory, thoracic and mediastinal disorders			

Oropharyngeal pain			
subjects affected / exposed	11 / 125 (8.80%)	15 / 126 (11.90%)	
occurrences (all)	11	18	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 125 (2.40%)	8 / 126 (6.35%)	
occurrences (all)	3	8	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	16 / 125 (12.80%)	6 / 126 (4.76%)	
occurrences (all)	22	9	
Influenza			
subjects affected / exposed	11 / 125 (8.80%)	12 / 126 (9.52%)	
occurrences (all)	11	12	
Nasopharyngitis			
subjects affected / exposed	34 / 125 (27.20%)	38 / 126 (30.16%)	
occurrences (all)	68	80	
Pharyngitis			
subjects affected / exposed	4 / 125 (3.20%)	7 / 126 (5.56%)	
occurrences (all)	5	7	
Upper respiratory tract infection			
subjects affected / exposed	11 / 125 (8.80%)	11 / 126 (8.73%)	
occurrences (all)	14	16	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported