Clinical trial results:
A randomised, double-blind, placebo-controlled trial to assess safety, tolerability, pharmacokinetics and pharmacodynamics of liraglutide in obese children aged 7 to 11 years

Summary

EudraCT number	2014-004454-34
Trial protocol	Outside EU/EEA
Global end of trial date	13 April 2017

Results information

Result version number	v1 (current)
This version publication date	25 October 2017
First version publication date	25 October 2017

Trial information

Trial identification

Sponsor protocol code	NN8022-4181

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02696148
WHO universal trial number (UTN)	U1111-1162-9171

Notes:

Sponsors

Sponsor organisation name	Novo Nordisk A/S
Sponsor organisation address	Novo Allé, 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-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	18 September 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 April 2017
Global end of trial reached?	Yes
Global end of trial date	13 April 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the safety and tolerability of multiple once-daily doses of liraglutide at doses up to 3.0 mg in obese children aged 7−11 years and at Tanner stage 1.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil. 1 Oct 2013) and ICH Good Clinical Practice (10 Jun 1996) and 21 CFR 312.120.

Background therapy:

Not applicable.

Evidence for comparator:

Not applicable.

Actual start date of recruitment	14 March 2016
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	United States: 24
Worldwide total number of subjects	24
EEA total number of subjects	0

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)	24
Adolescents (12-17 years)	0
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 3 sites in the United States.

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

Blinding implementation details:

Liraglutide and placebo were supplied in similar 3 mL FlexPen® devices and were visually identical, and packed and labelled to fulfil the requirements for double-blind procedures. Equal volumes of liraglutide and placebo were administered.

Arms

Are arms mutually exclusive?	Yes
Arm title	Liraglutide

Arm description:

Subjects received liraglutide once daily. Treatment was initiated with 0.3 mg liraglutide daily for one week and increased in weekly steps until a maximum dose of 3.0 mg liraglutide or maximum tolerated dose. Following was the dose escalation regimen for liraglutide: week 1: 0.3 mg, week 2: 0.6 mg, week 3: 0.9 mg, week 4: 1.2 mg, week 5: 1.8 mg, week 6: 2.4 mg, and week 7: 3.0 mg. The treatment period consisted of 7 mandatory treatment weeks with 6 optional flex weeks (one flex week between each of the 7 treatment weeks). A flex week on an unchanged or lowered dose was to be included in case the dose escalation criteria were not met at the end of a mandatory treatment week. Thus, the duration of the treatment period could be prolonged from 7 to 13 weeks, in case a flex week was needed between all 7 treatment weeks.

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

Dosage and administration details:

Liraglutide, 6.0 mg/mL in a 3 mL FlexPen® was administered once daily via subcutaneous (s.c.) abdominal injections in the morning (9 a.m. ±2 hours).

Arm title	Placebo

Arm description:

Subjects received liraglutide matching placebo once daily. Each placebo injection volume was based on the correspondent liraglutide dose (0.3 mg, 0.6 mg, 0.9 mg, 1.2 mg, 1.8 mg, 2.4 mg, and 3.0 mg). The treatment period consisted of 7 mandatory treatment weeks with 6 optional flex weeks (one flex week between each of the 7 treatment weeks). A flex week on an unchanged or lowered dose was to be included in case the dose escalation criteria were not met at the end of a mandatory treatment week. Thus, the duration of the treatment period could be prolonged from 7 to 13 weeks, in case a flex week was needed between all 7 treatment weeks.

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 in a 3 mL FlexPen® was administered once daily via s.c. abdominal injections in the morning (9 a.m. ±2 hours).

Number of subjects in period 1	Liraglutide	Placebo
Started	16	8
Completed	14	6
Not completed	2	2
Consent withdrawn by subject	1	-
Lost to follow-up	1	-
Withdrawal by parent/guardian	-	2

Baseline characteristics

Reporting groups

Reporting group title	Liraglutide

Reporting group description:

Subjects received liraglutide once daily. Treatment was initiated with 0.3 mg liraglutide daily for one week and increased in weekly steps until a maximum dose of 3.0 mg liraglutide or maximum tolerated dose. Following was the dose escalation regimen for liraglutide: week 1: 0.3 mg, week 2: 0.6 mg, week 3: 0.9 mg, week 4: 1.2 mg, week 5: 1.8 mg, week 6: 2.4 mg, and week 7: 3.0 mg. The treatment period consisted of 7 mandatory treatment weeks with 6 optional flex weeks (one flex week between each of the 7 treatment weeks). A flex week on an unchanged or lowered dose was to be included in case the dose escalation criteria were not met at the end of a mandatory treatment week. Thus, the duration of the treatment period could be prolonged from 7 to 13 weeks, in case a flex week was needed between all 7 treatment weeks.

Reporting group title	Placebo

Reporting group description:

Subjects received liraglutide matching placebo once daily. Each placebo injection volume was based on the correspondent liraglutide dose (0.3 mg, 0.6 mg, 0.9 mg, 1.2 mg, 1.8 mg, 2.4 mg, and 3.0 mg). The treatment period consisted of 7 mandatory treatment weeks with 6 optional flex weeks (one flex week between each of the 7 treatment weeks). A flex week on an unchanged or lowered dose was to be included in case the dose escalation criteria were not met at the end of a mandatory treatment week. Thus, the duration of the treatment period could be prolonged from 7 to 13 weeks, in case a flex week was needed between all 7 treatment weeks.

Reporting group values	Liraglutide	Placebo	Total
Number of subjects	16	8	24
Age Categorical Units: Subjects			
Children (2-11 years)	16	8	24
Age Continuous Units: years			
arithmetic mean	9.7	10.4	
standard deviation	± 1.1	± 1.1	-
Gender Categorical Units: Subjects			
Female	8	1	9
Male	8	7	15

End points

End points reporting groups

Reporting group title	Liraglutide

Reporting group description:

Subjects received liraglutide once daily. Treatment was initiated with 0.3 mg liraglutide daily for one week and increased in weekly steps until a maximum dose of 3.0 mg liraglutide or maximum tolerated dose. Following was the dose escalation regimen for liraglutide: week 1: 0.3 mg, week 2: 0.6 mg, week 3: 0.9 mg, week 4: 1.2 mg, week 5: 1.8 mg, week 6: 2.4 mg, and week 7: 3.0 mg. The treatment period consisted of 7 mandatory treatment weeks with 6 optional flex weeks (one flex week between each of the 7 treatment weeks). A flex week on an unchanged or lowered dose was to be included in case the dose escalation criteria were not met at the end of a mandatory treatment week. Thus, the duration of the treatment period could be prolonged from 7 to 13 weeks, in case a flex week was needed between all 7 treatment weeks.

Reporting group title	Placebo

Reporting group description:

Subjects received liraglutide matching placebo once daily. Each placebo injection volume was based on the correspondent liraglutide dose (0.3 mg, 0.6 mg, 0.9 mg, 1.2 mg, 1.8 mg, 2.4 mg, and 3.0 mg). The treatment period consisted of 7 mandatory treatment weeks with 6 optional flex weeks (one flex week between each of the 7 treatment weeks). A flex week on an unchanged or lowered dose was to be included in case the dose escalation criteria were not met at the end of a mandatory treatment week. Thus, the duration of the treatment period could be prolonged from 7 to 13 weeks, in case a flex week was needed between all 7 treatment weeks.

Primary: Number of treatment emergent adverse events

End point title	Number of treatment emergent adverse events[1]

End point description:

A treatment emergent adverse event (TEAE) was defined as an event that either:
1) had an onset time after the first time of exposure to investigational medicinal product (IMP), liraglutide or placebo and no later than the follow-up visit (i.e., 10-17 days after the last dose)
2) or had an onset time before the first time of exposure to IMP and increased in severity during the treatment period and no later than the follow-up visit.
Results are based on the safety analysis set, which included all subjects who were exposed to at least one dose of the IMP.

End point type	Primary

End point timeframe:

Recorded from the time of first dosing and until completion of follow up visit (59-108 days after first dosing)

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 primary endpoint investigated safety and was analysed using descriptive statistics, and thus no statistical analysis was performed.

End point values	Liraglutide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16[2]	8[3]		
Units: Number of events	37	12		

Notes:

[2] - Out of 16 subjects analysed, 9 subjects were reported with 37 AEs.

[3] - Out of 8 subjects analysed, 5 subjects were reported with 12 AEs.

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the liraglutide concentration curve from 0-24 hours (AUC0-24h) at steady state

End point title	Area under the liraglutide concentration curve from 0-24 hours (AUC0-24h) at steady state[4]

End point description:

Results are based on the full analysis set, which included all subjects who were randomised and received at least one dose of trial product. Number of subjects analysed = number of subjects contributed to the analysis.

End point type	Secondary

End point timeframe:

Following the last dose (49-91 days after first dosing)

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: For this endpoint, only samples from subjects treated with liraglutide were included. Therefore, the placebo-treated subjects did not contribute to the analyses.

End point values	Liraglutide			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: h x nmol/L				
geometric mean (confidence interval 95%)	1161 (1002 to 1398)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the time of first dosing and until completion of follow up visit (59-108 days after first dosing).

Adverse event reporting additional description:

All the following mentioned AEs are treatment emergent, i.e., TEAEs. Results are based on the safety analysis set.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20

Reporting groups

Reporting group title	Liraglutide

Reporting group description:

Subjects received liraglutide once daily. Treatment was initiated with 0.3 mg liraglutide daily for one week and increased in weekly steps until a maximum dose of 3.0 mg liraglutide or maximum tolerated dose. Following was the dose escalation regimen for liraglutide: week 1: 0.3 mg, week 2: 0.6 mg, week 3: 0.9 mg, week 4: 1.2 mg, week 5: 1.8 mg, week 6: 2.4 mg, and week 7: 3.0 mg. The treatment period consisted of 7 mandatory treatment weeks with 6 optional flex weeks (one flex week between each of the 7 treatment weeks). A flex week on an unchanged or lowered dose was to be included in case the dose escalation criteria were not met at the end of a mandatory treatment week. Thus, the duration of the treatment period could be prolonged from 7 to 13 weeks, in case a flex week was needed between all 7 treatment weeks.

Reporting group title	Placebo

Reporting group description:

Subjects received liraglutide matching placebo once daily. Each placebo injection volume was based on the correspondent liraglutide dose (0.3 mg, 0.6 mg, 0.9 mg, 1.2 mg, 1.8 mg, 2.4 mg, and 3.0 mg). The treatment period consisted of 7 mandatory treatment weeks with 6 optional flex weeks (one flex week between each of the 7 treatment weeks). A flex week on an unchanged or lowered dose was to be included in case the dose escalation criteria were not met at the end of a mandatory treatment week. Thus, the duration of the treatment period could be prolonged from 7 to 13 weeks, in case a flex week was needed between all 7 treatment weeks.

Serious adverse events	Liraglutide	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 16 (0.00%)	0 / 8 (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	9 / 16 (56.25%)	5 / 8 (62.50%)	

Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 16 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 16 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 16 (6.25%)	1 / 8 (12.50%)	
occurrences (all)	1	1	
Headache			
subjects affected / exposed	2 / 16 (12.50%)	3 / 8 (37.50%)	
occurrences (all)	3	4	
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	0 / 16 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Injection site erythema			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Injection site induration			
subjects affected / exposed	2 / 16 (12.50%)	0 / 8 (0.00%)	
occurrences (all)	2	0	
Injection site reaction			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Orbital oedema			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			

Abdominal discomfort			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	
occurrences (all)	3	0	
Abdominal pain upper			
subjects affected / exposed	2 / 16 (12.50%)	0 / 8 (0.00%)	
occurrences (all)	6	0	
Diarrhoea			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Dyspepsia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	3 / 16 (18.75%)	0 / 8 (0.00%)	
occurrences (all)	3	0	
Salivary hypersecretion			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	4 / 16 (25.00%)	0 / 8 (0.00%)	
occurrences (all)	5	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Nasal congestion			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Rhinorrhoea			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Sinus congestion			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			

Rash			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Muscle spasms			
subjects affected / exposed	0 / 16 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Muscle tightness			
subjects affected / exposed	0 / 16 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Infections and infestations			
Gastritis viral			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 16 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 February 2016	1) A discrepancy in the key inclusion criteria regarding the time of tanner stage was corrected in the summary. 2) Self-injection with test medium at visit 1 (in week 1) was added to the Flow char for clarification. 3) The PK sampling time window for liraglutide at visit 12 (follow-up visit) was updated for more flexibility for the subjects. 4) The subject information (SI)/informed consent (IC) for parents or legally acceptable representative (LARs) was updated with inclusion of the findings from the pre-clinical juvenile toxicity study as per FDA request. The protocol was updated accordingly ensuring the full information is reflected in the protocol. 5) A discrepancy regarding the number of days from visit 2 (in week 0) to visit 3-8 (in weeks 1-6) was corrected. 6) The protocol was updated with specifications of procedures in case a subject fails to attend a visit fasting, or has forgotten to perform self-measured plasma glucose (SMPG) and/or withhold their daily liraglutide/liraglutide placebo dose before coming to the trial site.
06 July 2016	1) Based on external advisor and Investigators feedback, children with obesity enter puberty earlier than other children. The request to modify the inclusion criterion to allow children with premature adrenarche (development of pubic hair without the children having entered true puberty) was based on the association of this finding with increased body mass index. 2) The SI/IC for parents or LARs was also updated with the change in inclusion criteria related to Tanner stage 1. 3) The protocol was updated with information describing that arrangements can be made with the investigator to stay at site overnight before a visit, as needed.
06 July 2016	With amendment no. 2, the trial protocol population was modified to include prepubertal children (Tanner stage 1) and prepubertal children with premature adrenarche. This amendment no. 3 updated the trial protocol with information on how to document the exclusion of conditions other than premature adrenache.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported