



Clinical trial results:

A randomised, double-blind, placebo-controlled trial to assess safety, tolerability and pharmacokinetics of liraglutide in obese adolescent subjects aged 12 to 17 years.

Summary

EudraCT number	2012-000038-20
Trial protocol	DE
Global end of trial date	26 May 2014

Results information

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

Trial information

Trial identification

Sponsor protocol code	NN8022-3967
-----------------------	-------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01789086
WHO universal trial number (UTN)	U1111-1126-8119

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	07 November 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 May 2014
Global end of trial reached?	Yes
Global end of trial date	26 May 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the safety and tolerability of liraglutide at doses up to 3.0 mg in an obese adolescent population aged 12-17 years and Tanner stage 2-5.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (59th WMA General Assembly, Seoul, 2008) and ICH Good Clinical Practice (01 May 1996) and 21 CFR 312.120.

Background therapy:

Not applicable

Evidence for comparator:

Not applicable.

Actual start date of recruitment	07 February 2013
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	Germany: 21
Worldwide total number of subjects	21
EEA total number of subjects	21

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)	21
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 one site in Germany.

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:

Not applicable.

Arms

Are arms mutually exclusive?	Yes
------------------------------	-----

Arm title	Liraglutide 3.0 mg
------------------	--------------------

Arm description:

Eligible subjects were randomised to receive liraglutide or placebo in 2:1 ratio, subcutaneously (s.c., under skin), for a period of 5–6 weeks. Initial dose of liraglutide was 0.6 mg/day. The dose was escalated by 0.6 mg/day in weekly steps to a maximum of 3.0 mg/day. Follow-up visit was planned 5-14 days after the end of treatment.

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:

Initial dose of liraglutide was 0.6 mg/day, given once-daily subcutaneous abdominal injections in the morning. The dose was escalated by 0.6 mg/day in weekly steps to a maximum of 3.0 mg/day.

Arm title	Placebo
------------------	---------

Arm description:

Eligible subjects were randomised to receive liraglutide or placebo in 2:1 ratio, subcutaneously (s.c., under skin), for a period of 5–6 weeks. Initial dose of placebo was 0.6 mg/day. The dose was escalated by 0.6 mg/day in weekly steps to a maximum of 3.0 mg/day. Follow-up visit was planned 5-14 days after the end of treatment.

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:

Initial dose of placebo was 0.6 mg/day, given once-daily subcutaneous abdominal injections in the morning. The dose was escalated by 0.6 mg/day in weekly steps to a maximum of 3.0 mg/day.

Number of subjects in period 1	Liraglutide 3.0 mg	Placebo
Started	14	7
Completed	13	7
Not completed	1	0
Storage temperature deviation of trial product	1	-

Baseline characteristics

Reporting groups

Reporting group title	Liraglutide 3.0 mg
-----------------------	--------------------

Reporting group description:

Eligible subjects were randomised to receive liraglutide or placebo in 2:1 ratio, subcutaneously (s.c., under skin), for a period of 5–6 weeks. Initial dose of liraglutide was 0.6 mg/day. The dose was escalated by 0.6 mg/day in weekly steps to a maximum of 3.0 mg/day. Follow-up visit was planned 5-14 days after the end of treatment.

Reporting group title	Placebo
-----------------------	---------

Reporting group description:

Eligible subjects were randomised to receive liraglutide or placebo in 2:1 ratio, subcutaneously (s.c., under skin), for a period of 5–6 weeks. Initial dose of placebo was 0.6 mg/day. The dose was escalated by 0.6 mg/day in weekly steps to a maximum of 3.0 mg/day. Follow-up visit was planned 5-14 days after the end of treatment.

Reporting group values	Liraglutide 3.0 mg	Placebo	Total
Number of subjects	14	7	21
Age categorical			
Units: Subjects			
Adolescents (12-17 years)	14	7	21
Age continuous			
Units: years			
arithmetic mean	15.1	14.4	-
standard deviation	± 0.9	± 1.8	-
Gender categorical			
Units: Subjects			
Female	11	3	14
Male	3	4	7
Body Weight			
Units: Kg			
arithmetic mean	103.5	109.6	-
standard deviation	± 12.8	± 30.8	-
Boby Mass Index (BMI)			
Units: Kg/m2			
arithmetic mean	36.5	35.7	-
standard deviation	± 3.7	± 5.4	-
Glycosylated Haemoglobin (HbA1C)			
Units: Percentage			
arithmetic mean	5.4	5.5	-
standard deviation	± 0.3	± 0.3	-
Fasting Plasma Glucose (FPG)			
Units: mmol/L			
arithmetic mean	5.25	5.47	-
standard deviation	± 0.45	± 0.3	-

End points

End points reporting groups

Reporting group title	Liraglutide 3.0 mg
-----------------------	--------------------

Reporting group description:

Eligible subjects were randomised to receive liraglutide or placebo in 2:1 ratio, subcutaneously (s.c., under skin), for a period of 5–6 weeks. Initial dose of liraglutide was 0.6 mg/day. The dose was escalated by 0.6 mg/day in weekly steps to a maximum of 3.0 mg/day. Follow-up visit was planned 5-14 days after the end of treatment.

Reporting group title	Placebo
-----------------------	---------

Reporting group description:

Eligible subjects were randomised to receive liraglutide or placebo in 2:1 ratio, subcutaneously (s.c., under skin), for a period of 5–6 weeks. Initial dose of placebo was 0.6 mg/day. The dose was escalated by 0.6 mg/day in weekly steps to a maximum of 3.0 mg/day. Follow-up visit was planned 5-14 days after the end of treatment.

Primary: Number of treatment emergent adverse events (TEAEs) recorded.

End point title	Number of treatment emergent adverse events (TEAEs) recorded. ^[1]
-----------------	--

End point description:

An adverse event is defined as treatment emergent if it has onset date on or after the first day of exposure and not later than the follow-up visit or has onset date before the first day of exposure and increases in severity during treatment and no later than the follow-up visit.

End point type	Primary
----------------	---------

End point timeframe:

From time of first dosing and until the end of the post-treatment follow-up period (i.e., 5-14 days after the last dosing visit).

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 investigates safety and is analysed using descriptive statistics, and thus no statistical analysis is performed.

End point values	Liraglutide 3.0 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14 ^[2]	7 ^[3]		
Units: Number of events	86	7		

Notes:

[2] - 86 adverse events were reported by 14 subjects.

[3] - 7 adverse events were reported by 4 subjects.

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of anti-liraglutide antibody.

End point title	Incidence of anti-liraglutide antibody.
-----------------	---

End point description:

Blood samples for determination of anti-liraglutide antibodies were drawn at the screening visit (visit 1) and the follow-up visit (visit 8). Samples were analysed for anti-liraglutide antibody findings .

End point type	Secondary
----------------	-----------

End point timeframe:

Time frame: Week 0 to week 6 + 5 to 14 days of subsequent follow-up.

End point values	Liraglutide 3.0 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	7		
Units: Incidence of anti-liraglutide antibody	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Ctrough-at steady state at each dose step.

End point title	Ctrough-at steady state at each dose step. ^[4]
-----------------	---

End point description:

In order to obtain Ctrough (liraglutide plasma concentrations) values at steady state at each dose-escalation step, one blood sample was drawn prior to the subjects taking their daily dose of liraglutide at visits 3 (7 days), 4 (14 days), 5 (21 days), 6 (28 days) and 7 (35 days).

End point type	Secondary
----------------	-----------

End point timeframe:

At 7, 14, 21, 28 and 35 days of treatment.

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: Samples from liraglutide treated subjects were included for pharmacokinetic analysis. Samples from placebo treated subjects were not considered for pharmacokinetic analysis, so placebo arm is not included in this endpoint.

End point values	Liraglutide 3.0 mg			
Subject group type	Reporting group			
Number of subjects analysed	13 ^[5]			
Units: pmol/L				
geometric mean (geometric coefficient of variation)				
Day 7	5596 (± 31.31)			
Day 14	10263 (± 26.5)			
Day 21	13800 (± 38.25)			
Day 28	12788 (± 77.31)			
Day 35	25188 (± 40.05)			

Notes:

[5] - Only 12 subjects contributed in Ctrough-at steady state at day 35.

Statistical analyses

No statistical analyses for this end point

Secondary: Model-derived AUC_T at steady-state.

End point title	Model-derived AUC _T at steady-state. ^[6]
End point description:	Area under the concentration-time (AUC _T) curve at steady state from 0–24 hours, after dose.
End point type	Secondary
End point timeframe:	Last dose day, after up to 6 weeks treatment.

Notes:

[6] - 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: Samples from liraglutide treated subjects were included for pharmacokinetic analysis. Samples from placebo treated subjects were not considered for pharmacokinetic analysis, so placebo arm is not included in this endpoint.

End point values	Liraglutide 3.0 mg			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: nM*h				
geometric mean (confidence interval 95%)	836 (745 to 962)			

Statistical analyses

No statistical analyses for this end point

Secondary: Model-derived t_{1/2} at steady-state.

End point title	Model-derived t _{1/2} at steady-state. ^[7]
End point description:	Mean plasma half-life (t _{1/2}) of liraglutide, at steady-state.
End point type	Secondary
End point timeframe:	Last dose day, after up to 6 weeks treatment.

Notes:

[7] - 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: Samples from liraglutide treated subjects were included for pharmacokinetic analysis. Samples from placebo treated subjects were not considered for pharmacokinetic analysis, so placebo arm is not included in this endpoint.

End point values	Liraglutide 3.0 mg			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: hour				
geometric mean (confidence interval 95%)	8.6 (8.5 to 8.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Model-derived CL/F at steady-state.

End point title | Model-derived CL/F at steady-state.^[8]

End point description:

Mean apparent clearance (CL/F) of liraglutide at steady state.

End point type | Secondary

End point timeframe:

Last dose day, after up to 6 weeks treatment

Notes:

[8] - 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: Samples from liraglutide treated subjects were included for pharmacokinetic analysis. Samples from placebo treated subjects were not considered for pharmacokinetic analysis, so placebo arm is not included in this endpoint.

End point values	Liraglutide 3.0 mg			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: Litre/hour				
geometric mean (confidence interval 95%)	0.96 (0.85 to 1.11)			

Statistical analyses

No statistical analyses for this end point

Secondary: Model-derived V/F at steady-state.

End point title | Model-derived V/F at steady-state.^[9]

End point description:

Mean apparent volume of distribution (V/F) of liraglutide, at steady state.

End point type | Secondary

End point timeframe:

Last dose day, after up to 6 weeks treatment.

Notes:

[9] - 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: Samples from liraglutide treated subjects were included for pharmacokinetic analysis. Samples from placebo treated subjects were not considered for pharmacokinetic analysis, so placebo arm is not included in this endpoint.

End point values	Liraglutide 3.0 mg			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: Litre				
geometric mean (confidence interval 95%)	10.3 (9.5 to 11.3)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From screening visit and until the end of the post-treatment follow-up period (i.e., 5-14 days after the last dosing visit).

Adverse event reporting additional description:

An adverse event is any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a product, whether or not considered related to the product.

Assessment type	Non-systematic
-----------------	----------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	17.0
--------------------	------

Reporting groups

Reporting group title	Liraglutide 3.0 mg
-----------------------	--------------------

Reporting group description:

Eligible subjects were randomised to receive liraglutide or placebo in 2:1 ratio, subcutaneously (s.c., under skin), for a period of 5–6 weeks. Initial dose of liraglutide was 0.6 mg/day. The dose was escalated by 0.6 mg/day in weekly steps to a maximum of 3.0 mg/day. Follow-up visit was planned 5-14 days after the end of treatment.

Reporting group title	Placebo
-----------------------	---------

Reporting group description:

Eligible subjects were randomised to receive liraglutide or placebo in 2:1 ratio, subcutaneously (s.c., under skin), for a period of 5–6 weeks. Initial dose of placebo was 0.6 mg/day. The dose was escalated by 0.6 mg/day in weekly steps to a maximum of 3.0 mg/day. Follow-up visit was planned 5-14 days after the end of treatment.

Serious adverse events	Liraglutide 3.0 mg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 14 (0.00%)	0 / 7 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Liraglutide 3.0 mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 14 (100.00%)	4 / 7 (57.14%)	
Investigations			
Transaminases increased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences (all)	1	0	

Injury, poisoning and procedural complications Arthropod sting subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 7 (0.00%) 0	
Vascular disorders Haematoma subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 2	0 / 7 (0.00%) 0	
Nervous system disorders Headache subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all) Migraine subjects affected / exposed occurrences (all) Visual field defect subjects affected / exposed occurrences (all)	7 / 14 (50.00%) 9 2 / 14 (14.29%) 2 1 / 14 (7.14%) 1 1 / 14 (7.14%) 1	0 / 7 (0.00%) 0 1 / 7 (14.29%) 1 0 / 7 (0.00%) 0 0 / 7 (0.00%) 0	
General disorders and administration site conditions Injection site pain subjects affected / exposed occurrences (all) Injection site pruritus subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	3 / 14 (21.43%) 5 1 / 14 (7.14%) 1 1 / 14 (7.14%) 1	0 / 7 (0.00%) 0 0 / 7 (0.00%) 0 0 / 7 (0.00%) 0	
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Nausea	7 / 14 (50.00%) 17	2 / 7 (28.57%) 3	

subjects affected / exposed occurrences (all)	7 / 14 (50.00%) 13	0 / 7 (0.00%) 0	
Vomiting subjects affected / exposed occurrences (all)	5 / 14 (35.71%) 5	0 / 7 (0.00%) 0	
Diarrhoea subjects affected / exposed occurrences (all)	3 / 14 (21.43%) 3	0 / 7 (0.00%) 0	
Abdominal pain upper subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 2	0 / 7 (0.00%) 0	
Abdominal distension subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 7 (0.00%) 0	
Abdominal pain lower subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 7 (0.00%) 0	
Abdominal wall haematoma subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 7 (0.00%) 0	
Reproductive system and breast disorders Dysmenorrhoea subjects affected / exposed occurrences (all)	3 / 14 (21.43%) 3	0 / 7 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders Oropharyngeal pain subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 5	1 / 7 (14.29%) 1	
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 7 (0.00%) 0	
Pruritus subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 7 (0.00%) 0	
Musculoskeletal and connective tissue			

disorders			
Arthralgia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Back pain			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Myalgia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 14 (14.29%)	1 / 7 (14.29%)	
occurrences (all)	2	1	
Upper respiratory tract infection			
subjects affected / exposed	2 / 14 (14.29%)	1 / 7 (14.29%)	
occurrences (all)	2	1	
Gastroenteritis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Sinusitis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported