Clinical trial results:
Efficacy and safety of liraglutide versus lixisenatide as add-on to metformin in subjects with type 2 diabetes.

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

EudraCT number	2012-004984-27
Trial protocol	LT FI GB CZ DE HU LV FR
Global end of trial date	19 November 2014

Results information

Result version number	v1 (current)
This version publication date	17 April 2016
First version publication date	17 April 2016

Trial information

Trial identification

Sponsor protocol code	NN2211-3867

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01973231
WHO universal trial number (UTN)	U1111-1136-3644

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)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 May 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 November 2014
Global end of trial reached?	Yes
Global end of trial date	19 November 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the effect of liraglutide versus lixisenatide as add-on to metformin on glycaemic control after 26 weeks treatment in subjects with type 2 diabetes mellitus (T2DM)

Protection of trial subjects:

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

Background therapy:

Stable dose of Metformin (maximum tolerated dose, equal to or above 1000 mg/day and up to 3000 mg/day).

Evidence for comparator:

Not applicable

Actual start date of recruitment	24 October 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	Czech Republic: 59
Country: Number of subjects enrolled	Finland: 8
Country: Number of subjects enrolled	France: 30
Country: Number of subjects enrolled	Germany: 49
Country: Number of subjects enrolled	Hungary: 56
Country: Number of subjects enrolled	Italy: 40
Country: Number of subjects enrolled	Latvia: 48
Country: Number of subjects enrolled	Lithuania: 34
Country: Number of subjects enrolled	United Kingdom: 80
Worldwide total number of subjects	404
EEA total number of subjects	404

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	321
From 65 to 84 years	82
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 56 sites in 9 countries as follows:
Czech Republic: 5 sites; Finland: 4 sites; France: 6 sites; Germany: 8 sites; Hungary: 6 sites; Italy: 5 sites; Latvia: 6 sites; Lithuania: 5 sites; UK: 11 sites.

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	Not blinded

Blinding implementation details:

Not Applicable

Arms

Are arms mutually exclusive?	Yes
Arm title	Liraglutide

Arm description:

Liraglutide was administered subcutaneously (s.c.; under the skin) once daily in addition to the subject's stable pre-trial metformin (maximum tolerated dose, equal to or above 1000 mg/day and up to 3000 mg/day) for a total duration of 26 weeks. Starting dose of liraglutide was 0.6 mg/day, with weekly dose escalations of 0.6 mg/day until the maintenance dose of 1.8 mg/day was reached.

Arm type	Experimental
Investigational medicinal product name	Liraglutide
Investigational medicinal product code	
Other name	Victoza®
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Liraglutide was to be injected subcutaneously in the thigh, upper arm (deltoid region) or abdomen. The injection site did not have to be consistent throughout the trial. Injections could be done at any time of the day irrespective of meals. It was recommended that the time of injection was consistent throughout the trial. Subjects were instructed to perform an air shot before the first use of a new pre-filled pen. Subjects were to follow a dose escalation. Liraglutide was to be initiated with a starting dose of 0.6 mg/day, with subsequent weekly dose escalations of 0.6 mg/day in accordance with the approved dose escalation for liraglutide until the maintenance dose of 1.8 mg/day was reached. Escalation from 0.6 mg/day to 1.8 mg/day could be extended by 7 days if subjects did not tolerate an increase in dose during dose escalation according to the investigator’s opinion. The liraglutide dose of 1.8 mg/day was to remain unchanged throughout the remainder of the trial.

Arm title	Lixisenatide

Arm description:

Lixisenatide was administered s.c. once daily, within the hour prior to the first meal of the day or the evening meal in addition to subject's stable pre-trial metformin (maximum tolerated dose, equal to or above 1000mg/day and up to 3000mg/day) for a total duration of 26 weeks. Starting dose of lixisenatide was 10 µg once daily, the dose was escalated to 20 µg once daily from day 15 after randomisation.

Arm type	Active comparator

Investigational medicinal product name	Lixisenatide
Investigational medicinal product code	
Other name	Lyxumia®
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Lixisenatide was to be administered once daily, within the hour prior to the first meal of the day or the evening meal, in accordance with the approved SmPC (Summary of Product Characteristics) at the time of trial initiation and recruitment of subjects. Dose escalation for lixisenatide was according to the approved label. Following a starting dose of 10 µg, the dose was to be escalated to 20 µg from day 15 after randomisation. If a dose of lixisenatide was missed, it was to be injected within the hour prior to the next meal. Injections were to be done subcutaneously in the thigh, abdomen or upper arm. Trial drug medication with lixisenatide after dose escalation was to be continued at a fixed dose throughout the trial.

Number of subjects in period 1	Liraglutide	Lixisenatide
Started	202	202
Completed	191	190
Not completed	11	12
Consent withdrawn by subject	7	9
unclassified	2	1
Lost to follow-up	1	1
Protocol deviation	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Liraglutide
Reporting group description:	
Liraglutide was administered subcutaneously (s.c.; under the skin) once daily in addition to the subject's stable pre-trial metformin (maximum tolerated dose, equal to or above 1000 mg/day and up to 3000 mg/day) for a total duration of 26 weeks. Starting dose of liraglutide was 0.6 mg/day, with weekly dose escalations of 0.6 mg/day until the maintenance dose of 1.8 mg/day was reached.	
Reporting group title	Lixisenatide
Reporting group description:	
Lixisenatide was administered s.c. once daily, within the hour prior to the first meal of the day or the evening meal in addition to subject's stable pre-trial metformin (maximum tolerated dose, equal to or above 1000mg/day and up to 3000mg/day) for a total duration of 26 weeks. Starting dose of lixisenatide was 10 µg once daily, the dose was escalated to 20 µg once daily from day 15 after randomisation.	

Reporting group values	Liraglutide	Lixisenatide	Total
Number of subjects	202	202	404
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	155	166	321
From 65-84 years	46	36	82
85 years and over	1	0	1
Age Continuous Units: years			
arithmetic mean	56.3	56.1	
standard deviation	± 10.6	± 10	-
Gender, Male/Female Units: participants			
Female	70	90	160
Male	132	112	244
Glycosylated Haemoglobin (HbA1c) Units: Percent (%) glycosylated haemoglobin			
arithmetic mean	8.4	8.43	
standard deviation	± 0.723	± 0.785	-
Fasting plasma glucose (FPG) Units: mmol/L			
arithmetic mean	10.47	10.25	
standard deviation	± 2.368	± 2.254	-
Body Weight Units: kg			
arithmetic mean	101.89	100.58	

standard deviation	± 23.344	± 19.949	-

End points

End points reporting groups

Reporting group title	Liraglutide
Reporting group description:	
Liraglutide was administered subcutaneously (s.c.; under the skin) once daily in addition to the subject's stable pre-trial metformin (maximum tolerated dose, equal to or above 1000 mg/day and up to 3000 mg/day) for a total duration of 26 weeks. Starting dose of liraglutide was 0.6 mg/day, with weekly dose escalations of 0.6 mg/day until the maintenance dose of 1.8 mg/day was reached.	
Reporting group title	Lixisenatide
Reporting group description:	
Lixisenatide was administered s.c. once daily, within the hour prior to the first meal of the day or the evening meal in addition to subject's stable pre-trial metformin (maximum tolerated dose, equal to or above 1000mg/day and up to 3000mg/day) for a total duration of 26 weeks. Starting dose of lixisenatide was 10 µg once daily, the dose was escalated to 20 µg once daily from day 15 after randomisation.	

Primary: Change in glycosylated haemoglobin (HbA1c)

End point title	Change in glycosylated haemoglobin (HbA1c)
End point description:	
Change from baseline in HbA1c after 26 weeks of treatment.	
End point type	Primary
End point timeframe:	
From baseline to week 26.	

End point values	Liraglutide	Lixisenatide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	194	191		
Units: Percent (%) glycosylated haemoglobin				
arithmetic mean (standard deviation)	-1.809 (± 0.9159)	-1.238 (± 1.0085)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Liraglutide v Lixisenatide
Number of subjects included in analysis	385
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-0.62

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	-0.44

Secondary: Change in fasting plasma glucose (FPG)

End point title	Change in fasting plasma glucose (FPG)

End point description:

Change from baseline in FPG after 26 weeks of treatment.

End point type	Secondary

End point timeframe:

From baseline to week 26

End point values	Liraglutide	Lixisenatide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	194	189		
Units: mmol/L				
arithmetic mean (standard deviation)	-2.904 (± 2.2309)	-1.644 (± 2.1511)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in body weight

End point title	Change in body weight

End point description:

Change from baseline in body weight after 26 weeks of treatment.

End point type	Secondary

End point timeframe:

From baseline to week 26

End point values	Liraglutide	Lixisenatide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	194	191		
Units: kg				
arithmetic mean (standard deviation)	-4.24 (± 4.273)	-3.69 (± 4.746)		

Statistical analyses

No statistical analyses for this end point

Secondary: Subjects who achieve HbA1c below 7.0% (53 mmol/mol) (American Diabetes Association (ADA) target) (yes/no)

End point title	Subjects who achieve HbA1c below 7.0% (53 mmol/mol) (American Diabetes Association (ADA) target) (yes/no)

End point description:

Subjects who achieved HbA1c below 7.0% (53 mmol/mol) after 26 weeks of treatment (yes/no).

End point type	Secondary

End point timeframe:

After 26 weeks of treatment

End point values	Liraglutide	Lixisenatide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	194	191		
Units: percentage (%) of subjects				
number (not applicable)				
Yes	74.2	45.5		
No	25.8	54.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Subjects who achieve HbA1c equal to or below 6.5% (48 mmol/mol) (American Association of Clinical Endocrinologists [AACE] target) (yes/no)

End point title	Subjects who achieve HbA1c equal to or below 6.5% (48 mmol/mol) (American Association of Clinical Endocrinologists [AACE] target) (yes/no)

End point description:

Subjects who achieved HbA1c below equal to or below 6.5% (48 mmol/mol) after 26 weeks of treatment (yes/no).

End point type	Secondary

End point timeframe:

After 26 weeks of treatment

End point values	Liraglutide	Lixisenatide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	194	191		
Units: percentage (%) of subjects				
number (not applicable)				
Yes	54.6	26.2		
No	45.4	73.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Subjects who achieve HbA1c below 7.0% (53 mmol/mol) and no weight gain (yes/no)

End point title	Subjects who achieve HbA1c below 7.0% (53 mmol/mol) and no weight gain (yes/no)

End point description:

Subjects who achieved HbA1c below 7.0% (53 mmol/mol) and no weight gain after 26 weeks of treatment (yes/no).

End point type	Secondary

End point timeframe:

After 26 weeks of treatment

End point values	Liraglutide	Lixisenatide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	194	191		
Units: percentage (%) of subjects				
number (not applicable)				
Yes	66.5	41.9		
No	33.5	58.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of treatment emergent adverse events (TEAEs)

End point title	Number of treatment emergent adverse events (TEAEs)

End point description:

A TEAE was defined as an event that had onset date on or after the first day of exposure to randomised treatment and no later than 7 days after the last day of randomised treatment. Severity was assessed by investigator.

End point type	Secondary

End point timeframe:

During 26 weeks of treatment

End point values	Liraglutide	Lixisenatide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	202	202		
Units: Events				
Events	540	435		
Serious	13	7		
Severe	10	3		
Moderate	109	84		
Mild	421	348		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Week 0-26	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups	
Reporting group title	Liraglutide

Reporting group description:

Liraglutide was administered subcutaneously (s.c.; under the skin) once daily in addition to the subject's stable pre-trial metformin (maximum tolerated dose, equal to or above 1000 mg/day and up to 3000 mg/day) for a total duration of 26 weeks. Starting dose of liraglutide was 0.6 mg/day, with weekly dose escalations of 0.6 mg/day until the maintenance dose of 1.8 mg/day was reached.

Reporting group title	Lixisenatide

Reporting group description:

Lixisenatide was administered s.c. once daily, within the hour prior to the first meal of the day or the evening meal in addition to subject's stable pre-trial metformin (maximum tolerated dose, equal to or above 1000 mg/day and up to 3000mg/day) for a total duration of 26 weeks. Starting dose of lixisenatide was 10 µg once daily, the dose was escalated to 20 µg once daily from day 15 after randomisation.

Serious adverse events	Liraglutide	Lixisenatide	
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 202 (5.94%)	7 / 202 (3.47%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	1 / 202 (0.50%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Thermal burn			
subjects affected / exposed	0 / 202 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			

subjects affected / exposed	0 / 202 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 202 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	0 / 202 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	1 / 202 (0.50%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Ischaemic stroke			
subjects affected / exposed	1 / 202 (0.50%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 202 (0.50%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 202 (0.50%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	1 / 202 (0.50%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastric ulcer haemorrhage			
subjects affected / exposed	1 / 202 (0.50%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal ulcer haemorrhage			
subjects affected / exposed	1 / 202 (0.50%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Prostatic dysplasia			
subjects affected / exposed	0 / 202 (0.00%)	1 / 202 (0.50%)	
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	1 / 202 (0.50%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	1 / 202 (0.50%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety disorder due to a general medical condition			
subjects affected / exposed	0 / 202 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Rotator cuff syndrome			
subjects affected / exposed	1 / 202 (0.50%)	0 / 202 (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			

Diabetic foot infection			
subjects affected / exposed	1 / 202 (0.50%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 202 (0.50%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			
subjects affected / exposed	0 / 202 (0.00%)	1 / 202 (0.50%)	
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	Lixisenatide	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	90 / 202 (44.55%)	83 / 202 (41.09%)	
Investigations			
Lipase increased			
subjects affected / exposed	17 / 202 (8.42%)	5 / 202 (2.48%)	
occurrences (all)	17	5	
Nervous system disorders			
Headache			
subjects affected / exposed	15 / 202 (7.43%)	17 / 202 (8.42%)	
occurrences (all)	31	35	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	25 / 202 (12.38%)	20 / 202 (9.90%)	
occurrences (all)	39	22	
Dyspepsia			
subjects affected / exposed	11 / 202 (5.45%)	6 / 202 (2.97%)	
occurrences (all)	11	9	
Nausea			
subjects affected / exposed	44 / 202 (21.78%)	44 / 202 (21.78%)	
occurrences (all)	67	60	

Vomiting subjects affected / exposed occurrences (all)	14 / 202 (6.93%) 18	18 / 202 (8.91%) 22	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	13 / 202 (6.44%) 13	20 / 202 (9.90%) 22	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	13 / 202 (6.44%) 13	5 / 202 (2.48%) 5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 July 2013	1.Changing inclusion criteria 3 and 4 according to ADA and EASD position statement: defining maximum tolerated dose for metformin and increasing HbA1c lower limit from 7.0% to 7.5% 2.Define "true abstinence" in exclusion criterion 3 3.Adding pancreatitis as MESI

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Not applicable

Notes: