Clinical trial results:
The effect of lixisenatide in type 1 diabetes

Summary

EudraCT number	2013-002259-14
Trial protocol	GB
Global end of trial date	03 May 2016

Results information

Result version number	v1 (current)
This version publication date	09 February 2018
First version publication date	09 February 2018

Trial information

Trial identification

Sponsor protocol code	TRG12-05

Additional study identifiers

ISRCTN number	ISRCTN00290196
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Oxford
Sponsor organisation address	Joint Research Office, Churchill Hospital, Oxford, United Kingdom, OX3 7LE
Public contact	Dr Irene Kennedy, Diabetes Trials Unit, University of Oxford, +44 (0)1865857257, trg@dtu.ox.ac.uk
Scientific contact	Dr Irene Kennedy, Diabetes Trials Unit, University of Oxford, +44 (0)1865857257, trg@dtu.ox.ac.uk

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	03 May 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 May 2016
Global end of trial reached?	Yes
Global end of trial date	03 May 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the main trial is to determine whether adding lixisenatide to basal bolus insulin (combination of long acting insulin once a day called basal with short acting insulin with meals, called bolus) significantly improves glycaemic (blood sugar) control during the 3 hour post prandial period (i.e. following a meal) compared to basal bolus insulin and a 'dummy' or placebo injection.

Protection of trial subjects:

The trial was conducted in conformance with Good Clinical Practice (GCP) standards and applicable local statutes and regulations regarding ethical committee review, informed consent and the protection of human subjects participating in biomedical research. The following additional measures, defined for this individual trial, were in-place for the protection of the trial subjects:

- The main trial was preceded by a preliminary safety trial which assessed the amount of meal-time insulin dose reduction that avoided hypoglycaemic episodes while maintaining blood glucose levels within an acceptable range when dual treatment with GLP-1 receptor agonist and insulin was started.

- To avoid hypoglycaemia in trial participants, their usual dose of insulin was reduced at the beginning of treatment periods, and titrated to maintain blood glucose within the protocol-defined range.

- In the event that a participant experienced severe hypoglycaemia (an event requiring third-party assistance) at any point during the trial, Investigational Medicinal Product (IMP) would be discontinued permanently.

Background therapy:

Inclusion criteria for the trial specify participants must be taking a stable insulin dose (within 20%) over 3 months prior to recruitment.

Evidence for comparator: -

Actual start date of recruitment	02 May 2014
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 Kingdom: 27
Worldwide total number of subjects	27
EEA total number of subjects	27

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)	0
Adults (18-64 years)	26
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was single-centre, carried out at the Clinical Research Unit (CRU), Oxford Centre for Diabetes, Endocrinology and Metabolism (OCDEM), UK, between 2nd May 2014 (First Patient First Visit) and 3rd May 2016 (Last Patient Last Visit)

Pre-assignment

Screening details:

Participants aged 18-70 years inclusive providing written informed consent were eligible if they were diagnosed with stable type 1 diabetes for at least 12 months (Stable insulin dose (within 20%) over 3 months prior to recruitment), used a Basal-Bolus insulin regimen, HbA1c between 6.5% and 10.0% (inclusive) and BMI < 35 Kg/m2.

Pre-assignment period milestones

Number of subjects started	38[1]
Number of subjects completed	27

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Participants failed to meet eligibility criteria.: 11

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The number of participants starting the pre-assignment period are those who provided Informed Consent and were screened. The number enrolled is the number eligible who then went on to be enrolled i.e. randomised. The difference is due to those individuals who failed screening.

Period 1

Period 1 title	Main trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

Participants were randomised to one of two treatment arms in a double blind cross-over trial. An independent statistician generated the randomization code list and this was added in a concealed fashion to the Trial Management System (TMS). It was blinded to all personnel apart from: The independent statistician who generated it; the IT team member who uploaded it onto the TMS; the IMP packaging team and the pharmacy team who managed the 24-hour emergency unblinding service.

Arms

Are arms mutually exclusive?	Yes
Arm title	Lixisenatide followed by matching placebo

Arm description:

Lixisenatide treatment period (4 weeks) followed by a washout period (4 weeks) then matching placebo treatment period (4 weeks) followed by a final washout period (4 weeks). Participants were asked to inject the trial medication using an injection pen once each morning (between 8-10 am) in addition to their prescribed insulin medication.

Arm type	Cross-over design
Investigational medicinal product name	Lixisenatide
Investigational medicinal product code	AVE0010
Other name	Lyxumia
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Lixisenatide 10µg/day injected subcutaneously between 8-10am for 2 weeks followed by lixisenatide

20µg/day injected for a further 2 weeks then a 28-day washout period.

Investigational medicinal product name	Matching placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Matching placebo 10µg/day injected subcutaneously between 8-10am for 2 weeks followed by matching placebo 20µg/day injected for a further 2 weeks then a 28-day washout period leading to the closeout visit.

Arm title	Matching placebo followed by lixisenatide

Arm description:

Matching placebo treatment period (4 weeks) followed by a washout period (4 weeks) then lixisenatide treatment period (4 weeks) followed by a final washout period (4 weeks). Participants were asked to inject the trial medication using an injection pen once each morning (between 8-10 am) in addition to their prescribed insulin medication.

Arm type	Cross-over design
Investigational medicinal product name	Matching placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Matching placebo 10µg/day injected subcutaneously between 8-10am for 2 weeks followed by matching placebo 20µg/day injected for a further 2 weeks then a 28-day washout period leading to the closeout visit.

Investigational medicinal product name	Lixisenatide
Investigational medicinal product code	AVE0010
Other name	Lyxumia
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Lixisenatide 10µg/day injected subcutaneously between 8-10am for 2 weeks followed by lixisenatide 20µg/day injected for a further 2 weeks then a 28-day washout period.

Number of subjects in period 1	Lixisenatide followed by matching placebo	Matching placebo followed by lixisenatide
Started	13	14
Completed	12	13
Not completed	1	1
Subject decision to stop visits, consent unchanged	1	-
Pregnancy	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Lixisenatide followed by matching placebo
Reporting group description:	
Lixisenatide treatment period (4 weeks) followed by a washout period (4 weeks) then matching placebo treatment period (4 weeks) followed by a final washout period (4 weeks). Participants were asked to inject the trial medication using an injection pen once each morning (between 8-10 am) in addition to their prescribed insulin medication.	
Reporting group title	Matching placebo followed by lixisenatide
Reporting group description:	
Matching placebo treatment period (4 weeks) followed by a washout period (4 weeks) then lixisenatide treatment period (4 weeks) followed by a final washout period (4 weeks). Participants were asked to inject the trial medication using an injection pen once each morning (between 8-10 am) in addition to their prescribed insulin medication.	

Reporting group values	Lixisenatide followed by matching placebo	Matching placebo followed by lixisenatide	Total
Number of subjects	13	14	27
Age categorical Units: Subjects			
Adults (18-64 years)	13	13	26
From 65-84 years	0	1	1
Gender categorical Units: Subjects			
Female	6	8	14
Male	7	6	13
Smoking status Units: Subjects			
Current smoker	2	1	3
Current non-smoker	11	13	24
Body Mass Index (BMI) Units: Kg/cm2			
arithmetic mean	26.7	27.0	
standard deviation	± 3.5	± 3.8	-
Waist circumference Units: cm			
arithmetic mean	91.9	91.6	
standard deviation	± 10.1	± 14.8	-
HbA1c Units: mmol/L			
arithmetic mean	66.2	64.2	
standard deviation	± 9.7	± 6.8	-
Fasting Plasma Glucose (FPG) Units: mmol/L			
arithmetic mean	9.8	9.9	
standard deviation	± 5.4	± 3.9	-
C-peptide Units: nmol/L			
arithmetic mean	0.0	0.0	

standard deviation	± 0.1	± 0.0	-

Subject analysis sets

Subject analysis set title	Full analysis population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Data for one participant was removed from the full analysis population for Arm 2 (matching placebo followed by lixisenatide) due to pregnancy post-randomisation. Twenty-six participants were therefore included in the initial full analysis data-set.

Data for two of the remaining twenty-six participants was subsequently also excluded from the primary analysis because one participant dropped out of the study visits after the first treatment period and one participant was missing baseline primary endpoint data. This meant that determination of treatment affect was not possible for these two individuals' data.

The primary end-point results analysis data presented in this report relates to the remaining 24 of the 27 participants randomised.

The Safety Population (SP) consists of all randomised individuals who received at least one dose of the study medication, hence adverse event information in this report is presented for all 27 participants randomised.

Reporting group values	Full analysis population		
Number of subjects	26		
Age categorical Units: Subjects			
Adults (18-64 years)	25		
From 65-84 years	1		
Gender categorical Units: Subjects			
Female	13		
Male	13		
Smoking status Units: Subjects			
Current smoker	3		
Current non-smoker	23		
Body Mass Index (BMI) Units: Kg/cm2			
arithmetic mean	27.01		
standard deviation	± 3.57		
Waist circumference Units: cm			
arithmetic mean	92.42		
standard deviation	± 12.22		
HbA1c Units: mmol/L			
arithmetic mean	65.58		
standard deviation	± 8.07		
Fasting Plasma Glucose (FPG) Units: mmol/L			
arithmetic mean	10.16		

standard deviation	± 4.38		
C-peptide			
Units: nmol/L			
arithmetic mean	0.03		
standard deviation	± 0.04		

End points

End points reporting groups

Reporting group title	Lixisenatide followed by matching placebo

Reporting group description:

Lixisenatide treatment period (4 weeks) followed by a washout period (4 weeks) then matching placebo treatment period (4 weeks) followed by a final washout period (4 weeks). Participants were asked to inject the trial medication using an injection pen once each morning (between 8-10 am) in addition to their prescribed insulin medication.

Reporting group title	Matching placebo followed by lixisenatide

Reporting group description:

Matching placebo treatment period (4 weeks) followed by a washout period (4 weeks) then lixisenatide treatment period (4 weeks) followed by a final washout period (4 weeks). Participants were asked to inject the trial medication using an injection pen once each morning (between 8-10 am) in addition to their prescribed insulin medication.

Subject analysis set title	Full analysis population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Data for one participant was removed from the full analysis population for Arm 2 (matching placebo followed by lixisenatide) due to pregnancy post-randomisation. Twenty-six participants were therefore included in the initial full analysis data-set.

Data for two of the remaining twenty-six participants was subsequently also excluded from the primary analysis because one participant dropped out of the study visits after the first treatment period and one participant was missing baseline primary endpoint data. This meant that determination of treatment affect was not possible for these two individuals' data.

The primary end-point results analysis data presented in this report relates to the remaining 24 of the 27 participants randomised.

The Safety Population (SP) consists of all randomised individuals who received at least one dose of the study medication, hence adverse event information in this report is presented for all 27 participants randomised.

Primary: The change in the percentage of Continuous Glucose Monitoring (CGM) readings between 4 and 10 mmol/l (inclusive) during the 3 hour post-prandial period, before and after treatment with lixisenatide compared to matching placebo.

End point title	The change in the percentage of Continuous Glucose Monitoring (CGM) readings between 4 and 10 mmol/l (inclusive) during the 3 hour post-prandial period, before and after treatment with lixisenatide compared to matching placebo.

End point description:

The primary end-point is to determine whether adding lixisenatide to basal bolus insulin significantly improves glycaemic control during the 3 hour post prandial period compared to basal bolus insulin and a placebo injection.

End point type	Primary

End point timeframe:

Up to 4 months.

End point values	Lixisenatide followed by matching placebo	Matching placebo followed by lixisenatide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11[1]	13[2]		
Units: Change in percentage of participants				
arithmetic mean (standard deviation)	-4.70 (± 26.3)	-9.86 (± 29.75)		

Notes:

[1] - One participant only completed period 1 and a second was missing baseline primary endpoint data.

[2] - Data for one participant was removed from the analysis data-set due to pregnancy post-randomisation.

Statistical analyses

Statistical analysis title	The Within-subject differences

Statistical analysis description:

The analysis was based on the means and standard deviations of the within-subject difference to reflect the resultant treatment effect and the paired nature of the design. The treatment effect was estimated based on an average of within-subject differences, after testing for the assumptions of no carryover or period effect, and that the within-subject differences were normally distributed. The estimated treatment effects are presented in means and standard deviations with 95% interval ranges.

Comparison groups	Matching placebo followed by lixisenatide v Lixisenatide followed by matching placebo
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	< 0.05
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[3] - Efficacy study.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Safety was assessed from screening through to each participant's closout visit. The closeout visit took place a minimum of 28 days after last dose of trial medication.

Adverse event reporting additional description:

All Adverse Events were documented within 24 hours of awareness with sponsor notified of Serious Adverse Events or pregnancy within 24 hours of awareness using sponsor-supplied forms.

Assessment type	Systematic

Dictionary used

Dictionary name	Events not coded
Dictionary version	N/A

Reporting groups

Reporting group title	Lixisenatide followed by matching placebo

Reporting group description:

Lixisenatide treatment period (4 weeks) followed by a washout period (4 weeks) then matching placebo treatment period (4 weeks) followed by a final washout period (4 weeks). Participants were asked to inject the trial medication using an injection pen once each morning (between 8-10 am) in addition to their prescribed insulin medication.

Reporting group title	Matching placebo followed by lixisenatide

Reporting group description:

Matching placebo treatment period (4 weeks) followed by a washout period (4 weeks) then lixisenatide treatment period (4 weeks) followed by a final washout period (4 weeks). Participants were asked to inject the trial medication using an injection pen once each morning (between 8-10 am) in addition to their prescribed insulin medication.

Serious adverse events	Lixisenatide followed by matching placebo	Matching placebo followed by lixisenatide	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 13 (0.00%)	1 / 14 (7.14%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
General disorders and administration site conditions			
Loss of consciousness			
subjects affected / exposed	0 / 13 (0.00%)	1 / 14 (7.14%)	
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: 0 %

Non-serious adverse events	Lixisenatide followed by matching placebo	Matching placebo followed by lixisenatide	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 13 (100.00%)	14 / 14 (100.00%)	
Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	0 / 13 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Non-specific event			
subjects affected / exposed	2 / 13 (15.38%)	3 / 14 (21.43%)	
occurrences (all)	2	3	
Headache			
subjects affected / exposed	2 / 13 (15.38%)	2 / 14 (14.29%)	
occurrences (all)	3	3	
Eye disorders			
Diabetes eye complications			
subjects affected / exposed	0 / 13 (0.00%)	2 / 14 (14.29%)	
occurrences (all)	0	3	
Gastrointestinal disorders			
Gastrointestinal side-effects			
subjects affected / exposed	4 / 13 (30.77%)	5 / 14 (35.71%)	
occurrences (all)	7	7	
Endocrine disorders			
Hypoglycaemia			
subjects affected / exposed	12 / 13 (92.31%)	14 / 14 (100.00%)	
occurrences (all)	292	511	
Infections and infestations			
Infection			
subjects affected / exposed	5 / 13 (38.46%)	2 / 14 (14.29%)	
occurrences (all)	5	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 March 2014	Substantial amendment 1.0 - summary of changes: - Amend the type of Continuous Glucose Monitoring device used during the trial. - Extend the Body Mass Index eligibility criterion from < or = 27 kg/m2 to < 30 kg/m2. - Clarify how the Part A trial results will be analysed. - Ensure that visit procedures are consistent and will permit the collection of eligibility data at screening. - To seek permission to store surplus blood samples collected during the Part B trial for up to 5 years following the end of the trial, after which time they will be destroyed.
09 July 2014	Substantial amendment 2.0 - Summary of changes: - To increase the Body Mass Index (BMI) eligibility criterion from < 30 kg/m2 to < 35 kg/m2. - To remove the following inclusion criterion: 'Insulin treatment since diabetes'. - To amend the blood collection tubes used for the following tests during the trial: Glucose-dependant insulinotropic peptide or gastric inhibitory peptide (GIP), Glucagon-Like-Peptide1 (GLP1), Glucagon and the counter-regulatory hormones, adrenaline, noradrenaline, cortisol and pancreatic polypeptide.
05 December 2014	Substantial amendment 3.0 - Summary of changes: - To increase the upper age limit eligibility criterion from aged 18-65 years to 18-70 years. - To increase the upper glycated haemoglobin (HbA1c) eligibility criterion limit from 7.0 - 9.0% inclusive to 7.0 - 10.0% inclusive. - To increase the upper C-peptide value (C-peptide negative group only) eligibility criterion from Random or fasting C-peptide <0.02 nmol/l to <0.1 nmol/l. - Include a breath test procedure to measure gastric emptying. - Clarify that the ancillary study procedures are optional and take place once during the trial. To also document separate Informed Consent for the ancillary study procedures. - Revise the length of some of the Part B trial visits. - Update the Gastric Inhibitory Peptide (GIP) and Glucagon Like Peptide-1 (GLP-1) assay names. - To update other trial documents in-line with the above protocol updates (Participant Information Leaflet, Informed Consent Form, Protocol summary and the advertising poster). - To notify that an updated version of existing Investigator Brochure is now issued (Edition 11 dated 21 April 2014).
21 August 2015	Substantial amendment 4.0 - Summary of changes: - To decrease the lower glycated haemoglobin (HbA1c) limit eligibility criterion from 7.0 - 10.0% inclusive to 6.5 - 10.0% inclusive. - To Update to the existing single-centre clinical site team (addition of one further research clinician).

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.

The study closed to recruitment on 5th January 2016. This deadline was fixed in-line with the expiry date of the study medication. At this point a total of 27 participants were randomised onto the main study compared to the target of 30.

Notes: