Clinical trial results:
The effect of Lixisenatide on triacylglycerol and glucose metabolism in patients with type 2 diabetes

Summary

EudraCT number	2013-002826-22
Trial protocol	GB
Global end of trial date	18 January 2016

Results information

Result version number	v1 (current)
This version publication date	19 April 2017
First version publication date	19 April 2017

Trial information

Trial identification

Sponsor protocol code	CRC333/LIXISL06684

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02049034
WHO universal trial number (UTN)	-
Other trial identifiers	Sanofi identifier: LIXISL06684

Notes:

Sponsors

Sponsor organisation name	University of Surrey
Sponsor organisation address	Daphne Jackson Rd, Manor Park, Guildford, United Kingdom, GU2 7WG
Public contact	Gill Fairbairn, University of Surrey, ++44 1483 686434, g.fairbairn@surrey.ac.uk
Scientific contact	Professor Margot Umpleby, University of Surrey, ++44 1483 686434, m.umpleby@surrey.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	01 March 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 January 2016
Global end of trial reached?	Yes
Global end of trial date	18 January 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The total rate of glucose appearance following the breakfast meal at visits 3 and 7, measured as AUC (0-180 minutes) and AUC (0-240 minutes) where the meal is given at 0 minutes.

Protection of trial subjects:

This was not an efficacy study. All safety assessments were standard.
During the study, adverse events were collected and documented at every visit, regardless of relationship to study medication. These events were coded using the MedDRA (Medical Dictionary for Regulatory Activities) dictionary version 18.1 September 2015 by blinded Surrey CRC data management personnel and checked by the study physician.
The following criteria were used to identify adverse events:
Any unfavourable or unintended sign or symptom
Any deterioration in laboratory data, vital signs or found on physical examination.
All concomitant medications taken during the study were recorded.

Background therapy:

Allowable concomitant diabetes therapy: Metformin

Permitted concomitant therapy: statins, antihypertensives.

Evidence for comparator:

The type of control group: As it was a cross-over trial the participants acted as their own controls. The placebo and GLP-1 injections were indistinguishable and were provided in the same pen-format for subcutaneous injection.
Rationale behind design: A randomised double-blind placebo controlled study design was chosen to study the effect of lixisenatide against a placebo treatment where both the participant and the research group were blinded to the order of the treatment received.
Known or potential problems with design or control groups chosen in relation to the study: Using a cross-over trial can mean that a carry-over effect occurs from the first period to the second period of the trial. This was minimised by using a double-blinded approach and by the presence of a four-week washout period between the treatment arms. Statistical analyses were conducted to determine whether a period effect was present. In this eventuality, comparisons between treatments were made solely at data from period one.

Actual start date of recruitment	01 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: 8
Worldwide total number of subjects	8
EEA total number of subjects	8

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)	8
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited via the Primary Care Research Network South-East (PCRN SE), approached practices within reasonable travelling distance of Guildford to invite them to support this study, from any REC approved registered research data base, advertisements in local papers including Metro and Evening Standard from Feb 2014-Aug 2015.

Pre-assignment

Screening details:

There were no wash out or pre assignment periods for screening. Interested patients with type 2 diabetes inadequately controlled by metformin were interviewed on the phone to confirm the inclusion criteria, 24 patients were invited to screening. 14 patients failed to meet inclusion (HbA1c, smoking and weight) and 2 patients withdrew consent.

Period 1

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

Blinding implementation details:

This is a double blind crossover study. Subjects will be randomised into 2 groups. One group will receive a once daily subcutaneous injection of lixisenatide for 4 weeks followed by a 4 week washout then once daily subcutaneous injection of placebo for 4 weeks. The other group will receive a once daily subcutaneous placebo injection for 4 weeks followed by a 4 week washout then once daily subcutaneous injection of lixisenatide for 4 week. The placebo and GLP-1 injection were indistinguishable

Arms

Are arms mutually exclusive?	No
Arm title	Placebo

Arm description:

Lixisenatide and placebo are considered as investigational medicinal product (IMP). Metformin is not considered an investigational product but is an allowed antidiabetic medication to be taken concomitantly.
Identity of investigational products(s)
Lixisenatide was supplied as disposable pre-filled pen-injectors for subcutaneous injection: 10mcg lixisenatide green pens; 20 mcg lixisenatide purple pens. Dose titration-10mcg lixisenatide for 14 days, 20 mcg for 14 days.
Placebo for lixisenatide was supplied as green and purple coloured disposable pen-injectors containing 3 mL of a sterile aqueous solution.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	PL1
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo for lixisenatide was supplied as green and purple coloured disposable pen-injectors containing 3 mL of a sterile aqueous solution.

Arm title	lixisenatide

Arm description:

Lixisenatide and placebo are considered as investigational medicinal product (IMP). Metformin is not considered an investigational product but is an allowed antidiabetic medication to be taken concomitantly. Identity of investigational products(s) Lixisenatide was supplied as disposable pre-filled pen-injectors for subcutaneous injection: 10mcg lixisenatide green pens; 20 mcg lixisenatide

purple pens. Dose titration-10mcg lixisenatide for 14 days, 20 mcg for 14 days. Placebo for lixisenatide was supplied as green and purple coloured disposable pen-injectors containing 3 mL of a sterile aqueous solution.

Arm type	Experimental
Investigational medicinal product name	lixisenatide
Investigational medicinal product code	320367-13-3
Other name	GLP-1 agonist, Lyxumia
Pharmaceutical forms	Suspension for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Lixisenatide was supplied as disposable pre-filled pen-injectors for subcutaneous injection: 10mcg lixisenatide green pens; 20 mcg
lixisenatide purple pens. Dose titration-10mcg lixisenatide for 14 days, 20 mcg for 14 days.

Number of subjects in period 1	Placebo	lixisenatide
Started	8	8
Completed	8	8

Baseline characteristics

Reporting groups	
Reporting group title	overall trial

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	8	8	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Adults (40 - 65 years)	8	8	
Age continuous Units: years			
arithmetic mean	57.3		
standard deviation	± 5.26	-	
Gender categorical Units: Subjects			
Female	0	0	
Male	8	8	
Body mass index			
Body mass index measured at baseline			
Units: Subjects			
27 - 40 kg/m2	8	8	
Weight			
Body weight at baseline			
Units: Subjects			
Weight	8	8	
FFM			
Fat Free Mass at baseline			
Units: Subjects			
FFM	8	8	
Creatinine			
Plasma Creatinine			
Units: Subjects			
64-104 umol/L	8	8	
Fasting glucose Units: Subjects			
4.1-6.0 mmol/L	8	8	

Amylase Units: Subjects			
less than 118 U/L	8	8	
ALT			
Alanine transaminase			
Units: Subjects			
less than 50 IU/L	8	8	
Total Cholesterol Units: Subjects			
less than 4 mmol/L	8	8	
Plasma TAG			
Plasma triacylglycerol			
Units: Subjects			
P-TAG	8	8	
HbA1c			
Haemoglobin A1c			
Units: Subjects			
HbA1C	8	8	
lipase Units: Subjects			
Lipase (5-65 U/L)	8	8	
Calcitonin Units: Subjects			
Calcitonin (less than 11.8 ng/ml)	8	8	
Body mass index			
Body mass index at baseline- lixisenatide arm			
Units: kg/m2			
arithmetic mean	30.3		
standard deviation	± 2.9	-	
Body weight			
body weight at baseline			
Units: kg			
arithmetic mean	93.1		
standard deviation	± 9.8	-	
FFM			
Fat free mass at baseline			
Units: kg			
arithmetic mean	66.5		
standard deviation	± 6.5	-	
Creatinine Units: mcmol/L			
arithmetic mean	76.6		
standard deviation	± 11.9	-	
Fasting glucose Units: mmol/L			
arithmetic mean	8.4		
standard deviation	± 1.5	-	
Amylase			
Enzyme			
Units: U/L			
arithmetic mean	44.9		

standard deviation	± 15.3	-	
ALT			
Alanine Transaminase			
Units: IU/L			
arithmetic mean	42.8		
standard deviation	± 18.6	-	
Total Cholesterol			
Units: mmol/L			
arithmetic mean	3.8		
standard deviation	± 0.7	-	
Plasma TAG			
Plasma Triglyceride			
Units: mmol/L			
arithmetic mean	1.76		
standard deviation	± 0.78	-	
HbA1C			
Haemoglobin A1C			
Units: mmol/mol			
arithmetic mean	66.5		
standard deviation	± 7.2	-	
Lipase			
Units: U/L			
arithmetic mean	34.5		
standard deviation	± 7.7	-	
Calcitonin			
Units: ng/L			
arithmetic mean	3.4		
standard deviation	± 1.5	-	

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Lixisenatide and placebo are considered as investigational medicinal product (IMP). Metformin is not considered an investigational product but is an allowed antidiabetic medication to be taken concomitantly.
Identity of investigational products(s)
Lixisenatide was supplied as disposable pre-filled pen-injectors for subcutaneous injection: 10mcg lixisenatide green pens; 20 mcg lixisenatide purple pens. Dose titration-10mcg lixisenatide for 14 days, 20 mcg for 14 days.
Placebo for lixisenatide was supplied as green and purple coloured disposable pen-injectors containing 3 mL of a sterile aqueous solution.

Reporting group title	lixisenatide

Reporting group description:

Lixisenatide and placebo are considered as investigational medicinal product (IMP). Metformin is not considered an investigational product but is an allowed antidiabetic medication to be taken concomitantly. Identity of investigational products(s) Lixisenatide was supplied as disposable pre-filled pen-injectors for subcutaneous injection: 10mcg lixisenatide green pens; 20 mcg lixisenatide purple pens. Dose titration-10mcg lixisenatide for 14 days, 20 mcg for 14 days. Placebo for lixisenatide was supplied as green and purple coloured disposable pen-injectors containing 3 mL of a sterile aqueous solution.

Primary: Area under curve the total rate of glucose appearance; AUC total glu Ra 0-180 min

End point title	Area under curve the total rate of glucose appearance; AUC total glu Ra 0-180 min

End point description:

Area under the curve (AUC) for glucose concentration (mmol/L*min) for periods 0-180min, 0-240min and for the whole response curve (0-360min) after a mixed meal at 0 min, at the end of 4 weeks treatment with either lixisenatide or placebo (visits V3 or V7, depending on the randomisation). Lixisenatide/placebo injection was self-administered at -30 min. Results are mean ± SEM.

End point type	Primary

End point timeframe:

4 week once daily injection of lixisenatide or placebo, blood samples obtained at 4 weeks

End point values	Placebo	lixisenatide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	8		
Units: mcmol/kg				
arithmetic mean (standard error)	4883 (± 275)	2866 (± 274)		

Attachments (see zip file)	Total Glucose Ra/Total GluRa_lixi.png

Statistical analyses

Statistical analysis title	Superiority testing

Statistical analysis description:

This was a double blind cross over study. A general linear mixed model with repeated measures was used employing SAS PROC MIXED, with explanatory variables period and treatment. The variance covariance matrix used for the repeated measure time course measurements was SP(POW). Participant was a random effect.
Significance was accepted at 5% level, without use of multiplicity adjustment.

Comparison groups	lixisenatide v Placebo
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.002 [2]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	2017.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	1156.48
upper limit	2877.77
Variability estimate	Standard error of the mean

Notes:

[1] - A general linear mixed model with repeated measures was used employing SAS PROC MIXED, with explanatory variables period and treatment. The variance covariance matrix used for the repeated measure time course measurements was SP(POW). Participant was a random effect.
Significance was accepted at 5% level, without use of multiplicity adjustment.
[2] - P-value for the total glucose Ra chart attached were all at p <0.05.

Primary: Area under curve of the total rate of glucose appearance; AUC total gluRa 0-240 min

End point title	Area under curve of the total rate of glucose appearance; AUC total gluRa 0-240 min

End point description:

Area under the curve (AUC) for glucose Rd measurements (µmol/kg) for periods 0-180min, 0-240min and for the whole response curve (0-360min) after a mixed meal at 0 min at the end of 4 weeks treatment with either lixisenatide or placebo (visits V3 or V7, depending on the randomisation). Lixisenatide/placebo injection was self-administered at -30 min. Results are mean ± SEM.

End point type	Primary

End point timeframe:

4 week once daily injection of lixisenatide or placebo, blood samples obtained at 4 weeks

End point values	Placebo	lixisenatide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	8		
Units: mcmol/kg				
arithmetic mean (standard error)	5371 (± 265)	3979 (± 227)		

Statistical analyses

Statistical analysis title	Superiority testing

Statistical analysis description:

The study was a double blind crossover study comparing placebo injection with lixisenatide injection.

Comparison groups	Placebo v lixisenatide
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.002 [4]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	1391.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	615.23
upper limit	2168.52
Variability estimate	Standard error of the mean

Notes:

[3] - The study was a double blind crossover study comparing placebo injection with lixisenatide injection. A general linear mixed model with repeated measures was used employing SAS PROC MIXED, with explanatory variables period and treatment. The variance covariance matrix used for the repeated measure time course measurements was SP(POW). Participant was a random effect.
Significance was accepted at 5% level, without use of multiplicity adjustment.
[4] - Significance was accepted at 5% level, without use of multiplicity adjustment.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

This includes events from the first trial related activity after the subject has signed the informed consent and until post treatment follow-up period as defined in the protocol.

Adverse event reporting additional description:

The following criteria were used to identify adverse events: Any unfavourable or unintended sign or symptom, Any deterioration in laboratory data, vital signs or found on physical examination.
All concomitant medications taken during the study were recorded

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

The study was a double blind crossover study comparing placebo injection with lixisenatide injection. Placebo for lixisenatide was supplied as green and purple coloured disposable pen-injectors containing 3 mL of a sterile aqueous solution.

Reporting group title	lixisenatide

Reporting group description:

The study was a double blind crossover study comparing placebo injection with lixisenatide injection. 4 week once daily injection of lixisenatide: Dose titration-10mcg lixisenatide for 14 days, 20 mcg for 14 days.

Serious adverse events	Placebo	lixisenatide	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 8 (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	Placebo	lixisenatide	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 8 (87.50%)	5 / 8 (62.50%)	
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	2 / 8 (25.00%)	0 / 8 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			

Diabetic neuropathy			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Eye disorders			
Belpharitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 8 (12.50%)	2 / 8 (25.00%)	
occurrences (all)	2	2	
Haemorrhoids			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	2	
Spigelian hernia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Gingivitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Rhinitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	2	
Oral herpes			

subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Tooth abscess			
subjects affected / exposed	1 / 8 (12.50%)	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
14 April 2014	Protocol V5, 21/08/2013 with 3 appendices approval date: 14/04/2014 Reason for amendment: To improve recruitment of participants. Patients will be recruited via the Primary Care Research Network South East (PCRN SE), who will approach practices within reasonable travelling distance of Guildford to invite them to support this study. Suitable patients will be contacted by letter and those that are interested will be contacted by phone to ensure they fulfil the inclusion/exclusion criteria. They will then be sent further information about the study. In addition to this we will contact University of Surrey staff by email, indicating our criteria and inviting them to contact us if they are interested in taking part, then sending them the written information sheet (PIS) and then we will contact them again after a 2-3 days to see if they want to arrange a screening visit. Additionally also by letter from the REC approved registered research database (for example Diabetes Alliance for Research in England; DARE) coordinators inviting them to take part in the study and phone the team for more information or reply by return of the enclosed return slip in the letter (in the envelope provided) giving their permission to be contacted by the research team. The cover letter from DARE team is enclosed.
16 May 2014	Protocol V5, 21/08/2013 with 4 appendices approval date 16/05/2014 1- To improve recruitment of participants. 2- The current inclusion criteria of HbA1c and BMI are narrow making recruitment very difficult such that we have not been able to recruit any patients to date into the trial. Widening these criteria will improve recruitment without affecting the integrity of study. Criteria changed from: HbA1c 7.5-8.5% (inclusive), BMI 30-35 kg/m2 (inclusive), to: HbA1c 7.5-9.5% (inclusive) BMI 29-38 kg/m2 (inclusive),
19 August 2014	Protocol V5, 21/08/2013 with 5 appendices approval date: 19/08/2014 To improve recruitment of participants. Protocol V5, section on participant recruitment was amended as follows: We will advertise the study in local papers including Metro and Evening Standard on paper as well as digitally available App for the above newspapers. Please refer to appendices 2, 4 & 5. Protocol V5, Selection of patients, exclusion criteria, page 13: Patients on beta blockers are now included in inclusion criteria.

09 March 2015	Protocol V5, 21/08/2013 with 6 appendices approval date: 09/03/2015 To verify the stable diabetes control- We added an HbA1c measurement to visit 1 - in order to have up-to-date reassurance of the stability of HbA1c at the start of the study. To provide further reassurance, we will ensure that the metformin dose is unchanged since their last GP visit and so will enter the statement "no changes to metformin dose since that last GP surgery check up". To improve recruitment of participants- The current inclusion criteria of BMI (29-38 kg/m2) are narrow, making recruitment very difficult. Widening these criteria will improve recruitment without affecting the integrity of the study. Amendment to expenses claim- We have found that eight visits, of which four are over seven hours in duration, over the course of the three months study, is affecting the recruitment rate from patients who are in employment due to the low remuneration. We believe the increase in compensation payment should increase recruitment numbers from people in employment who often have to take unpaid leave to meet the time commitments of the study. We will pay the extra reimbursement to the patients who have already been on the trial and received their payment at the original rate. Change to personnel- Two personnel, one a replacement student and the other recruitment officer have left the University, so these have been assigned off study with their end dates.

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.

1- The timing of the IMP at visit 4 and 8. The IMP, given at -270 min, would have been preferable to be given at 0 time. 2- A crossover effect was demonstrated statistically for a number lipid parameters reducing the power of calculation.

Notes: