



## Clinical trial results:

**A randomized, controlled multi-centre trial of 26 weeks of subcutaneous Liraglutide (a GLP1 receptor agonist), with or without continuous positive airway pressure (CPAP), in patients with Type 2 Diabetes Mellitus (T2DM) and Obstructive Sleep Apnoea (OSA)**

### Summary

EudraCT number	2014-000988-41
Trial protocol	GB
Global end of trial date	10 October 2019

### Results information

Result version number	v1 (current)
This version publication date	25 October 2020
First version publication date	25 October 2020

### Trial information

#### Trial identification

Sponsor protocol code	UoL000977
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#### Additional study identifiers

ISRCTN number	ISRCTN16250774
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	U1111-1139-0677

Notes:

### Sponsors

Sponsor organisation name	Liverpool Clinical Trials Centre, University of Liverpool
Sponsor organisation address	1-3 Brownlow Street, Liverpool, United Kingdom, L69 3GL
Public contact	Charlotte Rawcliffe Liverpool Clinical Trials Centre University of Liverpool L69 3GL, Charlotte Rawcliffe Liverpool Clinical Trials Centre University of Liverpool L69 3GL, 0151 794 8167, clr001@liverpool.ac.uk
Scientific contact	Charlotte Rawcliffe Liverpool Clinical Trials Centre University of Liverpool L69 3GL, Charlotte Rawcliffe Liverpool Clinical Trials Centre University of Liverpool L69 3GL, 0151 794 8167, clr001@liverpool.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
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Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	08 October 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 October 2019
Global end of trial reached?	Yes
Global end of trial date	10 October 2019
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

Primary objective

To determine whether twenty six weeks of Liraglutide treatment (up to 1.8mg) can provide a useful treatment for obese patients with T2DM and OSA, either as a stand-alone treatment or as an add-on treatment to continuous positive airway pressure (CPAP). We are primarily concerned with change from baseline in AHI (the principal measure of OSA severity).

Protection of trial subjects:

Consent was obtained prior to each patient participating in the trial, after a full explanation had been given of the treatment options, including the conventional and generally accepted methods of treatment. All risks and potential benefits were explained to the patients, and all patients were provided with Patient Information Sheets prior to consent. Patients were given the right to refuse their consent to participate in the trial, and to withdraw at any time.

The study also had a Trial Steering Committee that provided overall supervision of the trial, particularly focusing on the progress of the trial, adherence to the protocol, patient safety and consideration of new information. The TSC included experienced diabetes and sleep respiratory experts and clinical trialists. Meetings were held annually, but additional meetings could have been held if required.

Background therapy:

N/A

Evidence for comparator:

The co-existence of obesity and insulin resistance in Type 2 Diabetes Mellitus (T2DM) and Obstructive Sleep Apnoea (OSA) provide a robust and plausible rationale for the therapeutic administration of Liraglutide to T2DM patients with OSA. The study is being undertaken to understand possible effects of Liraglutide, both as a monotherapy and in combination with continuous positive airway pressure (CPAP), on OSA symptoms and glycaemic control in obese OSA patients with T2DM. The data collected will help shape optimal treatment strategies for this challenging clinical population.

Actual start date of recruitment	11 November 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

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Country: Number of subjects enrolled	United Kingdom: 132
Worldwide total number of subjects	132
EEA total number of subjects	132

Notes:

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**Subjects enrolled per age group**

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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)	120
From 65 to 84 years	12
85 years and over	0

## Subject disposition

### Recruitment

#### Recruitment details:

Recruitment was estimated to be over a period of 24 months and took place in one centre – Aintree University Hospital, England (UK) – which expected to recruit 5-6 patients per month. Aintree site opened to recruitment on 10/09/2015. First patient randomised 12/11/2015; Last patient randomised 18/02/2019. 132 participants were recruited in total.

### Pre-assignment

#### Screening details:

232 patients were screened and 132 were randomised. Subjects were recruited from diabetes or sleep apnoea clinics within the Aintree. Eligible subjects attended a screening visit between 2-21 days prior to randomisation and included medical history, concomitant medications, physical exam, blood tests and overnight home study.

### Period 1

Period 1 title	Intervention Phase (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

#### Blinding implementation details:

N/A

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Arm A: Control Arm

#### Arm description:

Control arm, comprising conventional care for existing T2DM patients with no intervention for OSA. This group did not use placebo medication. Patients were asked to continue with their usual anti-diabetes medications and if titration of any anti-diabetes drugs is necessary, due to worsening glycaemic control, this was achieved by avoiding the use of any Liraglutide and patients were given subcutaneous insulin (using either once daily or twice daily formulations). Patients were not be given CPAP for this period.

Arm type	No intervention
No investigational medicinal product assigned in this arm	
<b>Arm title</b>	Arm B: CPAP

#### Arm description:

Will receive conventional care plus CPAP. The CPAP device that will be used will be ResMed S9 (or other similar device) fixed pressure device in accordance with the standard clinical protocols.

Arm type	Experimental
Investigational medicinal product name	Liraglutide
Investigational medicinal product code	
Other name	Victoza
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

#### Dosage and administration details:

Liraglutide was administered as a once-daily subcutaneous injection in the abdomen, thigh or upper arm. It was given at a starting dose of 0.6 mg once daily, increasing after one week to 1.2mg once daily. After at least one week of treatment with 1.2mg the patient was reviewed again and the dose increased to 1.8mg once daily.

The patients who could not tolerate the increased dose after the first week were asked to continue at 0.6mg daily and were re-challenged with the higher dose (1.2mg) after 4-weeks. If the intolerance persisted, patients were asked to remain on the lowest, tolerated dose. The trial specific prescription would allow the prescriber to specify individual doses and quantities for those patients who did not tolerate the intended dose.

<b>Arm title</b>	Arm C: Liraglutide
Arm description: Will receive conventional care plus Liraglutide (up to 1.8mg).	
Arm type	CPAP Device
No investigational medicinal product assigned in this arm	
<b>Arm title</b>	Arm D: Liraglutide + CPAP
Arm description: Will receive conventional care plus Liraglutide plus CPAP. The CPAP device that will be used will be ResMed S9 (or other similar device) fixed pressure device in accordance with the standard clinical protocols.	
Arm type	Experimental
Investigational medicinal product name	Liraglutide
Investigational medicinal product code	
Other name	Victoza
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

**Dosage and administration details:**

Liraglutide was administered as a once-daily subcutaneous injection in the abdomen, thigh or upper arm. It was given at a starting dose of 0.6 mg once daily, increasing after one week to 1.2mg once daily. After at least one week of treatment with 1.2mg the patient was reviewed again and the dose increased to 1.8mg once daily.

The patients who could not tolerate the increased dose after the first week were asked to continue at 0.6mg daily and were re-challenged with the higher dose (1.2mg) after 4-weeks. If the intolerance persisted, patients were asked to remain on the lowest, tolerated dose. The trial specific prescription would allow the prescriber to specify individual doses and quantities for those patients who did not tolerate the intended dose.

<b>Number of subjects in period 1</b>	Arm A: Control Arm	Arm B: CPAP	Arm C: Liraglutide
Started	33	33	33
Completed	33	33	33

<b>Number of subjects in period 1</b>	Arm D: Liraglutide + CPAP
Started	33
Completed	33

## Baseline characteristics

### Reporting groups

Reporting group title	Arm A: Control Arm
Reporting group description: Control arm, comprising conventional care for existing T2DM patients with no intervention for OSA. This group did not use placebo medication. Patients were asked to continue with their usual anti-diabetes medications and if titration of any anti-diabetes drugs is necessary, due to worsening glycaemic control, this was achieved by avoiding the use of any Liraglutide and patients were given subcutaneous insulin (using either once daily or twice daily formulations). Patients were not be given CPAP for this period.	
Reporting group title	Arm B: CPAP
Reporting group description: Will receive conventional care plus CPAP. The CPAP device that will be used will be ResMed S9 (or other similar device) fixed pressure device in accordance with the standard clinical protocols.	
Reporting group title	Arm C: Liraglutide
Reporting group description: Will receive conventional care plus Liraglutide (up to 1.8mg).	
Reporting group title	Arm D: Liraglutide + CPAP
Reporting group description: Will receive conventional care plus Liraglutide plus CPAP. The CPAP device that will be used will be ResMed S9 (or other similar device) fixed pressure device in accordance with the standard clinical protocols.	

Reporting group values	Arm A: Control Arm	Arm B: CPAP	Arm C: Liraglutide
Number of subjects	33	33	33
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: months median inter-quartile range (Q1-Q3)	52 48 to 57	57 49 to 60	55 45 to 61
Gender categorical Units: Subjects			
Female	17	20	19
Male	16	13	14
Ethnicity Units: Subjects			
Other	1	2	0
White	32	31	33
Smoking Status			

Units: Subjects			
Current Smoker	5	3	5
Ex Smoker	15	7	13
Never Smoked	13	23	15
Height			
Units: cm			
median	165	165	168
inter-quartile range (Q1-Q3)	161 to 177	160 to 174	164 to 172
Weight			
Units: kg			
median	106.9	107.8	105.9
inter-quartile range (Q1-Q3)	97.7 to 127.3	97.4 to 130.9	93.7 to 115.2
Waist			
Units: cm			
median	124	127	121
inter-quartile range (Q1-Q3)	120 to 134	117 to 136	111 to 132
Waist:Hip Ratio			
Units: cm			
median	1.035	1.02	1.03
inter-quartile range (Q1-Q3)	.99 to 1.073	.98 to 1.07	0.992 to 1.07

<b>Reporting group values</b>	Arm D: Liraglutide + CPAP	Total	
Number of subjects	33	132	
Age categorical			
Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Units: months			
median	54	-	
inter-quartile range (Q1-Q3)	46 to 61	-	
Gender categorical			
Units: Subjects			
Female	11	67	
Male	22	65	
Ethnicity			
Units: Subjects			
Other	0	3	
White	33	129	
Smoking Status			
Units: Subjects			
Current Smoker	9	22	
Ex Smoker	13	48	

Never Smoked	11	62	
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Height Units: cm median inter-quartile range (Q1-Q3)	173 165 to 177	-	
Weight Units: kg median inter-quartile range (Q1-Q3)	106.9 93.6 to 124.4	-	
Waist Units: cm median inter-quartile range (Q1-Q3)	123 116 to 131	-	
Waist:Hip Ratio Units: cm median inter-quartile range (Q1-Q3)	1.02 .99 to 1.058	-	



## End points

### End points reporting groups

Reporting group title	Arm A: Control Arm
Reporting group description: Control arm, comprising conventional care for existing T2DM patients with no intervention for OSA. This group did not use placebo medication. Patients were asked to continue with their usual anti-diabetes medications and if titration of any anti-diabetes drugs is necessary, due to worsening glycaemic control, this was achieved by avoiding the use of any Liraglutide and patients were given subcutaneous insulin (using either once daily or twice daily formulations). Patients were not be given CPAP for this period.	
Reporting group title	Arm B: CPAP
Reporting group description: Will receive conventional care plus CPAP. The CPAP device that will be used will be ResMed S9 (or other similar device) fixed pressure device in accordance with the standard clinical protocols.	
Reporting group title	Arm C: Liraglutide
Reporting group description: Will receive conventional care plus Liraglutide (up to 1.8mg).	
Reporting group title	Arm D: Liraglutide + CPAP
Reporting group description: Will receive conventional care plus Liraglutide plus CPAP. The CPAP device that will be used will be ResMed S9 (or other similar device) fixed pressure device in accordance with the standard clinical protocols.	
Subject analysis set title	Intention To Treat
Subject analysis set type	Intention-to-treat
Subject analysis set description: Full analysis set following the intention-to-treat principle with 18 patients removed as data not available for final analysis	
Subject analysis set title	Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description: Analysis of all patients to receive treatment (1 patient ended study prior to receiving treatment)	
Subject analysis set title	Full Analysis set
Subject analysis set type	Full analysis
Subject analysis set description: Being the set of patients recruited into the study	

### Primary: AHI (i.e. OSA severity).

End point title	AHI (i.e. OSA severity).
End point description: To determine whether twenty six weeks of Liraglutide treatment (up to 1.8mg) can provide a useful treatment for obese patients with T2DM and OSA, either as a stand-alone treatment or as an add-on treatment to continuous positive airway pressure (CPAP). We are primarily concerned with change from baseline in AHI (the principal measure of OSA severity).	
End point type	Primary
End point timeframe: Change in AHI between baseline and Twenty six weeks	

End point values	Arm A: Control Arm	Arm B: CPAP	Arm C: Liraglutide	Arm D: Liraglutide + CPAP
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	29	28	31	26
Units: AHI				
median (inter-quartile range (Q1-Q3))	-5.2 (-12.3 to 5.6)	-7.95 (-15.825 to 1.725)	-10.4 (-12.5 to -3.65)	-10.9 (-19.525 to -7.525)

<b>Attachments (see zip file)</b>	AHI by arm/AHIbox.pdf
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### Statistical analyses

Statistical analysis title	Primary Outcome (CPAP)
Comparison groups	Arm A: Control Arm v Arm B: CPAP v Arm C: Liraglutide v Arm D: Liraglutide + CPAP
Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	superiority <sup>[1]</sup>
P-value	= 0.028 <sup>[2]</sup>
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-6.35
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-13.722
upper limit	1.019
Variability estimate	Standard error of the mean
Dispersion value	2.861

Notes:

[1] - Analysis of Covariance

[2] - Adjusted for multiple comparisons, a value of <0.01 required to determine statistical significance

Statistical analysis title	Primary Outcome (Liraglutide)
Comparison groups	Arm A: Control Arm v Arm B: CPAP v Arm C: Liraglutide v Arm D: Liraglutide + CPAP
Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006 <sup>[3]</sup>
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-8.1
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-15.518
upper limit	-0.692
Variability estimate	Standard error of the mean
Dispersion value	2.878

Notes:

[3] - Adjusted for multiple comparisons, a value of <0.01 required to determine statistical significance

## Secondary: HbA1c

End point title	HbA1c
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End point description:

Assess the change from baseline in HbA1c.

End point type	Secondary
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End point timeframe:

Change in HbA1c between baseline and Twenty six weeks

End point values	Arm A: Control Arm	Arm B: CPAP	Arm C: Liraglutide	Arm D: Liraglutide + CPAP
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	27	31	28
Units: HbA1c				
median (inter-quartile range (Q1-Q3))	-1 (-5 to 4.5)	1 (-4.5 to 4)	-10 (-15.5 to -5)	-11 (-19 to -4.25)

## Statistical analyses

Statistical analysis title	HbA1C (CPAP)
Comparison groups	Arm A: Control Arm v Arm B: CPAP v Arm C: Liraglutide v Arm D: Liraglutide + CPAP
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.405
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.395
upper limit	5.954
Variability estimate	Standard error of the mean
Dispersion value	2.13

Statistical analysis title	HbA1c (Liraglutide)
Comparison groups	Arm D: Liraglutide + CPAP v Arm A: Control Arm v Arm B: CPAP v Arm C: Liraglutide

Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-10.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.861
upper limit	-6.524
Variability estimate	Standard error of the mean
Dispersion value	2.127

## Secondary: Body Weight

End point title	Body Weight
End point description:	Assess the change from baseline in body weight.
End point type	Secondary
End point timeframe:	Change between baseline and twenty six weeks

End point values	Arm A: Control Arm	Arm B: CPAP	Arm C: Liraglutide	Arm D: Liraglutide + CPAP
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	25	31	28
Units: kg				
median (inter-quartile range (Q1-Q3))	-1.8 (-3.525 to 0.65)	-0.3 (-5.6 to 1.8)	-6.9 (-10.4 to -2.35)	-4.05 (-6.275 to -2.6)

## Statistical analyses

Statistical analysis title	Body Weight (CPAP)
Comparison groups	Arm A: Control Arm v Arm B: CPAP v Arm C: Liraglutide v Arm D: Liraglutide + CPAP
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.404
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.339
upper limit	3.336
Variability estimate	Standard error of the mean
Dispersion value	1.193

<b>Statistical analysis title</b>	Body Weight (Liraglutide)
Comparison groups	Arm A: Control Arm v Arm B: CPAP v Arm C: Liraglutide v Arm D: Liraglutide + CPAP
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.094
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-4.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.17
upper limit	-2.487
Variability estimate	Standard error of the mean
Dispersion value	1.195

## Secondary: Oxygen Desturation Index

End point title	Oxygen Desturation Index
End point description:	
End point type	Secondary
End point timeframe:	
Change between baseline and twenty=six weeks	

End point values	Arm A: Control Arm	Arm B: CPAP	Arm C: Liraglutide	Arm D: Liraglutide + CPAP
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	26	30	21
Units: ODI				
median (inter-quartile range (Q1-Q3))	-6.5 (-14.05 to 2.05)	-7.65 (-14.875 to 4.3)	-7.2 (-12.275 to 0.825)	-12.2 (-19.7 to 5)

## Statistical analyses

<b>Statistical analysis title</b>	ODI (CPAP)
Comparison groups	Arm B: CPAP v Arm A: Control Arm v Arm C: Liraglutide v Arm D: Liraglutide + CPAP
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.614
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.479
upper limit	4.996
Variability estimate	Standard error of the mean
Dispersion value	3.437

<b>Statistical analysis title</b>	ODI (Liraglutide)
Comparison groups	Arm A: Control Arm v Arm B: CPAP v Arm C: Liraglutide v Arm D: Liraglutide + CPAP
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.151
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-5.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.041
upper limit	3.943
Variability estimate	Standard error of the mean
Dispersion value	3.491

## Secondary: Waist:Hip Ratio

End point title	Waist:Hip Ratio
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End point description:

End point type	Secondary
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End point timeframe:

Change between baseline and twenty-six weeks

End point values	Arm A: Control Arm	Arm B: CPAP	Arm C: Liraglutide	Arm D: Liraglutide + CPAP
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	25	31	28
Units: ratio				
median (inter-quartile range (Q1-Q3))	-0.01 (-0.04 to -0.01)	-0.02 (-0.04 to 0.05)	-0.04 (-0.075 to -0.01)	-0.01 (-0.04 to 0.03)

### Statistical analyses

Statistical analysis title	Wast:HIP (CPAP)
Comparison groups	Arm A: Control Arm v Arm B: CPAP v Arm C: Liraglutide v Arm D: Liraglutide + CPAP
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.711
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.033
upper limit	0.048
Variability estimate	Standard error of the mean
Dispersion value	0.021

Statistical analysis title	Waist:Hip (Liraglutide)
Comparison groups	Arm A: Control Arm v Arm B: CPAP v Arm C: Liraglutide v Arm D: Liraglutide + CPAP
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.094
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.03

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.075
upper limit	0.006
Variability estimate	Standard error of the mean
Dispersion value	0.021



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Reported for the duration of the study

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	5
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### Reporting groups

Reporting group title	Arm A:
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Reporting group description:

Control arm, comprising conventional care for existing T2DM patients with no intervention for OSA. This group did not use placebo medication. Patients were asked to continue with their usual anti-diabetes medications and if titration of any anti-diabetes drugs is necessary, due to worsening glycaemic control, this was achieved by avoiding the use of any Liraglutide and patients were given subcutaneous insulin (using either once daily or twice daily formulations). Patients were not be given CPAP for this period.

Reporting group title	Arm B:
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Reporting group description:

Will receive conventional care plus Liraglutide (up to 1.8mg).

Reporting group title	Arm C:
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Reporting group description:

Will receive conventional care plus CPAP. The CPAP device that will be used will be ResMed S9 (or other similar device) fixed pressure device in accordance with the standard clinical protocols.

Reporting group title	Arm D:
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Reporting group description:

Will receive conventional care plus Liraglutide plus CPAP. The CPAP device that will be used will be ResMed S9 (or other similar device) fixed pressure device in accordance with the standard clinical protocols.

Serious adverse events	Arm A:	Arm B:	Arm C:
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 33 (12.12%)	1 / 33 (3.03%)	1 / 33 (3.03%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Toxicity to various agents			
subjects affected / exposed	0 / 33 (0.00%)	0 / 33 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Thoracotomy	Additional description: Bronchoscopy and dianostic frozen section of right lower lobe		

subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Hyperglycaemia			
Additional description: Hyperglycaemia			
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Tendon Rupture			
subjects affected / exposed	0 / 33 (0.00%)	0 / 33 (0.00%)	1 / 33 (3.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
Additional description: Urosepsis (Renal infection E-coli bladder)			
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

<b>Serious adverse events</b>	Arm D:		
Total subjects affected by serious adverse events			

subjects affected / exposed	1 / 32 (3.13%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Toxicity to various agents			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Thoracotomy	Additional description: Bronchoscopy and dianostic frozen section of right lower lobe		
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Hyperglycaemia	Additional description: Hyperglycaemia		
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Tendon Rupture			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Lower respiratory tract infection			

subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urosepsis	Additional description: Urosepsis (Renal infection E-coli bladder)		
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Arm A:	Arm B:	Arm C:
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 33 (45.45%)	22 / 33 (66.67%)	16 / 33 (48.48%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Sinus polyp			
subjects affected / exposed	0 / 33 (0.00%)	0 / 33 (0.00%)	1 / 33 (3.03%)
occurrences (all)	0	0	1
Vascular disorders			
Patent ductus arteriosus			
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	0 / 33 (0.00%)
occurrences (all)	0	1	0
Post procedural haemorrhage			
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	0 / 33 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Inflammation			
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	0 / 33 (0.00%)
occurrences (all)	1	0	0
Injection site erythema			
subjects affected / exposed	0 / 33 (0.00%)	2 / 33 (6.06%)	0 / 33 (0.00%)
occurrences (all)	0	2	0
Injection site pain			
subjects affected / exposed	0 / 33 (0.00%)	0 / 33 (0.00%)	0 / 33 (0.00%)
occurrences (all)	0	0	0
Mass			

subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1	0 / 33 (0.00%) 0	0 / 33 (0.00%) 0
Immune system disorders Polymyalgia rheumatica subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 33 (0.00%) 0	0 / 33 (0.00%) 0
Reproductive system and breast disorders Menorrhagia subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1	0 / 33 (0.00%) 0	0 / 33 (0.00%) 0
Respiratory, thoracic and mediastinal disorders Asthma subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	1 / 33 (3.03%) 1	1 / 33 (3.03%) 1
Chronic obstructive pulmonary disease subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1	0 / 33 (0.00%) 0	0 / 33 (0.00%) 0
Cough subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	4 / 33 (12.12%) 4	2 / 33 (6.06%) 2
Dyspnoea subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	1 / 33 (3.03%) 1	0 / 33 (0.00%) 0
Influenza subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 33 (0.00%) 0	0 / 33 (0.00%) 0
Lower respiratory tract infection subjects affected / exposed occurrences (all)	4 / 33 (12.12%) 4	1 / 33 (3.03%) 1	8 / 33 (24.24%) 8
Nasopharyngitis subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 33 (0.00%) 0	0 / 33 (0.00%) 0
Vocal cord disorder subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	1 / 33 (3.03%) 1	0 / 33 (0.00%) 0

Wheezing subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1	0 / 33 (0.00%) 0	0 / 33 (0.00%) 0
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 33 (0.00%) 0	1 / 33 (3.03%) 1
Injury, poisoning and procedural complications Blister subjects affected / exposed occurrences (all)  Hand fracture subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0  0 / 33 (0.00%) 0	1 / 33 (3.03%) 1  1 / 33 (3.03%) 1	0 / 33 (0.00%) 0  0 / 33 (0.00%) 0
Cardiac disorders Aortic valve incompetence subjects affected / exposed occurrences (all)  Atrial septal defect subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0  0 / 33 (0.00%) 0	0 / 33 (0.00%) 0  0 / 33 (0.00%) 0	1 / 33 (3.03%) 1  0 / 33 (0.00%) 0
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)  Iron deficiency anaemia subjects affected / exposed occurrences (all)  Splenic cyst subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0  0 / 33 (0.00%) 0  0 / 33 (0.00%) 0	1 / 33 (3.03%) 1  0 / 33 (0.00%) 0  0 / 33 (0.00%) 0	1 / 33 (3.03%) 1  0 / 33 (0.00%) 0  1 / 33 (3.03%) 1
Ear and labyrinth disorders Ear infection subjects affected / exposed occurrences (all)  Middle ear effusion	1 / 33 (3.03%) 1	0 / 33 (0.00%) 0	0 / 33 (0.00%) 0

subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	0 / 33 (0.00%)
occurrences (all)	1	0	0
Vertigo			
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	0 / 33 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
eye infection			
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	0 / 33 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	0 / 33 (0.00%)
occurrences (all)	0	1	0
Abdominal pain			
subjects affected / exposed	0 / 33 (0.00%)	3 / 33 (9.09%)	0 / 33 (0.00%)
occurrences (all)	0	3	0
Abdominal pain upper			
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	0 / 33 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			
subjects affected / exposed	1 / 33 (3.03%)	9 / 33 (27.27%)	2 / 33 (6.06%)
occurrences (all)	1	9	2
Dyspepsia			
subjects affected / exposed	0 / 33 (0.00%)	2 / 33 (6.06%)	0 / 33 (0.00%)
occurrences (all)	0	2	0
Food poisoning			
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	0 / 33 (0.00%)
occurrences (all)	0	1	0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	0 / 33 (0.00%)
occurrences (all)	1	0	0
nausea			
subjects affected / exposed	0 / 33 (0.00%)	5 / 33 (15.15%)	1 / 33 (3.03%)
occurrences (all)	0	5	1
Oropharyngeal pain			

subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	1 / 33 (3.03%)
occurrences (all)	0	1	1
Salivary gland cyst			
subjects affected / exposed	0 / 33 (0.00%)	0 / 33 (0.00%)	1 / 33 (3.03%)
occurrences (all)	0	0	1
Salivary gland disorder			
subjects affected / exposed	0 / 33 (0.00%)	0 / 33 (0.00%)	0 / 33 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	0 / 33 (0.00%)	7 / 33 (21.21%)	1 / 33 (3.03%)
occurrences (all)	0	7	1
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	0 / 33 (0.00%)
occurrences (all)	1	0	0
Hepatic cyst			
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	0 / 33 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Cellulitis			
subjects affected / exposed	0 / 33 (0.00%)	0 / 33 (0.00%)	2 / 33 (6.06%)
occurrences (all)	0	0	2
Eczema			
subjects affected / exposed	0 / 33 (0.00%)	0 / 33 (0.00%)	0 / 33 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	0 / 33 (0.00%)
occurrences (all)	0	1	0
Carbuncle			
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	0 / 33 (0.00%)
occurrences (all)	0	1	0
Rosacea			
subjects affected / exposed	0 / 33 (0.00%)	0 / 33 (0.00%)	0 / 33 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			



Hypoglycaemia subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	1 / 33 (3.03%) 1	0 / 33 (0.00%) 0
Thyroid cyst subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 33 (0.00%) 0	1 / 33 (3.03%) 1
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	1 / 33 (3.03%) 1	0 / 33 (0.00%) 0
Back pain subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1	0 / 33 (0.00%) 0	0 / 33 (0.00%) 0
Contusion subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	2 / 33 (6.06%) 2	0 / 33 (0.00%) 0
Hand fracture subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 33 (0.00%) 0	0 / 33 (0.00%) 0
Rib fracture subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 33 (0.00%) 0	1 / 33 (3.03%) 1
Infections and infestations			
Cystitis subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	1 / 33 (3.03%) 1	0 / 33 (0.00%) 0
Gastroenteritis subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	1 / 33 (3.03%) 1	0 / 33 (0.00%) 0
Influenza subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	1 / 33 (3.03%) 1	0 / 33 (0.00%) 0
Localised infection subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	1 / 33 (3.03%) 1	0 / 33 (0.00%) 0
Sepsis			

subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	1 / 33 (3.03%) 1	0 / 33 (0.00%) 0
Subcutaneous abscess subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1	0 / 33 (0.00%) 0	0 / 33 (0.00%) 0
Viral infection subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	1 / 33 (3.03%) 1	0 / 33 (0.00%) 0
Metabolism and nutrition disorders			
Gout subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1	0 / 33 (0.00%) 0	0 / 33 (0.00%) 0
Vitamin D deficiency subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 33 (0.00%) 0	0 / 33 (0.00%) 0
Upper limb fracture subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 33 (0.00%) 0	1 / 33 (3.03%) 1

<b>Non-serious adverse events</b>	Arm D:		
Total subjects affected by non-serious adverse events subjects affected / exposed	12 / 32 (37.50%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps) Sinus polyp subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0		
Vascular disorders Patent ductus arteriosus subjects affected / exposed occurrences (all)  Post procedural haemorrhage subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0  0 / 32 (0.00%) 0		
General disorders and administration site conditions Inflammation			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Injection site erythema</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Injection site pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Mass</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 32 (0.00%)</p> <p>0</p> <p>0 / 32 (0.00%)</p> <p>0</p> <p>1 / 32 (3.13%)</p> <p>1</p> <p>0 / 32 (0.00%)</p> <p>0</p>		
<p>Immune system disorders</p> <p>Polymyalgia rheumatica</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 32 (3.13%)</p> <p>1</p>		
<p>Reproductive system and breast disorders</p> <p>Menorrhagia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 32 (0.00%)</p> <p>0</p>		
<p>Respiratory, thoracic and mediastinal disorders</p> <p>Asthma</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Chronic obstructive pulmonary disease</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Cough</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dyspnoea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Influenza</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 32 (0.00%)</p> <p>0</p> <p>0 / 32 (0.00%)</p> <p>0</p> <p>1 / 32 (3.13%)</p> <p>1</p> <p>0 / 32 (0.00%)</p> <p>0</p> <p>1 / 32 (3.13%)</p> <p>1</p>		

Lower respiratory tract infection subjects affected / exposed occurrences (all)	4 / 32 (12.50%) 4		
Nasopharyngitis subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 0		
Vocal cord disorder subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0		
Wheezing subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0		
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0		
Injury, poisoning and procedural complications Blister subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0		
Hand fracture subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0		
Cardiac disorders Aortic valve incompetence subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0		
Atrial septal defect subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0		
Iron deficiency anaemia			

subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Splenic cyst			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Ear and labyrinth disorders			
Ear infection			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Middle ear effusion			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Vertigo			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Eye disorders			
eye infection			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Abdominal pain			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Abdominal pain upper			
subjects affected / exposed	3 / 32 (9.38%)		
occurrences (all)	3		
Diarrhoea			
subjects affected / exposed	4 / 32 (12.50%)		
occurrences (all)	4		
Dyspepsia			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Food poisoning			

subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
nausea			
subjects affected / exposed	4 / 32 (12.50%)		
occurrences (all)	4		
Oropharyngeal pain			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Salivary gland cyst			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Salivary gland disorder			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	4 / 32 (12.50%)		
occurrences (all)	4		
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Hepatic cyst			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Cellulitis			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Eczema			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Rash			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Carbuncle</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Rosacea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 32 (3.13%)</p> <p>1</p> <p>0 / 32 (0.00%)</p> <p>0</p> <p>1 / 32 (3.13%)</p> <p>1</p>		
<p>Endocrine disorders</p> <p>Hypoglycaemia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Thyroid cyst</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 32 (0.00%)</p> <p>0</p> <p>0 / 32 (0.00%)</p> <p>0</p>		
<p>Musculoskeletal and connective tissue disorders</p> <p>Arthralgia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Back pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Contusion</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Hand fracture</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Rib fracture</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 32 (0.00%)</p> <p>0</p> <p>0 / 32 (0.00%)</p> <p>0</p> <p>0 / 32 (0.00%)</p> <p>0</p> <p>1 / 32 (3.13%)</p> <p>1</p> <p>0 / 32 (0.00%)</p> <p>0</p>		
<p>Infections and infestations</p> <p>Cystitis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Gastroenteritis</p>	<p>0 / 32 (0.00%)</p> <p>0</p>		

subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Influenza			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Localised infection			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Sepsis			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Subcutaneous abscess			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Viral infection			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Vitamin D deficiency			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Upper limb fracture			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 May 2015	<p>Amendment 2: (2&amp;3 combined) - Protocol, PIS, ICF and SmPC updates</p> <p>Change 1: Protocol updated from V2 (15/09/2014) to V3 (12/02/2015) Amendments to the protocol included changes to the following sections:</p> <ul style="list-style-type: none"><li>- 1 PROTOCOL SUMMARY<ul style="list-style-type: none"><li>- Main Exclusion Criteria</li><li>- Number of Sites</li></ul></li><li>5 STUDY POPULATION<ul style="list-style-type: none"><li>- 5.2 Exclusion Criteria<ul style="list-style-type: none"><li>- 1. Medical History and Concurrent Diseases:</li><li>- 5. Prohibited Treatments and/or Therapies</li></ul></li></ul></li><li>6 ENROLMENT AND RANDOMISATION<ul style="list-style-type: none"><li>- 6.2 Enrolment/Baseline:</li></ul></li><li>7 TRIAL TREATMENTS<ul style="list-style-type: none"><li>- 7.1 Introduction<ul style="list-style-type: none"><li>- 7.3.1 Handling and Dispensing</li><li>- 7.3.2 Preparation, Dosage and Administration of Study Treatment</li><li>- 7.3.4 Accountability Procedures for Study Treatment</li></ul></li><li>- 7.5.1 Medications Not Permitted/Precautions Required</li></ul></li><li>8 ASSESSMENTS AND PROCEDURES<ul style="list-style-type: none"><li>- 8.1 Schedule of Trial Procedures<ul style="list-style-type: none"><li>- 8.1 Screening Assessments (Visit 1)<ul style="list-style-type: none"><li>- 8.1.2 Baseline Assessments</li></ul></li></ul></li></ul></li><li>9 STATISTICAL CONSIDERATIONS<ul style="list-style-type: none"><li>- 9.3 Sample Size: Planned recruitment rate added</li></ul></li><li>10 PHARMACOVIGILANCE<ul style="list-style-type: none"><li>- 10.6 Reference Safety Information - Link to SmPC added</li></ul></li><li>16 TRIAL OVERSIGHT<ul style="list-style-type: none"><li>- 16.1 Trial Management Group - corrections of typographical errors</li></ul></li></ul> <p>Change 2: PIS updated from V3 (15/09/2014) to V4 (12/02/2015)</p> <p>Change 3: ICF updated from V3 (15/09/2014) to V4 (12/02/2015)</p> <p>Change 4: GP Letter updated from V2 (17/10/2014) to V3 (12/02/2015)</p>

28 May 2015	<p>Amendment 1: Submitted with Amendment 2</p> <p>Change 1: Protocol updated from V1 (May 2014) to V2 (15/09/2014)  Amendments to the protocol included:  Main Inclusion Criteria: *caveat inserted to include patients currently treated with DPP-IV inhibitors  Exclusion criteria 12: clarified to patients with residual neurological deficit  Screening Assessments:  • Introductory paragraph inserted  • All participants to have a standard multichannel overnight sleep study (limited respiratory polysomnogram) to confirm the diagnosis of OSA in a consistent manner.  • Pathway for patients identified from the Diabetes Clinic added.  • 24 hour blood pressure monitoring deleted  • Patient Treatment Diary added  8.1.2 Visit 2  • Participants to attend fasted  8.1.3 Visit 5  • Additional Visit added to collect prescription and/or CPAP device (ARMs B, C &amp; D only)  • Optional visit for Arm A patients who should be given the choice of a visit or telephone consultation.  8.1.4 Treatment Intervention (26 weeks)  • Clarification of follow-up visits and support telephone calls to reflect internal templates, as well  9.2.2 Secondary Outcome Measures  • Oxygen desaturation index (ODI) added  • Left ventricular tissue function updated to tissue velocity  10.8 Adverse Events - Reporting Procedures  • In accordance with LCTU standard practice, reporting requirements reduced from 70 days to 28 days after discontinuation of IMP</p> <p>Change 2: PIS updated from V1 (July 2014) to V2 (15/09/2014)  Amendments to the PIS includes the following additional visits added  • Visit 5 added – additional visit to collect CPAP/prescription/trial Arm review  • Visits 6, 7 &amp; 8 added plus fortnightly support telephone calls  Total number of visits for all Arm's increased from 8 to 11  • Drug dispensing: visits added</p> <p>Change 3: ICF updated from V1 (July 2014) to V2 (15/09/2014)  Researcher(s) anonymised and amended to PI only</p> <p>Change 4: GP Letter updated from V1 (May 2014) to V2 (17/10/2014)</p>
29 January 2016	<p>Amendment 3 (2&amp;3 combined): Protocol, PIS, ICF update, advert</p> <p>Change 1: Protocol updated from V3 (12/02/2015) to V3 (27/03/2015)  Amendments to the protocol included changes to the following sections:</p> <p>8 ASSESSMENTS AND PROCEDURES  - 8.1 Schedule of trial procedure  - 8.1.3 Visit 5  - 8.1.6 Optional Research Samples</p> <p>Change 2: PIS updated from V4 (12/02/2015) to V4 (27/03/2015)</p> <p>Change 3: ICF updated from V4 (12/02/2015) to V4 (27/03/2015)</p> <p>Submission: Recruitment Poster Diabetes V2 (04/12/2015)  Submission: Recruitment Poster Sleep V2 (04/12/2015)  Submission: Recruitment Advert V3 (05/01/2016)  Submission: Screening Form/Checklist V1 (16/10/2015)</p>

18 March 2016	<p>Amendment 4: Protocol update</p> <p>Change 1: Protocol updated from V3 (27/03/2015) to V4 (25/11/2015) Amendments to the protocol included changes to the following sections:</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> <li>- Section 1</li> <li>- Protocol Summary</li> <li>- 5.1 Detailed Inclusion Criteria</li> </ul> <p>Exclusion Criteria</p> <ul style="list-style-type: none"> <li>- Section 5.2</li> </ul> <p>2.3 Objectives</p> <p>6.1 Screening:</p> <p>7.3.1 Formulation, Packaging, Labelling, Storage and Stability</p> <p>7.4 Continuous Positive Airway Pressure (CPAP)</p> <p>8.1 Schedule of Trial Procedures</p> <ul style="list-style-type: none"> <li>- 8.1.1 Screening Assessments (Visit 1 - Clinical Sciences, UHA)</li> </ul> <p>13.4.7 Recruitment:</p> <p>Section updated to include the provision for advertising.</p>
29 June 2016	<p>29/06/2016</p> <p>Amendment 5: Protocol and PIS update</p> <p>Change 1: Protocol updated from V4 (25/05/2015) to V5 (12/05/2016) Amendments to the protocol included changes to the following sections:</p> <ul style="list-style-type: none"> <li>- 5.2 Detailed Exclusion Criteria</li> <li>- 5.3.3 Withdrawal from Trial Completely: Sentence added</li> <li>- 6.2 Enrolment/Randomisation</li> <li>- 8.1 Schedule of Trial Procedures</li> <li>- 8.1.1 Screening Assessments/Randomisation (Visit 1 - Clinical Sciences, UHA)</li> <li>- 8.1.2 Baseline Assessments/Randomisation (Visits 2, 3 &amp; 4)</li> <li>- 8.1.5 Follow-up Investigations (Visits 9, 10 &amp; 11)</li> </ul> <p>9 Statistical Considerations:</p> <ul style="list-style-type: none"> <li>- 9.2.2 Secondary</li> <li>- 9.3 Sample Size</li> <li>- 9.5 Outline of analysis plan</li> </ul> <p>Change 2: PIS updated from V4 (27/03/2015) to V5 (12/05/2016)</p>
17 October 2017	<p>Amendment 7: Protocol and PIS update (Patients needing to re-consent)</p> <p>Change 1: Protocol updated from V5 (12/05/2016) to V6 (26/07/2017) Amendments to the protocol included changes to the following pages:</p> <p>All references to MARIARC have been changed to Liverpool Magnetic Resonance Imaging Centre (LiMRIC)</p> <p>Page 14: Schematic of study design updated</p> <p>Page 24: Criteria specific to MRI removed from main criteria and specific section for MRI scanning created as below</p> <p>Additional Exclusion Criteria for MRI Scanning</p> <p>Page 27: Randomisation information changed to allow patient not eligible for scanning to be randomised to main study</p> <p>Page 37: Information added regarding Oral Glucose Tolerance Test</p> <p>Page 38: Information for Duplex Ultrasonography moved to visit 2</p> <p>Page 39: Follow up visits at weeks 2, 4 and 6 amended to allow optional of telephone calls or visits:</p> <p>Page 40: The specific number of 8 from each treatment arm for adipose tissue biopsy removed.</p>
23 November 2017	<p>Amendment 8: RSI Update</p> <p>Cholelithiasis and Cholecystitis added to RSI</p>

03 June 2019	<p>Amendment 9: Protocol update</p> <p>Novo Nordisk (study funder) has agreed a reduction in the number of patients needed to be recruited to the study. They have agreed that in each of the four arms they need 32 patients to analyse (128 in total). Due to the dropout rate being only 2.5% instead of the anticipated 10% it has been agreed that only 132 patients in total need to be recruited.</p> <p>Change 1: Protocol updated from V6 (26/07/2017) to V7 (21/01/2019) Amendments to the protocol included changes to the following sections:</p> <p>Section: Contact Details Section 1: Protocol Summary Section 4: Overall Design Section 3: Sample Size Section 6.2: Enrolment/Randomisation Section 10.2.3: Reporting of Pregnancy Section 10.6: Reference Safety Information</p>
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Notes:

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## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported