



## Clinical trial results:

**GLOOCOSE Study - A randomised controlled trial of the sulfonylurea Gliclazide and the DPP4 inhibitor Linagliptin on the frequency of hypoglycaemia among patients with Type 2 Diabetes and chronic kidney disease (CKD) stage 3b and 4.**

### Summary

EudraCT number	2015-002309-12
Trial protocol	GB
Global end of trial date	08 June 2019

### Results information

Result version number	v1 (current)
This version publication date	16 June 2020
First version publication date	16 June 2020
Summary attachment (see zip file)	GLOOCOSE Study Final Report (GLOOCOSE STUDY FINAL REPORT.pdf)

### Trial information

#### Trial identification

Sponsor protocol code	16HH3133
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#### Additional study identifiers

ISRCTN number	ISRCTN17462005
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Andrew Frankel: Chief Investigator, REC: 15/LO/1548

Notes:

### Sponsors

Sponsor organisation name	Imperial College London, Joint Research Compliance Office (JRCO)
Sponsor organisation address	Room 221, Medical School Building, St Marys Campus, Norfolk Place, London, United Kingdom, W2 1PG
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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	08 June 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 June 2019
Global end of trial reached?	Yes
Global end of trial date	08 June 2019
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

1. To assess whether patients with type 2 diabetes and moderate to severe kidney disease have less hypoglycaemia when taking Linagliptin instead of Gliclazide
2. To assess whether these same patients have decreased glycaemic variability when taking Linagliptin compared to Gliclazide
3. To assess whether Linagliptin has any other advantages over Gliclazide by examining effects on serum and urine biomarkers associated with declining kidney function
4. To assess whether study participants are more satisfied on Linagliptin or Gliclazide

Protection of trial subjects:

Regular review of patient's diabetes control, especially pertaining to frequency of hypoglycaemic and hyperglycaemic episodes and symptoms. A member of the research team would meet with each study patient within a month of study end to go over his or her CGM results, and advise if their current diabetic treatment was satisfactory, or if it needed to be changed. A letter detailing their CGM results and the research team's recommendations would also be sent to the patients and their GPs.

Background therapy:

All subjects taking Metformin, Pioglitazone and/or basal insulin at the time of recruitment into the study, and as part of their routine diabetic management, will continue on their pre-randomisation dose/s during the 8 weeks following randomisation. The dose will vary between subjects, the licenced oral dose for Metformin ranges being between 500 mg once a day to 1 gm twice a day, with the dose adjustments according to the NICE guidelines. The licenced oral dose for Pioglitazone ranges from 15 mg to 45 mg daily.

Evidence for comparator: -

Actual start date of recruitment	04 May 2015
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: 23
Worldwide total number of subjects	23
EEA total number of subjects	23

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)	4
From 65 to 84 years	19
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

See below for study eligibility criteria. Eligibility screening was performed using clinic data held on the diabetic and renal patients attending Imperial College NHS Healthcare trust and relevant community clinics.

### Pre-assignment

Screening details:

The study inclusion criteria were:

1. Type 2 diabetes mellitus
2. Age between 21 - 80 years inclusive
3. eGFR of 15 - 45 ml/min/1.73 m<sup>2</sup>
4. HbA1c < 75 mmol/mol (< 9%)
5. Taking Gliclazide with or without Metformin, Pioglitazone and/or basal insulin
6. Stable diabetic control in last 2 months
7. Understands adequate verbal and written English

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	No intervention

Arm description:

Patients randomised to continue on their usual dose of Gliclazide (ranging from 40 mg once daily to a maximum dose of 320mg daily in divided doses)

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

Arm description:

Patients randomised to stop Gliclazide and switch to Linagliptin

Arm type	Active comparator
Investigational medicinal product name	Linagliptin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Linagliptin 5mg once daily

<b>Number of subjects in period 1<sup>[1]</sup></b>	No intervention	Linagliptin
Started	10	9
Completed	10	7
Not completed	0	2
Adverse event, non-fatal	-	1
CGM technical failure	-	1

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Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Difficult recruitment resulted in less patients recruited compared to initial recruitment aim. Although 23 were consented to the trial, 4 were withdrawn from the study prior to randomisation for failure to comply with research procedures.

## Baseline characteristics

### Reporting groups

Reporting group title	No intervention
Reporting group description:	
Patients randomised to continue on their usual dose of Gliclazide (ranging from 40 mg once daily to a maximum dose of 320mg daily in divided doses)	
Reporting group title	Linagliptin
Reporting group description:	
Patients randomised to stop Gliclazide and switch to Linagliptin	

Reporting group values	No intervention	Linagliptin	Total
Number of subjects	10	9	19
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: years			
median	72	71	-
full range (min-max)	50 to 76	57 to 79	-
Gender categorical			
Units: Subjects			
Female	2	0	2
Male	8	9	17
Ethnicity			
Units: Subjects			
Caucasian	6	6	12
Afrocaribbean	1	0	1
Asian	2	3	5
Other/Mixed	1	0	1
Weight			
Units: kilogram(s)			
median	97.5	80.2	-
full range (min-max)	60.8 to 116.6	64.8 to 103.8	-
Body mass index (BMI)			
Units: kilogram(s)/square meter			
median	33.1	29.4	-
full range (min-max)	25.7 to 39.5	22.4 to 33.8	-
Blood pressure			
For systolic blood pressure values only			

Units: mmHg median full range (min-max)	141 99 to 173	134 94 to 153	-
Duration of diabetes Units: years median full range (min-max)	13 6 to 23	14 3 to 30	-
HbA1c			
Glycated haemoglobin (mmol/mol)			
Units: mmol/mol median full range (min-max)	55 39 to 62	52 33 to 64	-
Fasting capillary blood glucose Units: mmol/L median full range (min-max)	7.5 5.6 to 10.3	6.5 4.7 to 10.9	-
Estimated Glomerular Filtration Rate eGFR MDRD Units: ml/min/1.73m2 median full range (min-max)	37 20 to 45	32 26 to 44	-
Urine albumin creatinine ratio (UACR) Units: mg/mmol median full range (min-max)	35 0 to 72	6 1 to 257	-
Urine protein creatinine ratio (UPCR) Units: mg/mmol median full range (min-max)	58 0 to 136	16 0 to 339	-

## End points

### End points reporting groups

Reporting group title	No intervention
Reporting group description:	
Patients randomised to continue on their usual dose of Gliclazide (ranging from 40 mg once daily to a maximum dose of 320mg daily in divided doses)	
Reporting group title	Linagliptin
Reporting group description:	
Patients randomised to stop Gliclazide and switch to Linagliptin	

### Primary: Change in outcome measures post-randomisation (Visit 5) compared to pre-randomisation (Visit 2)

End point title	Change in outcome measures post-randomisation (Visit 5) compared to pre-randomisation (Visit 2)
End point description:	
As above	
End point type	Primary
End point timeframe:	
Study visits take place over 11 weeks, and patients randomised to either continue their usual Gliclazide or switch to Linagliptin for 8 weeks	

End point values	No intervention	Linagliptin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10 <sup>[1]</sup>	7		
Units: As per outcomes				
median (full range (min-max))				
Change in hypoglycaemic frequency	-1 (-8 to 16)	0 (-6 to 0)		
Change in total time spent in hypoglycaemia	0 (-4 to 9)	0 (-5 to 0)		
Change in mean CGM glucose	0.1 (-1.1 to 1.1)	1.5 (-0.4 to 6.8)		
Change in estimated CGM HbA1c	0 (-8 to 7)	10 (-2 to 47)		
Change in time spent in normoglycemia	-3.2 (-12.9 to 6.1)	-12 (-64 to 10.4)		
Change in Percentage Coefficient of Variation	-0.7 (-12.1 to 12.9)	-9.2 (-15.7 to 6.3)		
Change in Standard Deviation	0 (-1 to 0.8)	-0.6 (-0.9 to 0.6)		
Change in Continuous Overall Net Glycaemic Action	-0.3 (-0.8 to 0.7)	0 (-0.7 to 0.7)		
Change in Mean Absolute Glucose	-0.2 (-0.4 to 0.5)	0.1 (-0.5 to 0.5)		
Change in Mean of Daily Differences	-0.2 (-1.5 to 0.2)	-0.4 (-0.7 to 0.3)		
Change in Mean Amplitude of Glucose Excursions	0.3 (-1.9 to 3.3)	-1.4 (-2.5 to 1.7)		
Change in time spent in hyperglycaemia >10 mmol/L	2.6 (-5.3 to 13.7)	11.3 (-10.2 to 69.0)		



Change in time spent in hyperglycaemia >13.9 mmol/	0.6 (-10.5 to 4.6)	0.8 (-2.7 to 61.9)		
Change in Low Blood Glucose Index	0 (-0.7 to 2.1)	-0.2 (-2.3 to 0)		
Change in High Blood Glucose Index	0.3 (-2.8 to 3)	1.7 (-1.6 to 22.8)		
Change in serum MCP-1	-12.1 (-55.2 to 14.0)	-18.1 (-47.5 to 20.9)		
Change in urine MCP-1	-15.9 (-363.5 to 10)	-7.3 (-123.8 to 154.4)		
Change in urine MCP-1/creatinine ratio	-4.4 (-30.6 to 1.5)	3.4 (-1 to 6.1)		
Change in serum TGF-B1	2.6 (-1.9 to 7.9)	2.6 (-0.3 to 6)		
Change in urine TGF-B1	0 (-198.5 to 72.6)	0 (-88 to 1023.4)		
Change in urine TGF-B1/creatinine ratio	0 (-39.7 to 5.3)	0 (-4.7 to 47.6)		
Change in overall DTSQ score	0.5 (-6 to 4)	2 (-6 to 10)		
Change in Question 2 DTSQ	0 (-3 to 1)	0 (-2 to 4)		
Change in Question 3 DTSQ	0.5 (-1 to 1)	0 (-2 to 1)		

Notes:

[1] - Based on 9 patient samples for all CGM measures

## Statistical analyses

<b>Statistical analysis title</b>	Mann Whitney
Statistical analysis description:	
Non-parametric independent samples	
Comparison groups	No intervention v Linagliptin
Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.86
upper limit	1.86

## Other pre-specified: Change in clinical measures post-randomisation (Visit 5) compared to pre-randomisation (Visit 2)

End point title	Change in clinical measures post-randomisation (Visit 5) compared to pre-randomisation (Visit 2)
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End point description:

End point type	Other pre-specified
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End point timeframe:

Study visits take place over 11 weeks, and patients randomised to either continue their usual Gliclazide or switch to Linagliptin for 8 weeks

<b>End point values</b>	No intervention	Linagliptin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10 <sup>[2]</sup>	7 <sup>[3]</sup>		
Units: See each individual endpoint				
median (full range (min-max))				
Change in weight, kg	0.3 (-1.1 to 4.8)	-0.5 (-3.8 to 0.1)		
Change in BMI, kg/m2	0.1 (-0.4 to 1.7)	-0.1 (-1.4 to 0)		
Change in BP, mmHg	5 (-29 to 22)	3 (-19 to 33)		
Change in HbA1c, mmol/mol	1.5 (-2.0 to 11.0)	8.0 (-2.0 to 18.0)		
Change in fasting CBG, mmol/L	0.5 (-0.9 to 1.2)	2.6 (0.6 to 6.8)		
Change in eGFR MDRD, ml/min/1.73m2	1.0 (-2.0 to 9.0)	-1.0 (-3.0 to 1.0)		
Change in urine ACR, mg/mmol	3.1 (-19.1 to 130.2)	-0.3 (-9.4 to 9.4)		
Change in urine PCR, mg/mmol	8.0 (-22.0 to 157.0)	-1.0 (-20.0 to 39.0)		

Notes:

[2] - Based on 9 patient samples for change in urine PCR

[3] - Based on 6 patient samples for change in urine ACR and urine PCR

## Statistical analyses

<b>Statistical analysis title</b>	Mann-Whitney test
Statistical analysis description:	
Non-parametric independent samples	
Comparison groups	Linagliptin v No intervention
Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.86
upper limit	1.86

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Until end of study recruitment period

Adverse event reporting additional description:

Subjects will be asked at each study visit and scheduled phone call before and after study visit 3 to assess and record:

- a) Episodes of symptomatic hypoglycaemia
- b) Episodes of symptomatic hyperglycaemia
- c) General health to include any adverse reactions/adverse events

Assessment type	Systematic
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### Dictionary used

Dictionary name	SNOMED CT
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Dictionary version	1
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### Reporting groups

Reporting group title	No intervention
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Reporting group description:

Patients randomised to continue on their usual dose of Gliclazide (ranging from 40 mg once daily to a maximum dose of 320mg daily in divided doses)

Reporting group title	Linagliptin
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Reporting group description:

Patients randomised to stop Gliclazide and switch to Linagliptin

Serious adverse events	No intervention	Linagliptin	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (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: 1 %

Non-serious adverse events	No intervention	Linagliptin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	
Hepatobiliary disorders			
Deranged LFTs	Additional description: Subject had deranged liver function tests (LFTs) that were investigated and followed up. Deranged LFTs was put down to a passed gallstone.		
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 June 2017	<p>The substantial amendments mainly pertained to broadening of the eligibility criteria and summarising the PIS length from 11 to 3 pages.</p> <p>The age limit of eligible study participants was extended to 21 to 80 years inclusive.</p> <p>The initial eligibility criteria stated that patients had to have type 2 diabetes of 10 years or more duration – this was removed, as duration of diabetes was not usually accurately coded or unavailable during searches, and also not considered to influence the study findings.</p> <p>The protocol was amended to include patients taking Gliclazide, either with or without Metformin, Pioglitazone and/or basal insulin. This change to the eligibility criteria intended to increase recruitment numbers while still allowing for comparison of study patients staying on their usual Gliclazide to those randomised to Linagliptin.</p> <p>The HbA1c cut off limit was raised from 65 mmol/mol (8%) to 75 mmol/mol (9%), with the aim of improving recruitment. Moreover, hypoglycaemia and glycaemic variability can still occur in patients at higher HbA1c levels.</p> <p>Duration of study recruitment was adjusted upward from two to three years, to allow for the slower recruitment rate.</p>

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 small number of patients may mean the study is underpowered to find statistical differences. Relatively short duration of randomisation to Linagliptin means maximum effect may not have been reached by 8 weeks, and limits the conclusions drawn.

Notes: