Clinical trial results:
Low-dose Glibenclamide in Type 2 Diabetes Mellitus - Part A (LEGEND-A)

Summary

EudraCT number	2015-002837-23
Trial protocol	GB
Global end of trial date	19 February 2018

Results information

Result version number	v1 (current)
This version publication date	01 August 2019
First version publication date	01 August 2019

Trial information

Trial identification

Sponsor protocol code	19062015

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT19062015
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Oxford
Sponsor organisation address	Churchill Hospital, Oxford, United Kingdom, OX3 7LE
Public contact	Ioannis Spiliotis, University of Oxford, ioannis.spiliotis@ocdem.ox.ac.uk
Scientific contact	Ioannis Spiliotis, University of Oxford, ioannis.spiliotis@ocdem.ox.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 November 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 March 2017
Global end of trial reached?	Yes
Global end of trial date	19 February 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To identify the dose of glibenclamide that causes a significant decrease in fasting plasma glucagon concentration.

Protection of trial subjects:

The main serious side-effect of glibenclamide is hypoglycaemia, however the overall risk is low and is dose- dependent. Furthermore, potential participants who have significant renal or liver disease will be excluded from the trial. The doses of glibenclamide used in the trial are lower than those used in normal clinical practice for the treatment of type 2 diabetes and therefore are very unlikely to result in severe hypoglycaemia episodes.

This trial will involve administration of glibenclamide at doses much lower than those used in clinical practice. There is currently no licensed formulation of glibenclamide that can easily and reproducibly deliver doses as low as 0.3mg. Therefore, an oral suspension of glibenclamide (GlibenTek), which can be titrated by volume, has been formulated by the company AmmTeK (Paris, France) and is already being used for a different clinical trial. GlibenTek will be supplied by Pharmaservices (Paris, France).

The study will involve 9 visits to the clinical trials unit for fasting blood tests every 3 or 4 days for a total of 21 days. The dosing schedule has been adjusted so as to minimise the inconvenience to participants by avoiding visits on weekends. In addition, home visits for blood sampling will be organised where possible for those participants who are unable to attend all the clinical trials unit visit.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 April 2016
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: 16
Worldwide total number of subjects	16
EEA total number of subjects	16

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)	6
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Inclusion criteria:
1. Diagnosis of Type 2 diabetes
2. age 18 years or over
3. Diet controlled or on metformin only for diabetic control
4. HbA1c 6.0% - 9.5% (42mmol/mol to 80mmol/mol) inclusive

Pre-assignment period milestones

Number of subjects started	19[1]
Number of subjects completed	16

Pre-assignment subject non-completion reasons

Reason: Number of subjects	did not meet inclusion criteria: 3

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 19 potential participants were screened, however only 16 met the inclusion criteria for the trial.

Period 1

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

Blinding implementation details:

n/a

Arms

Are arms mutually exclusive?	Yes
Arm title	High baseline fasting glucagon

Arm description:

High baseline fasting glucagon (defined as >= 15pmol/L). Increasing doses of glibenclamide oral suspension from 0.3mg/day to 6mg/day.

Arm type	Experimental
Investigational medicinal product name	Glibenclamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

Oral liquid suspension at strengths of 0.6 mg/ml and 6mg/ml. Dosing schedule ranged from 0.3mg to 6mg daily, split into morning and evening.

Arm title	Normal baseline fasting glucagon

Arm description:

Normal baseline fasting glucagon (defined as <15pmol/L). Increasing doses of glibenclamide oral suspension from 0.3mg/day to 6mg/day.

Arm type	Experimental

Investigational medicinal product name	Glibenclamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

Oral liquid suspension at strengths of 0.6mg/ml and 6mg/ml. Dosing schedule ranged from 0.3 - 6mg daily, split into morning and evening.

Number of subjects in period 1	High baseline fasting glucagon	Normal baseline fasting glucagon
Started	4	12
Completed	4	12

Baseline characteristics

Reporting groups	
Reporting group title	High baseline fasting glucagon
Reporting group description:	
High baseline fasting glucagon (defined as >= 15pmol/L). Increasing doses of glibenclamide oral suspension from 0.3mg/day to 6mg/day.	
Reporting group title	Normal baseline fasting glucagon
Reporting group description:	
Normal baseline fasting glucagon (defined as <15pmol/L). Increasing doses of glibenclamide oral suspension from 0.3mg/day to 6mg/day.	

Reporting group values	High baseline fasting glucagon	Normal baseline fasting glucagon	Total
Number of subjects	4	12	16
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Adults > 18	4	12	16
Age continuous Units: years			
arithmetic mean	52	68	
standard deviation	± 10	± 7	-
Gender categorical Units: Subjects			
Female	1	8	9
Male	3	4	7

End points

End points reporting groups

Reporting group title	High baseline fasting glucagon
Reporting group description:	
High baseline fasting glucagon (defined as >= 15pmol/L). Increasing doses of glibenclamide oral suspension from 0.3mg/day to 6mg/day.	
Reporting group title	Normal baseline fasting glucagon
Reporting group description:	
Normal baseline fasting glucagon (defined as <15pmol/L). Increasing doses of glibenclamide oral suspension from 0.3mg/day to 6mg/day.	

Primary: Concentration of plasma glucagon using fasting blood samples prior to each dose change

End point title	Concentration of plasma glucagon using fasting blood samples prior to each dose change
End point description:	
0.3mg glibenclamide dose. See attached spreadsheet for full analysis of results of doses 0.3mg-1.8mg glibenclamide.	
End point type	Primary
End point timeframe:	
Pre-dose blood sampling on day 3	

End point values	High baseline fasting glucagon	Normal baseline fasting glucagon		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	12		
Units: pmol/L				
arithmetic mean (standard error)	20.3 (± 2.3)	6.45 (± 1.1)		

Attachments (see zip file)	LEGEND-A glucagon analysis/LEGEND-A glucagon analysis.xls

Statistical analyses

Statistical analysis title	Two-way repeated measures ANOVA
Comparison groups	Normal baseline fasting glucagon v High baseline fasting glucagon
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	ANOVA
Parameter estimate	Mean difference (final values)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events will be recorded from the baseline assessment onwards, i.e. prior to the each dose change of the trial medication.

Assessment type	Systematic

Dictionary used

Dictionary name	SNOMED CT
Dictionary version	1.36.4

Reporting groups

Reporting group title	Hypoglycaemia

Reporting group description:

Hypoglycaemia (blood glucose <4.0mmol/L)

Reporting group title	Dizzy/tired/headache

Reporting group description:

Reported symptoms of dizziness, tiredness, or headache that were unrelated to hypoglycaemia events.

Reporting group title	Urinary tract infection

Reporting group description: -

Serious adverse events	Hypoglycaemia	Dizzy/tired/headache	Urinary tract infection
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Hypoglycaemia	Dizzy/tired/headache	Urinary tract infection
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 16 (62.50%)	3 / 16 (18.75%)	1 / 16 (6.25%)
General disorders and administration site conditions			
Headache	Additional description: Symptoms of dizziness, tiredness or headache unrelated to hypoglycaemia events.		
subjects affected / exposed	7 / 16 (43.75%)	3 / 16 (18.75%)	1 / 16 (6.25%)
occurrences (all)	12	3	1
Endocrine disorders			
Hypoglycaemia	Additional description: Either documented blood glucose <4.0mmol/L or symptoms consistent with hypoglycaemia in absence of blood glucose monitoring.		

subjects affected / exposed occurrences (all)	7 / 16 (43.75%) 12	3 / 16 (18.75%) 3	1 / 16 (6.25%) 1
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all)	7 / 16 (43.75%) 12	3 / 16 (18.75%) 3	1 / 16 (6.25%) 1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 August 2016	Change to inclusion criteria from HbA1c 53-80mmol/mol inclusive, to HbA1c 42-80mmol/mol.

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.

Full pharmacokinetic data does not currently exist for the low doses of glibenclamide used in this trial. The sample size of the "high" baseline glucagon is small & the prevalence of baseline fasting hyperglucagonaemia in this population is unknown.

Notes: