



## 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,<br>ioannis.spiliotis@ocdem.ox.ac.uk |
| Scientific contact           | Ioannis Spiliotis, University of Oxford,<br>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 <sup>[1]</sup> |
| 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                            |
| <b>Arm title</b>             | High baseline fasting glucagon |

Arm description:

High baseline fasting glucagon (defined as  $\geq 15$ pmol/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.

|                  |                                  |
|------------------|----------------------------------|
| <b>Arm title</b> | Normal baseline fasting glucagon |
|------------------|----------------------------------|

Arm description:

Normal baseline fasting glucagon (defined as  $<15$ pmol/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.

| <b>Number of subjects in period 1</b> | 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  $\geq 15$  pmol/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  $<15$  pmol/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                                   | $\pm 10$                       | $\pm 7$                          | -     |
| 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:<br>High baseline fasting glucagon (defined as $\geq 15$ pmol/L). Increasing doses of glibenclamide oral suspension from 0.3mg/day to 6mg/day. |                                  |
| Reporting group title  | Normal baseline fasting glucagon |
| Reporting group description:<br>Normal baseline fasting glucagon (defined as $<15$ pmol/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:<br>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:<br>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 ( $\pm 2.3$ )             | 6.45 ( $\pm 1.1$ )               |  |  |

|                            |   |
|----------------------------|---|
| 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<br>occurrences (all)   | 7 / 16 (43.75%)<br>12 | 3 / 16 (18.75%)<br>3 | 1 / 16 (6.25%)<br>1 |
| Infections and infestations<br>Urinary tract infection<br>subjects affected / exposed<br>occurrences (all) | 7 / 16 (43.75%)<br>12 | 3 / 16 (18.75%)<br>3 | 1 / 16 (6.25%)<br>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:

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### 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: