# Clinical trial results:
# The impact of subcutaneous glucagon before, during and after exercise. A study in patients with type 1 diabetes mellitus

## Summary

| | |
|---|---|
| EudraCT number | 2016-002127-28 |
| Trial protocol | DK |
| Global end of trial date | 07 July 2017 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 22 December 2019 |
| First version publication date | 22 December 2019 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | 16016762 |

**Additional study identifiers**

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

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Hvidovre Univeraity Hospital |
| Sponsor organisation address | Kettegård Allé 30, Hvidovre, Denmark, 2650 |
| Public contact | Isabelle, Hvidovre University Hospital, +45 51519085, Isabelle.Isa.Kristin.Steineck@regionh.dk |
| Scientific contact | Isabelle, Hvidovre University Hospital, +45 51519085, Isabelle.Isa.Kristin.Steineck@regionh.dk |

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 | Interim |
| Date of interim/final analysis | 29 July 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 07 July 2017 |
| Global end of trial reached? | Yes |
| Global end of trial date | 07 July 2017 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

1. To compare the increase in plasma glucose after 200µg glucagon given either after exercise or after resting for 45 minutes.

Protection of trial subjects:

1. Visual analogue score to collect data on nausea, pain, sweating and heartbeats
2. If a subject would have had a low blood glucose under 2.5 mmol/l then we would have stopped the trial

Background therapy:

Continuous subcutaneous insulin pump therapy

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 04 July 2016 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Denmark: 14 |
| Worldwide total number of subjects | 14 |
| EEA total number of subjects | 14 |

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) | 13 |
| From 65 to 84 years | 1 |

| | |
|---|---|
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Participants were recruited from the outpatient diabetes clinic at Copenhagen University Hospital in Hvidovre in the period September 2016 to May 2017.

### Pre-assignment

Screening details:

The screening was performed after an overnight fast. Information was collected on sex, age, race, diabetes duration, allergies, medical history and medications;  height, weight, blood pressure and heart rate were measured; questionnaires to identify hypoglycemia unawareness were filled out and a 12-lead electrocardiography.

### Pre-assignment period milestones

| | |
|---|---|
| Number of subjects started | 18[1] |
| Number of subjects completed | 14 |

### Pre-assignment subject non-completion reasons

| | |
|---|---|
| Reason: Number of subjects | Pregnancy: 1 |
| Reason: Number of subjects | Lack of time: 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: I includet 18 but only 14 completed

### Period 1

| | |
|---|---|
| Period 1 title | Overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Single blind |
| Roles blinded | Subject |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | No |
| **Arm title** | Glucagon after Cycling |

Arm description:

Participants consumed a standardized breakfast two hours prior to 45 minutes of cycling. A subcutaneous injection of 200 µg glucagon was given after cycling and frequent blood sampling occurred until two hours after exercise.

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | GlucaGen |
| Investigational medicinal product code | SUB02347MIG |
| Other name | |
| Pharmaceutical forms | Powder and solvent for solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

200 micro gram given subcutaneously in abdominal wall given one time after 45 minutes of cycling

| | |
|---|---|
| **Arm title** | Glucagon after Resting |

Arm description:

Participants consumed a standardized breakfast two hours prior to 45 minutes of resting. A subcutaneous injection of 200 µg glucagon was given after resting and frequent blood sampling occurred until two hours after the injection of glucagon.

| | |
|---|---|
| Arm type | control |

| | |
|---|---|
| Investigational medicinal product name | GlucaGen |
| Investigational medicinal product code | SUB02347MIG |
| Other name | |
| Pharmaceutical forms | Powder and solvent for solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

200 micro gram given subcutaneously in abdominal wall given one time after 45 minutes of resting

| **Arm title** | Glucagon before cycling |
|---|---|

Arm description:

Participants consumed a standardized breakfast two hours prior to 45 minutes of cycling. A subcutaneous injection of 200 µg glucagon was given before cycling and frequent blood sampling occurred until two hours after exercise.

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | GlucaGen |
| Investigational medicinal product code | SUB02347MIG |
| Other name | |
| Pharmaceutical forms | Powder and solvent for solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

200 micro gram given subcutaneously in abdominal wall given one time before 45 minutes of cycling

| **Number of subjects in period 1** | Glucagon after Cycling | Glucagon after Resting | Glucagon before cycling |
|---|---|---|---|
| Started | 14 | 14 | 13 |
| Completed | 14 | 14 | 13 |

## Baseline characteristics

### Reporting groups

| Reporting group title | Overall trial |
|---|---|

Reporting group description:

Fourteen insulin pump-treated individuals with type 1 diabetes completed three visits in a randomized, placebo-controlled, single-blinded crossover study. Baseline (mean and range) HbA1c 54 (43-65) mmol/mol or 7.1 (6.1-8.1) %, age 45 (23-66) years, BMI 26 (21-30) kg/m2, diabetes duration 26 (8-51) years.

| Reporting group values | Overall trial | Total | |
|---|---|---|---|
| Number of subjects | 14 | 14 | |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 13 | 13 | |
| From 65-84 years | 1 | 1 | |
| 85 years and over | 0 | 0 | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 45 | | |
| full range (min-max) | 23 to 66 | - | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 6 | 6 | |
| Male | 8 | 8 | |

### Subject analysis sets

| Subject analysis set title | Primary endpoint |
|---|---|
| Subject analysis set type | Full analysis |

Subject analysis set description:

The subjects in the study

| Reporting group values | Primary endpoint | | |
|---|---|---|---|
| Number of subjects | 14 | | |
| Age categorical<br>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) | 13 | | |
| From 65-84 years | 1 | | |
| 85 years and over | 0 | | |
| Age continuous<br>Units: years<br>arithmetic mean<br>full range (min-max) | | | |
| Gender categorical<br>Units: Subjects | | | |
| Female | | | |
| Male | | | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Glucagon after Cycling |

Reporting group description:

Participants consumed a standardized breakfast two hours prior to 45 minutes of cycling. A subcutaneous injection of 200 µg glucagon was given after cycling and frequent blood sampling occurred until two hours after exercise.

| | |
|---|---|
| Reporting group title | Glucagon after Resting |

Reporting group description:

Participants consumed a standardized breakfast two hours prior to 45 minutes of resting. A subcutaneous injection of 200 µg glucagon was given after resting and frequent blood sampling occurred until two hours after the injection of glucagon.

| | |
|---|---|
| Reporting group title | Glucagon before cycling |

Reporting group description:

Participants consumed a standardized breakfast two hours prior to 45 minutes of cycling. A subcutaneous injection of 200 µg glucagon was  given before cycling and frequent blood sampling occurred until two hours after exercise.

| | |
|---|---|
| Subject analysis set title | Primary endpoint |
| Subject analysis set type | Full analysis |

Subject analysis set description:

The subjects in the study

### Primary: The glucose response to glucagon when glucagon was given after cycling compared with after resting

| | |
|---|---|
| End point title | The glucose response to glucagon when glucagon was given after cycling compared with after resting[1] |

End point description:

| | |
|---|---|
| End point type | Primary |

End point timeframe:

120 minutes after the injection of glucagon

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Not applicable -please see article for further details

| End point values | Glucagon after Cycling | Glucagon after Resting | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 14 | 14 | | |
| Units: mmol/l | | | | |
| number (not applicable) | 2.6 | 1.8 | | |

### Statistical analyses

| Statistical analysis title | Primary outcome |
|---|---|

Statistical analysis description:

A paired t-test was used to compare the logarithmic incremental peak plasma glucose after cycling with after resting.

| | |
|---|---|
| Comparison groups | Glucagon after Cycling v Glucagon after Resting |

| | |
|---|---|
| Number of subjects included in analysis | 28 |
| Analysis specification | Pre-specified |
| Analysis type | other[2] |
| P-value | = 0.02 |
| Method | t-test, 2-sided |

Notes:

[2] - Obs: This was a crossover study so the number of subjects was not 28 but 14 because it was the same subjects who did the 2 arms.

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: | |
| 120 minutes after the glucagon injection | |
| Adverse event reporting additional description: | |
| Visual analogue scale given after the glucagon injection that was done in clinic | |
| Assessment type | Systematic |

| Dictionary used | |
|---|---|
| Dictionary name | Visual analogue scal |
| Dictionary version | na |

| Reporting groups | |
|---|---|
| Reporting group title | Glucagon after Cycling |
| Reporting group description: | |
| Participants consumed a standardized breakfast two hours prior to 45 minutes of cycling. A subcutaneous injection of 200 µg glucagon was given after cycling and frequent blood sampling occurred until two hours after exercise. | |
| Reporting group title | Glucagon after Resting |
| Reporting group description: | |
| Participants consumed a standardized breakfast two hours prior to 45 minutes of resting. A subcutaneous injection of 200 µg glucagon was given after resting and frequent blood sampling occurred until two hours after the injection of glucagon. | |
| Reporting group title | Glucagon before cycling |
| Reporting group description: | |
| Participants consumed a standardized breakfast two hours prior to 45 minutes of cycling. A subcutaneous injection of 200 µg glucagon was given before cycling and frequent blood sampling occurred until two hours after exercise. | |

| Serious adverse events | Glucagon after Cycling | Glucagon after Resting | Glucagon before cycling |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 14 (0.00%) | 0 / 14 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | | | |

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

| Non-serious adverse events | Glucagon after Cycling | Glucagon after Resting | Glucagon before cycling |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 1 / 14 (7.14%) | 1 / 14 (7.14%) |
| Gastrointestinal disorders | | | |
| Nausea | Additional description: One participant consistently reported nausea (mean VAS increased 2.83 cm) after glucagon injection in all three study visits. | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed<br>occurrences (all) | 1 / 14 (7.14%)<br>1 | 1 / 14 (7.14%)<br>1 | 1 / 14 (7.14%)<br>1 |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 02 November 2016 | 1. We included subjects with age op to 70 years old instead of age op to 65 years old.<br>2. In the first version of the protocol we included participants with " Sedentary or mild physical activity: Less than 150 minutes of moderate-intensity aerobic physical activity throughout the week and less than 75 minutes of vigorous-intensity aerobic physical activity throughout the week ." We deleted this inclusion criteria this<br>3. We added a new exclusion criteria: We added: "People with vigorous intensity aerobic physical activity such as swimming, jogging, aerobics, football, tennis, gym, workout etc, more than 3 hours or more per week. " |

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.

Not applicable. See article for details.

Notes:

## Online references

http://www.ncbi.nlm.nih.gov/pubmed/30643924