



## Clinical trial results:

### A phase 3, Randomized, Double-Blind, Parallel Group Safety Trial to Evaluate the Immunogenicity of Dasiglucagon And GlucaGen® Administered Subcutaneously in patients with Type 1 Diabetes Mellitus (T1DM)

#### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2017-000062-30   |
| Trial protocol           | DE AT            |
| Global end of trial date | 13 February 2018 |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 28 February 2019 |
| First version publication date | 28 February 2019 |

#### Trial information

##### Trial identification

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | ZP4207-16136 |
|-----------------------|--------------|

##### Additional study identifiers

|                                    |                    |
|------------------------------------|--------------------|
| ISRCTN number                      | -                  |
| ClinicalTrials.gov id (NCT number) | NCT03216226        |
| WHO universal trial number (UTN)   | -                  |
| Other trial identifiers            | IND Number: 127866 |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Zealand Pharma A/S   |
| Sponsor organisation address | Smedeland 26, Glostrup, Denmark, 2600                                      |
| Public contact               | Dorte Skydsgaard, Zealand Pharma A/S, +45 5060 3767, dsk@zealandpharma.com |
| Scientific contact           | Dorte Skydsgaard, Zealand Pharma A/S, +45 5060 3767, dsk@zealandpharma.com |

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                       | 22 October 2018  |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 13 February 2018 |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 13 February 2018 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective is to evaluate the immunogenicity of repeated single doses of dasiglucagon and GlucaGen following subcutaneous (s.c.) administration in T1DM patients.

Protection of trial subjects:

The trial was conducted in accordance of the World Medical Association Declaration of Helsinki, current guidelines for GCP and local regulations.

Background therapy: -

Evidence for comparator: -

|   |               |
|---|---------------|
| Actual start date of recruitment                          | 15 March 2017 |
| 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 | Austria: 31       |
| Country: Number of subjects enrolled | Germany: 17       |
| Country: Number of subjects enrolled | Canada: 54        |
| Country: Number of subjects enrolled | United States: 10 |
| Worldwide total number of subjects   | 112               |
| EEA total number of subjects         | 48                |

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)                      | 108 |
| From 65 to 84 years                       | 4   |

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

## Subject disposition

### Recruitment

Recruitment details:

The patients were recruited from 7 trial centers in Austria (1 center), Canada (3 centers), Germany (1 center) and the USA (2 centers) between 28 June 2017 (first patient enrolled) and 13 February 2018 (last patient completed trial).

### Pre-assignment

Screening details:

A total of 131 patients were screened of which 19 patients were not randomized.

### Period 1

|                              |  |
|------------------------------|--|
| Period 1 title               | overall trial (overall period)               |
| Is this the baseline period? | Yes  |
| Allocation method            | Randomised - controlled                      |
| Blinding used                | Double blind                                 |
| Roles blinded                | Subject, Investigator, Monitor, Data analyst |

Blinding implementation details:

Patients with T1DM were randomly assigned in a 1:1 ratio to receive 3 SC injections of either dasiglucagon (0.6 mg) or GlucaGen® (1 mg), with 1 week between doses. Since the products were not identical in appearance, unblinded trial personnel were responsible for the handling, preparation and administration of IMP.

### Arms

|  |  |
|--|--|
| Are arms mutually exclusive?           | Yes  |
| <b>Arm title</b>                       | Dasiglucagon                                 |
| Arm description: -                     |  |
| Arm type                               | Experimental                                 |
| Investigational medicinal product name | dasiglucagon                                 |
| Investigational medicinal product code |  |
| Other name                             |  |
| Pharmaceutical forms                   | Solution for injection in pre-filled syringe |
| Routes of administration               | Subcutaneous use                             |

Dosage and administration details:

Three doses of 0.6 mg dasiglucagon (0.6 mL) given at weekly intervals.

|  |   |
|--|---|
| <b>Arm title</b>                       | GlucaGen                                      |
| Arm description: -                     |   |
| Arm type                               | Active comparator                             |
| Investigational medicinal product name | Glucagen                                      |
| Investigational medicinal product code |   |
| Other name                             |   |
| Pharmaceutical forms                   | Powder and solvent for solution for injection |
| Routes of administration               | Subcutaneous use                              |

Dosage and administration details:

Three doses of 1mg Glucagen (1mL) given at weekly intervals.

| <b>Number of subjects in period 1</b>      | Dasiglucagon | GlucaGen |
|--|--------------|----------|
| Started                                    | 57           | 55       |
| Treated                                    | 57           | 54       |
| Completed                                  | 52           | 50       |
| Not completed                              | 5            | 5        |
| Adverse event, non-fatal                   | 3            | -        |
| Missed injection visit                     | 1            | 1        |
| Withdrawn: veins unsuitable for blood draw | -            | 1        |
| Protocol deviation                         | 1            | 3        |

## Baseline characteristics

### Reporting groups

|                                |              |
|--------------------------------|--------------|
| Reporting group title          | Dasiglucagon |
| Reporting group description: - |              |
| Reporting group title          | GlucaGen     |
| Reporting group description: - |              |

| Reporting group values          | Dasiglucagon | GlucaGen | Total |
|---------------------------------|--------------|----------|-------|
| Number of subjects              | 57           | 55       | 112   |
| Age categorical                 |              |          |       |
| Units: Subjects                 |              |          |       |
| Adults (18-64 years)            | 55           | 53       | 108   |
| From 65-84 years                | 2            | 2        | 4     |
| Age continuous                  |              |          |       |
| Units: years                    |              |          |       |
| arithmetic mean                 | 45.3         | 38.8     |       |
| standard deviation              | ± 12.21      | ± 13.65  | -     |
| Gender categorical              |              |          |       |
| Units: Subjects                 |              |          |       |
| Female                          | 16           | 23       | 39    |
| Male                            | 41           | 32       | 73    |
| Race                            |              |          |       |
| Units: Subjects                 |              |          |       |
| White                           | 50           | 53       | 103   |
| Other                           | 7            | 2        | 9     |
| Height                          |              |          |       |
| Units: centimetres              |              |          |       |
| arithmetic mean                 | 174.1        | 173.6    |       |
| standard deviation              | ± 9.54       | ± 7.65   | -     |
| Weight                          |              |          |       |
| Units: kilogram(s)              |              |          |       |
| arithmetic mean                 | 82.9         | 82.7     |       |
| standard deviation              | ± 18.44      | ± 16.25  | -     |
| BMI                             |              |          |       |
| Units: kilogram(s)/square meter |              |          |       |
| arithmetic mean                 | 27.2         | 27.4     |       |
| standard deviation              | ± 4.88       | ± 4.70   | -     |

### Subject analysis sets

|  |                     |
|--|---------------------|
| Subject analysis set title   | Full analysis set   |
| Subject analysis set type  | Full analysis       |
| Subject analysis set description:  |                     |
| All patients of the safety analysis set with at least 1 measurement of ADA titer at baseline |                     |
| Subject analysis set title   | Safety analysis set |
| Subject analysis set type  | Safety analysis     |
| Subject analysis set description:  |                     |
| All patients who were randomly assigned and received at least 1 dose of IMP                  |                     |

| <b>Reporting group values</b>          | Full analysis set | Safety analysis set |  |
|--|-------------------|---------------------|--|
| Number of subjects                     | 111               | 111                 |  |
| Age categorical<br>Units: Subjects     |                   |                     |  |
| Adults (18-64 years)                   | 107               | 107                 |  |
| From 65-84 years                       | 4                 | 4                   |  |
| Age continuous<br>Units: years         |                   |                     |  |
| arithmetic mean                        | 42.1              | 42.1                |  |
| standard deviation                     | ± 13.29           | ± 13.29             |  |
| Gender categorical<br>Units: Subjects  |                   |                     |  |
| Female                                 | 38                | 38                  |  |
| Male                                   | 73                | 73                  |  |
| Race<br>Units: Subjects                |                   |                     |  |
| White                                  | 102               | 102                 |  |
| Other                                  | 9                 | 9                   |  |
| Height<br>Units: centimetres           |                   |                     |  |
| arithmetic mean                        | 173.9             | 173.9               |  |
| standard deviation                     | ± 8.64            | ± 8.64              |  |
| Weight<br>Units: kilogram(s)           |                   |                     |  |
| arithmetic mean                        | 82.8              | 82.8                |  |
| standard deviation                     | ± 17.33           | ± 17.33             |  |
| BMI<br>Units: kilogram(s)/square meter |                   |                     |  |
| arithmetic mean                        | 27.3              | 27.3                |  |
| standard deviation                     | ± 4.77            | ± 4.77              |  |

## End points

### End points reporting groups

|  |                     |
|--|---------------------|
| Reporting group title  | Dasiglucagon        |
| Reporting group description: -   |                     |
| Reporting group title  | GlucaGen            |
| Reporting group description: -   |                     |
| Subject analysis set title   | Full analysis set   |
| Subject analysis set type  | Full analysis       |
| Subject analysis set description:  |                     |
| All patients of the safety analysis set with at least 1 measurement of ADA titer at baseline |                     |
| Subject analysis set title   | Safety analysis set |
| Subject analysis set type  | Safety analysis     |
| Subject analysis set description:  |                     |
| All patients who were randomly assigned and received at least 1 dose of IMP                  |                     |

### Primary: Overall ADA

|   |                            |
|---|----------------------------|
| End point title   | Overall ADA <sup>[1]</sup> |
| End point description:  |                            |
| For calculating the overall ADA incidence, patient numbers from both groups were summed and then divided by the number of evaluable patients. Baseline-positive patients without any samples available after IMP administration were excluded.                                |                            |
| Numbers and percentages of incidences in each treatment group and the incidence difference between dasiglucagon and GlucaGen® with its 95% exact confidence limits were planned to be provided but were not generated because no ADA-positive patients occurred in the trial. |                            |
| End point type  | Primary                    |
| End point timeframe:  |                            |
| From baseline to end of trial   |                            |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analyses were planned but were not generated because no ADA-positive patients occurred in the trial.

| End point values            | Dasiglucagon    | GlucaGen        | Full analysis set    |  |
|-----------------------------|-----------------|-----------------|----------------------|--|
| Subject group type          | Reporting group | Reporting group | Subject analysis set |  |
| Number of subjects analysed | 57              | 54              | 111                  |  |
| Units: Subjects             |                 |                 |                      |  |
| Yes                         | 0               | 0               | 0                    |  |
| No                          | 56              | 54              | 110                  |  |
| Missing                     | 1               | 0               | 1                    |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Treatment-induced ADA

|                 |                       |
|-----------------|-----------------------|
| End point title | Treatment-induced ADA |
|-----------------|-----------------------|



End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From baseline to end of trial

| End point values            | Dasiglucagon    | GlucaGen        | Full analysis set    |  |
|-----------------------------|-----------------|-----------------|----------------------|--|
| Subject group type          | Reporting group | Reporting group | Subject analysis set |  |
| Number of subjects analysed | 57              | 54              | 111                  |  |
| Units: subjects             |                 |                 |                      |  |
| Yes                         | 0               | 0               | 0                    |  |
| No                          | 56              | 54              | 110                  |  |
| Missing                     | 1               | 0               | 1                    |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Treatment-boosted ADA

|                 |                       |
|-----------------|-----------------------|
| End point title | Treatment-boosted ADA |
|-----------------|-----------------------|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From baseline to end of trial

| End point values            | Dasiglucagon    | GlucaGen        | Full analysis set    |  |
|-----------------------------|-----------------|-----------------|----------------------|--|
| Subject group type          | Reporting group | Reporting group | Subject analysis set |  |
| Number of subjects analysed | 57              | 54              | 111                  |  |
| Units: subjects             |                 |                 |                      |  |
| Yes                         | 0               | 0               | 0                    |  |
| No                          | 56              | 54              | 110                  |  |
| Missing                     | 1               | 0               | 1                    |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Incidence and titer of neutralizing activity of ADA-positive patients

|                 |  |
|-----------------|--|
| End point title | Incidence and titer of neutralizing activity of ADA-positive |
|-----------------|--|

End point description:

This secondary immunogenicity endpoint was not analyzed since there were no overall ADA incidents in the trial population.

End point type Secondary

End point timeframe:

From baseline to end of trial

| End point values            | Dasiglucagon    | GlucaGen        |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 57              | 54              |  |  |
| Units: Subjects             | 0               | 0               |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Pharmacokinetics - Area under the plasma concentration curve (0-30 minutes)

End point title Pharmacokinetics - Area under the plasma concentration curve (0-30 minutes)

End point description:

The area under the concentration-time curve from zero up to the concentration at 30 minutes. To calculate AUC the linear trapezoidal rule was used for the ascending part and the logarithmic trapezoidal rule was used for the descending part.

End point type Secondary

End point timeframe:

0-30 minutes

| End point values                     | Dasiglucagon    | GlucaGen        | Full analysis set    |  |
|--------------------------------------|-----------------|-----------------|----------------------|--|
| Subject group type                   | Reporting group | Reporting group | Subject analysis set |  |
| Number of subjects analysed          | 57              | 54              | 111                  |  |
| Units: pmol.h/L                      |                 |                 |                      |  |
| arithmetic mean (standard deviation) |                 |                 |                      |  |
| Visit 2                              | 425 (± 220)     | 548 (± 226)     | 485 (± 230)          |  |
| Visit 4                              | 499 (± 371)     | 546 (± 181)     | 522 (± 294)          |  |

## Statistical analyses

No statistical analyses for this end point

**Secondary: Pharmacokinetics - Area under the plasma concentration curve (0-90 minutes)**

|                 |   |
|-----------------|---|
| End point title | Pharmacokinetics - Area under the plasma concentration curve (0-90 minutes) |
|-----------------|---|

End point description:

The area under the concentration-time curve from zero up to the concentration at 90 minutes. To calculate AUC the linear trapezoidal rule was used for the ascending part and the logarithmic trapezoidal rule was used for the descending part.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

0-90 minutes

| End point values                     | Dasiglucagon    | GlucaGen        | Full analysis set    |  |
|--------------------------------------|-----------------|-----------------|----------------------|--|
| Subject group type                   | Reporting group | Reporting group | Subject analysis set |  |
| Number of subjects analysed          | 57              | 54              | 111                  |  |
| Units: pmol.h/L                      |                 |                 |                      |  |
| arithmetic mean (standard deviation) |                 |                 |                      |  |
| Visit 2                              | 1560 (± 615)    | 1290 (± 434)    | 1430 (± 549)         |  |
| Visit 4                              | 1640 (± 611)    | 1290 (± 379)    | 1470 (± 540)         |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Pharmacokinetics - Maximum concentration**

|                 |  |
|-----------------|--|
| End point title | Pharmacokinetics - Maximum concentration |
|-----------------|--|

End point description:

The measured maximum plasma concentration after administration at Visit 2 and Visit 4

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

0-120 minutes

| End point values                     | Dasiglucagon    | GlucaGen        | Full analysis set    |  |
|--------------------------------------|-----------------|-----------------|----------------------|--|
| Subject group type                   | Reporting group | Reporting group | Subject analysis set |  |
| Number of subjects analysed          | 57              | 54              | 111                  |  |
| Units: pmol/L                        |                 |                 |                      |  |
| arithmetic mean (standard deviation) |                 |                 |                      |  |
| Visit 2                              | 1390 (± 609)    | 1490 (± 537)    | 1440 (± 574)         |  |
| Visit 4                              | 1820 (± 2460)   | 1430 (± 498)    | 1630 (± 1790)        |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Pharmacokinetics - Time to maximum concentration

End point title Pharmacokinetics - Time to maximum concentration

End point description:

The actual sampling time recorded for the maximum concentration.

End point type Secondary

End point timeframe:

0-120 minutes

| End point values              | Dasiglucagon        | GlucaGen               | Full analysis set    |  |
|-------------------------------|---------------------|------------------------|----------------------|--|
| Subject group type            | Reporting group     | Reporting group        | Subject analysis set |  |
| Number of subjects analysed   | 57                  | 54                     | 111                  |  |
| Units: hours                  |                     |                        |                      |  |
| median (full range (min-max)) |                     |                        |                      |  |
| Visit 2                       | 0.5 (0.167 to 1.5)  | 0.483 (0.0833 to 0.55) | 0.5 (0.0833 to 1.5)  |  |
| Visit 4                       | 0.5 (0.0833 to 1.5) | 0.5 (0.0833 to 0.517)  | 0.5 (0.0833 to 1.5)  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Pharmacodynamics - Area under the effect curve (0-30 minutes)

End point title Pharmacodynamics - Area under the effect curve (0-30 minutes)

End point description:

The area under the baseline-adjusted effect curve from zero up to the concentration measured at 30 minutes. To calculate AUE the linear trapezoidal rule was used for the ascending part and the logarithmic trapezoidal rule was used for the descending part.

End point type Secondary

End point timeframe:

0-30 minutes

| End point values                     | Dasiglucagon    | GlucaGen        | Full analysis set    |  |
|--------------------------------------|-----------------|-----------------|----------------------|--|
| Subject group type                   | Reporting group | Reporting group | Subject analysis set |  |
| Number of subjects analysed          | 57              | 54              | 111                  |  |
| Units: mmol.h/L                      |                 |                 |                      |  |
| arithmetic mean (standard deviation) |                 |                 |                      |  |
| Visit 2                              | 0.799 (± 0.449) | 0.886 (± 0.504) | 0.841 (± 0.476)      |  |

|         |                      |                      |                      |  |
|---------|----------------------|----------------------|----------------------|--|
| Visit 4 | 0.869 ( $\pm$ 0.375) | 0.895 ( $\pm$ 0.511) | 0.881 ( $\pm$ 0.443) |  |
|---------|----------------------|----------------------|----------------------|--|

## Statistical analyses

No statistical analyses for this end point

## Secondary: Pharmacodynamics - Area under the effect curve (0-90 minutes)

|                 |   |
|-----------------|---|
| End point title | Pharmacodynamics - Area under the effect curve (0-90 minutes) |
|-----------------|---|

End point description:

The area under the baseline-adjusted effect curve from zero up to the concentration measured at 90 minutes. To calculate AUE the linear trapezoidal rule was used for the ascending part and the logarithmic trapezoidal rule was used for the descending part.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

0-90 minutes

| End point values                     | Dasiglucagon       | GlucaGen           | Full analysis set    |  |
|--------------------------------------|--------------------|--------------------|----------------------|--|
| Subject group type                   | Reporting group    | Reporting group    | Subject analysis set |  |
| Number of subjects analysed          | 57                 | 54                 | 111                  |  |
| Units: mmol.h/L                      |                    |                    |                      |  |
| arithmetic mean (standard deviation) |                    |                    |                      |  |
| Visit 2                              | 5.9 ( $\pm$ 2.42)  | 5.86 ( $\pm$ 3.14) | 5.88 ( $\pm$ 2.78)   |  |
| Visit 4                              | 6.47 ( $\pm$ 2.28) | 6.04 ( $\pm$ 2.63) | 6.26 ( $\pm$ 2.46)   |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Pharmacodynamics - CEmax

|                 |                          |
|-----------------|--------------------------|
| End point title | Pharmacodynamics - CEmax |
|-----------------|--------------------------|

End point description:

Change from baseline plasma glucose to maximum plasma glucose measured after dosing.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

0-120 minutes

| End point values                     | Dasiglucagon    | GlucaGen        | Full analysis set    |  |
|--------------------------------------|-----------------|-----------------|----------------------|--|
| Subject group type                   | Reporting group | Reporting group | Subject analysis set |  |
| Number of subjects analysed          | 57              | 54              | 111                  |  |
| Units: mmol/L                        |                 |                 |                      |  |
| arithmetic mean (standard deviation) |                 |                 |                      |  |
| Visit 2                              | 6.25 (± 2.5)    | 6 (± 3.01)      | 6.12 (± 2.75)        |  |
| Visit 4                              | 6.88 (± 2.43)   | 6.21 (± 2.65)   | 6.55 (± 2.55)        |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Pharmacodynamics - TEmax

|                        |   |
|------------------------|---|
| End point title        | Pharmacodynamics - TEmax  |
| End point description: | The time to reach the maximum change from baseline in plasma glucose measured after dosing. |
| End point type         | Secondary   |
| End point timeframe:   | 0-120 minutes   |

| End point values              | Dasiglucagon         | GlucaGen             | Full analysis set    |  |
|-------------------------------|----------------------|----------------------|----------------------|--|
| Subject group type            | Reporting group      | Reporting group      | Subject analysis set |  |
| Number of subjects analysed   | 57                   | 54                   | 111                  |  |
| Units: hours                  |                      |                      |                      |  |
| median (full range (min-max)) |                      |                      |                      |  |
| Visit 2                       | 1.5 (0.0833 to 1.57) | 1.5 (0.483 to 1.6)   | 1.5 (0.0833 to 1.6)  |  |
| Visit 4                       | 1.5 (0.167 to 1.58)  | 1.5 (0.0833 to 1.52) | 1.5 (0.0833 to 1.58) |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Pharmacodynamics - An increase in the plasma glucose concentration of ≥20 mg/dL within 30 minutes after treatment - Visit 2

|                        |   |
|------------------------|---|
| End point title        | Pharmacodynamics - An increase in the plasma glucose concentration of ≥20 mg/dL within 30 minutes after treatment - Visit 2 |
| End point description: |   |
| End point type         | Secondary   |
| End point timeframe:   | 0-30 minutes  |

| End point values            | Dasiglucagon    | GlucaGen        | Full analysis set    |  |
|-----------------------------|-----------------|-----------------|----------------------|--|
| Subject group type          | Reporting group | Reporting group | Subject analysis set |  |
| Number of subjects analysed | 57              | 54              | 111                  |  |
| Units: subjects             |                 |                 |                      |  |
| Yes                         | 54              | 51              | 105                  |  |
| No                          | 3               | 3               | 6                    |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Pharmacodynamics - An increase in the plasma glucose concentration of $\geq 20$ mg/dL within 30 minutes after treatment - Visit 4

|                 |   |
|-----------------|---|
| End point title | Pharmacodynamics - An increase in the plasma glucose concentration of $\geq 20$ mg/dL within 30 minutes after treatment - Visit 4 |
|-----------------|---|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

0-30 minutes

| End point values            | Dasiglucagon    | GlucaGen        | Full analysis set    |  |
|-----------------------------|-----------------|-----------------|----------------------|--|
| Subject group type          | Reporting group | Reporting group | Subject analysis set |  |
| Number of subjects analysed | 52              | 49              | 101                  |  |
| Units: subjects             |                 |                 |                      |  |
| Yes                         | 51              | 47              | 98                   |  |
| No                          | 1               | 2               | 3                    |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from the first trial-related activity after the patient has signed the informed consent to the end of the follow-up period.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 20.0 |
|--------------------|------|

### Reporting groups

|                       |              |
|-----------------------|--------------|
| Reporting group title | Dasiglucagon |
|-----------------------|--------------|

Reporting group description: -

|                       |          |
|-----------------------|----------|
| Reporting group title | GlucaGen |
|-----------------------|----------|

Reporting group description: -

| Serious adverse events                            | Dasiglucagon   | GlucaGen       |  |
|---|----------------|----------------|--|
| Total subjects affected by serious adverse events |                |                |  |
| subjects affected / exposed                       | 1 / 57 (1.75%) | 0 / 54 (0.00%) |  |
| number of deaths (all causes)                     | 0              | 0              |  |
| number of deaths resulting from adverse events    | 0              | 0              |  |
| Metabolism and nutrition disorders                |                |                |  |
| Hypoglycaemia                                     |                |                |  |
| subjects affected / exposed                       | 1 / 57 (1.75%) | 0 / 54 (0.00%) |  |
| occurrences causally related to treatment / all   | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all        | 0 / 0          | 0 / 0          |  |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events                            | Dasiglucagon     | GlucaGen         |  |
|---|------------------|------------------|--|
| Total subjects affected by non-serious adverse events |                  |                  |  |
| subjects affected / exposed                           | 42 / 57 (73.68%) | 43 / 54 (79.63%) |  |
| Nervous system disorders                              |                  |                  |  |
| Headache  |                  |                  |  |
| subjects affected / exposed                           | 8 / 57 (14.04%)  | 3 / 54 (5.56%)   |  |
| occurrences (all)                                     | 14               | 4                |  |
| Dizziness   |                  |                  |  |
| subjects affected / exposed                           | 2 / 57 (3.51%)   | 3 / 54 (5.56%)   |  |
| occurrences (all)                                     | 2                | 3                |  |



|   |   |   |  |
|---|---|---|--|
| Blood and lymphatic system disorders<br>Leukocytosis<br>subjects affected / exposed<br>occurrences (all)  | 2 / 57 (3.51%)<br>2   | 4 / 54 (7.41%)<br>5   |  |
| Gastrointestinal disorders<br>Nausea<br>subjects affected / exposed<br>occurrences (all)<br><br>Vomiting<br>subjects affected / exposed<br>occurrences (all)<br><br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all) | 26 / 57 (45.61%)<br>43<br><br>12 / 57 (21.05%)<br>18<br><br>4 / 57 (7.02%)<br>4 | 23 / 54 (42.59%)<br>33<br><br>8 / 54 (14.81%)<br>9<br><br>2 / 54 (3.70%)<br>2 |  |
| Skin and subcutaneous tissue disorders<br>Erythema<br>subjects affected / exposed<br>occurrences (all)  | 0 / 57 (0.00%)<br>0   | 3 / 54 (5.56%)<br>4   |  |
| Infections and infestations<br>Viral upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)<br><br>Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)           | 6 / 57 (10.53%)<br>7<br><br>2 / 57 (3.51%)<br>2                                 | 8 / 54 (14.81%)<br>9<br><br>4 / 54 (7.41%)<br>4                               |  |
| Metabolism and nutrition disorders<br>Hypoglycaemia<br>subjects affected / exposed<br>occurrences (all)<br><br>Hyperglycaemia<br>subjects affected / exposed<br>occurrences (all)   | 28 / 57 (49.12%)<br>581<br><br>3 / 57 (5.26%)<br>3                              | 29 / 54 (53.70%)<br>447<br><br>2 / 54 (3.70%)<br>8                            |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date           | Amendment   |
|----------------|---|
| 08 May 2017    | <p>In this substantial amendment, the following changes were made to the original protocol to revise details of the safety assessment of patients and correct changes, errors or inconsistencies in the description of the operational set up of the trial:</p> <ul style="list-style-type: none"><li>• Clarification on the statistical method and anti-drug antibody (ADA) assays</li><li>• Update of exclusion criterion on blood pressure</li><li>• Update of exclusion criterion on alcohol/drug abuse</li><li>• Specification of prohibited concomitant medication</li><li>• Additional ECG assessment added</li><li>• Clinical event of interest added</li><li>• Treatment options for patients experiencing hypo- or hyperglycemia prior dosing</li><li>• Monitoring of patients' electrolyte levels</li><li>• Monitoring of potential pregnancies</li><li>• Additional visits required for patients discontinuing treatment prematurely</li><li>• Specification on time windows for assessments</li><li>• Specification of the requirements at the dosing visits</li><li>• Responsibility of unblinded trial personnel</li><li>• Randomization of replacement patients</li><li>• Clarification to the reporting of (Serious) Adverse Events</li><li>• Clarification on case report forms</li><li>• Subgroup analysis added to the statistical section</li><li>• Administrative changes</li></ul> |
| 21 August 2017 | <p>This substantial amendment was prepared in order to investigate how pharmacodynamic and pharmacokinetic endpoints correlate with potential anti-drug antibody responses that may develop. In order to investigate this in patients that may develop antibodies late during the course of the trial, an extra visit was to be implemented for patients, who developed anti-drug antibodies after trial drug administration. The amendment also included an additional pharmacodynamic endpoint and specified that patients who discontinue the trial prematurely were not to be replaced.</p>   |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported