



## Clinical trial results:

## Dual-Hormone Closed-Loop Glucose Control in Adolescents with Type 1 Diabetes

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2020-005836-31 |
| Trial protocol           | DK             |
| Global end of trial date | 26 April 2022  |

### Results information

|                                |                   |
|--------------------------------|-------------------|
| Result version number          | v1 (current)      |
| This version publication date  | 11 September 2022 |
| First version publication date | 11 September 2022 |

### Trial information

#### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | DHCL2021 |
|-----------------------|----------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT04949867 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Steno Diabetes Center Copenhagen   |
| Sponsor organisation address | Borgmester Ib Juuls Vej 83, Herlev, Denmark, 2730  |
| Public contact               | Ajenthén G Ranjan, Steno Diabetes Center Copenhagen, 45 23742766, Ajenthén.Ranjan@regionh.dk |
| Scientific contact           | Ajenthén G Ranjan, Steno Diabetes Center Copenhagen, 45 23742766, Ajenthén.Ranjan@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                                       | Final         |
| Date of interim/final analysis                       | 16 June 2022  |
| Is this the analysis of the primary completion data? | Yes           |
| Primary completion date                              | 26 April 2022 |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 26 April 2022 |
| Was the trial ended prematurely?                     | No            |

Notes:

## General information about the trial

Main objective of the trial:

The aims of this two-phase project are to 1) demonstrate proof-of-concept and 2) to compare dual-hormone with single-hormone closed-loop glucose control.

Protection of trial subjects:

Participants were offered numbing creme before canulation for plasma sampling.

Background therapy: -

Evidence for comparator: -

|   |                   |
|---|-------------------|
| Actual start date of recruitment                          | 01 September 2021 |
| 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 | Denmark: 11 |
| Worldwide total number of subjects   | 11          |
| EEA total number of subjects         | 11          |

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)                 | 10 |
| Adults (18-64 years)                      | 1  |
| From 65 to 84 years                       | 0  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Participants were recruited from the outpatient clinic at Herlev Pediatric Department and Steno Diabetes Center Copenhagen from September 2021 to March 2022

### Pre-assignment

Screening details:

Parents of participants provided written informed consent, participants ages 15 years and up provided written informed assent. Afterwards they completed a screening visit for assessment of eligibility criteria. Procedures included physical examination, review of medical records and medications as well as routine blood sampling.

### Period 1

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

Blinding implementation details:

Participants were blinded to the study medication

### Arms

|                              |                          |
|------------------------------|--------------------------|
| Are arms mutually exclusive? | No                       |
| <b>Arm title</b>             | Dual-Hormone Closed-Loop |

Arm description:

Pump 1: Fiasp, Pump 2: Glucagon

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

Dosage and administration details:

Participants were fitted with Glucagon pump at t=0, which was inserted subcutaneously. Doses were calculated by the algorithm used in the study, DiaCon APS.

|  |   |
|--|---|
| Investigational medicinal product name | FiAsp   |
| Investigational medicinal product code | SUB08195MIG   |
| Other name                             |   |
| Pharmaceutical forms                   | Solution for solution for injection, Solution for solution for infusion |
| Routes of administration               | Subcutaneous use  |

Dosage and administration details:

Participants were fitted with insulin pump at time T=0, which was inserted subcutaneously. Dosages were calculated by the algorithm used in the study, DiaCon APS.

|                  |                            |
|------------------|----------------------------|
| <b>Arm title</b> | Single-Hormone Closed-Loop |
|------------------|----------------------------|

Arm description:

Pump 1: FiAsp

Pump 2: Saline (not set for injection)

|          |                   |
|----------|-------------------|
| Arm type | Active comparator |
|----------|-------------------|

|  |   |
|--|---|
| Investigational medicinal product name | FiAsp   |
| Investigational medicinal product code | SUB08195MIG   |
| Other name                             |   |
| Pharmaceutical forms                   | Solution for solution for infusion, Solution for solution for injection |
| Routes of administration               | Subcutaneous use  |

Dosage and administration details:

Participants were fitted with insulin pump at time T=0, which was inserted subcutaneously. Dosages were calculated by the algorithm used in the study, DiaCon APS.

| <b>Number of subjects in period 1</b> | Dual-Hormone<br>Closed-Loop | Single-Hormone<br>Closed-Loop |
|---------------------------------------|-----------------------------|-------------------------------|
| Started                               | 11                          | 11                            |
| Completed                             | 11                          | 11                            |

## Baseline characteristics

### Reporting groups

|                       |                               |
|-----------------------|-------------------------------|
| Reporting group title | Study period (overall period) |
|-----------------------|-------------------------------|

Reporting group description: -

| Reporting group values                                | Study period<br>(overall period) | Total |  |
|---|----------------------------------|-------|--|
| Number of subjects                                    | 11                               | 11    |  |
| Age categorical                                       |                                  |       |  |
| Units: Subjects                                       |                                  |       |  |
| In utero  | 0                                | 0     |  |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0                                | 0     |  |
| Newborns (0-27 days)                                  | 0                                | 0     |  |
| Infants and toddlers (28 days-23<br>months)           | 0                                | 0     |  |
| Children (2-11 years)                                 | 0                                | 0     |  |
| Adolescents (12-17 years)                             | 10                               | 10    |  |
| Adults (18-64 years)                                  | 1                                | 1     |  |
| From 65-84 years                                      | 0                                | 0     |  |
| 85 years and over                                     | 0                                | 0     |  |
| Age continuous  |                                  |       |  |
| Units: years  |                                  |       |  |
| arithmetic mean                                       | 14.8                             |       |  |
| standard deviation                                    | ± 1.47                           | -     |  |
| Gender categorical                                    |                                  |       |  |
| Units: Subjects                                       |                                  |       |  |
| Female  | 2                                | 2     |  |
| Male  | 9                                | 9     |  |
| BMI   |                                  |       |  |
| Units: kg/m <sup>2</sup>                              |                                  |       |  |
| arithmetic mean                                       | 21.4                             |       |  |
| standard deviation                                    | ± 2.42                           | -     |  |
| Diabetes Duration                                     |                                  |       |  |
| Units: Years  |                                  |       |  |
| arithmetic mean                                       | 5.73                             |       |  |
| standard deviation                                    | ± 2.45                           | -     |  |
| Total Daily Insulin                                   |                                  |       |  |
| Units: U/kg   |                                  |       |  |
| arithmetic mean                                       | 0.942                            |       |  |
| standard deviation                                    | ± 0.256                          | -     |  |
| Time in range (3.9 - 10.0 mmol/L)                     |                                  |       |  |
| Units: Percentage                                     |                                  |       |  |
| median  | 54                               |       |  |
| inter-quartile range (Q1-Q3)                          | 46 to 73                         | -     |  |
| Time below range (<3.9 mmol/L)                        |                                  |       |  |
| Units: Percentage                                     |                                  |       |  |
| median  | 3                                |       |  |
| inter-quartile range (Q1-Q3)                          | 1.5 to 6.5                       | -     |  |

|                                 |            |   |  |
|---------------------------------|------------|---|--|
| Time above range (>10.0 mmol/L) |            |   |  |
| Units: Percentage               |            |   |  |
| median                          | 43         |   |  |
| inter-quartile range (Q1-Q3)    | 22.5 to 52 | - |  |
| HbA1c                           |            |   |  |
| Units: millimole(s)/litre       |            |   |  |
| arithmetic mean                 | 54.6       |   |  |
| standard deviation              | ± 9.2      | - |  |

## End points

### End points reporting groups

|  |                            |
|--|----------------------------|
| Reporting group title                  | Dual-Hormone Closed-Loop   |
| Reporting group description:           |                            |
| Pump 1: Fiasp, Pump 2: Glucagon        |                            |
| Reporting group title                  | Single-Hormone Closed-Loop |
| Reporting group description:           |                            |
| Pump 1: FiAsp                          |                            |
| Pump 2: Saline (not set for injection) |                            |

### Primary: Percentage of time with glucose values < 3.9 mmol/l as measured by CGM

|                 |   |
|-----------------|---|
| End point title | Percentage of time with glucose values < 3.9 mmol/l as measured by CGM <sup>[1]</sup> |
|-----------------|---|

End point description:

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

End point timeframe:

Evaluation is performed after completion of the second study visit, i.e., after two times 26-hours

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: Categorical variables were reported as frequencies (percentage), whereas continuous were reported as mean (SD) or median (interquartile range [IQR]). Continuous data was assessed for normality using Shapiro-Wilk test. For normally distributed variables, paired student's t-test were used to conduct pair-wise comparisons between the two groups. For skewedly distributed variables despite log-transformation, the non-parametric Wilcoxon signed-rank test was used. Missing glucose data were estimated

| End point values                      | Dual-Hormone Closed-Loop | Single-Hormone Closed-Loop |  |  |
|---------------------------------------|--------------------------|----------------------------|--|--|
| Subject group type                    | Reporting group          | Reporting group            |  |  |
| Number of subjects analysed           | 11                       | 11                         |  |  |
| Units: Percentage                     |                          |                            |  |  |
| median (inter-quartile range (Q1-Q3)) | 1.6 (0 to 3.99)          | 1.28 (0 to 3.19)           |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of time with glucose values in the range 3.9-10.0 mmol/l measured by CGM

|                 |   |
|-----------------|---|
| End point title | Percentage of time with glucose values in the range 3.9-10.0 mmol/l measured by CGM |
|-----------------|---|

End point description:

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

End point timeframe:

Evaluation is performed after completion of the second study session, i.e. after two times 26-hours

| End point values                      | Dual-Hormone Closed-Loop | Single-Hormone Closed-Loop |  |  |
|---------------------------------------|--------------------------|----------------------------|--|--|
| Subject group type                    | Reporting group          | Reporting group            |  |  |
| Number of subjects analysed           | 11                       | 11                         |  |  |
| Units: Percentage                     |                          |                            |  |  |
| median (inter-quartile range (Q1-Q3)) | 68.1 (48.7 to 75.4)      | 75.7 (69.8 to 87.1)        |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of carbohydrate interventions to treat hypoglycemia

|                 |  |
|-----------------|--|
| End point title | Number of carbohydrate interventions to treat hypoglycemia |
|-----------------|--|

End point description:

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

End point timeframe:

Evaluation is performed after completion of the second study session, i.e. after two times 26-hours

| End point values                     | Dual-Hormone Closed-Loop | Single-Hormone Closed-Loop |  |  |
|--------------------------------------|--------------------------|----------------------------|--|--|
| Subject group type                   | Reporting group          | Reporting group            |  |  |
| Number of subjects analysed          | 11                       | 11                         |  |  |
| Units: Grams                         |                          |                            |  |  |
| arithmetic mean (standard deviation) | 6.8 ( $\pm$ 12.3)        | 9.5 ( $\pm$ 15.4)          |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of time with glucose values < 3.9 mmol/l as measured by YSI

|                 |  |
|-----------------|--|
| End point title | Percentage of time with glucose values < 3.9 mmol/l as measured by YSI |
|-----------------|--|

End point description:



|   |           |
|---|-----------|
| End point type  | Secondary |
| End point timeframe:  |           |
| Evaluation is performed after completion of the second study session, i.e. after two times 26-hours |           |

| End point values                      | Dual-Hormone Closed-Loop | Single-Hormone Closed-Loop |  |  |
|---------------------------------------|--------------------------|----------------------------|--|--|
| Subject group type                    | Reporting group          | Reporting group            |  |  |
| Number of subjects analysed           | 11                       | 11                         |  |  |
| Units: Percentage                     |                          |                            |  |  |
| median (inter-quartile range (Q1-Q3)) | 0.958 (0 to 3.83)        | 2.56 (0.479 to 8.47)       |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of time with glucose values in the range 3.9-10.0 mmol/l measured by YSI

|                 |   |
|-----------------|---|
| End point title | Percentage of time with glucose values in the range 3.9-10.0 mmol/l measured by YSI |
|-----------------|---|

End point description:

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

End point timeframe:

Evaluation is performed after completion of the second study session, i.e. after two times 26-hours

| End point values                      | Dual-Hormone Closed-Loop | Single-Hormone Closed-Loop |  |  |
|---------------------------------------|--------------------------|----------------------------|--|--|
| Subject group type                    | Reporting group          | Reporting group            |  |  |
| Number of subjects analysed           | 11                       | 11                         |  |  |
| Units: percent                        |                          |                            |  |  |
| median (inter-quartile range (Q1-Q3)) | 66.8 (56.9 to 78.9)      | 79.6 (75.2 to 87.4)        |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of time with glucose values >10.0 mmol/l as measured by CGM

|                 |  |
|-----------------|--|
| End point title | Percentage of time with glucose values >10.0 mmol/l as |
|-----------------|--|

End point description:

End point type Secondary

End point timeframe:

Evaluation is performed after completion of the second study session, i.e. after two times 26-hours

| End point values                      | Dual-Hormone Closed-Loop | Single-Hormone Closed-Loop |  |  |
|---------------------------------------|--------------------------|----------------------------|--|--|
| Subject group type                    | Reporting group          | Reporting group            |  |  |
| Number of subjects analysed           | 11                       | 11                         |  |  |
| Units: percent                        |                          |                            |  |  |
| median (inter-quartile range (Q1-Q3)) | 28.1 (18.4 to 50.0)      | 23.3 (12.3 to 27.2)        |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of time with glucose values >10.0 mmol/l as measured by YSI

End point title Percentage of time with glucose values >10.0 mmol/l as measured by YSI

End point description:

End point type Secondary

End point timeframe:

Evaluation is performed after completion of the second study session, i.e. after two times 26-hours

| End point values                      | Dual-Hormone Closed-Loop | Single-Hormone Closed-Loop |  |  |
|---------------------------------------|--------------------------|----------------------------|--|--|
| Subject group type                    | Reporting group          | Reporting group            |  |  |
| Number of subjects analysed           | 11                       | 11                         |  |  |
| Units: percent                        |                          |                            |  |  |
| median (inter-quartile range (Q1-Q3)) | 33.2 (16.1 to 40.7)      | 11.5 (3.83 to 23.0)        |  |  |

### Statistical analyses

No statistical analyses for this end point

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**Secondary: Percentage of time with glucose values < 3.0 mmol/l as measured by CGM**

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|                 |  |
|-----------------|--|
| End point title | Percentage of time with glucose values < 3.0 mmol/l as measured by CGM |
|-----------------|--|

End point description:

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

End point timeframe:

Evaluation is performed after completion of the second study session, i.e. after two times 26-hours

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| End point values                      | Dual-Hormone Closed-Loop | Single-Hormone Closed-Loop |  |  |
|---------------------------------------|--------------------------|----------------------------|--|--|
| Subject group type                    | Reporting group          | Reporting group            |  |  |
| Number of subjects analysed           | 11                       | 11                         |  |  |
| Units: percent                        |                          |                            |  |  |
| median (inter-quartile range (Q1-Q3)) | 0 (0 to 1.28)            | 0 (0 to 0)                 |  |  |

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Percentage of time with glucose values < 3.0 mmol/l as measured by YSI**

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|                 |  |
|-----------------|--|
| End point title | Percentage of time with glucose values < 3.0 mmol/l as measured by YSI |
|-----------------|--|

End point description:

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

End point timeframe:

Evaluation is performed after completion of the second study session, i.e. after two times 26-hours

---

| End point values                      | Dual-Hormone Closed-Loop | Single-Hormone Closed-Loop |  |  |
|---------------------------------------|--------------------------|----------------------------|--|--|
| Subject group type                    | Reporting group          | Reporting group            |  |  |
| Number of subjects analysed           | 11                       | 11                         |  |  |
| Units: percent                        |                          |                            |  |  |
| median (inter-quartile range (Q1-Q3)) | 0 (0 to 0.16)            | 0 (0 to 0.48)              |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Mean blood glucose value measured by CGM

|                 |  |
|-----------------|--|
| End point title | Mean blood glucose value measured by CGM |
|-----------------|--|

End point description:

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

End point timeframe:

Evaluation is performed after completion of the second study session, i.e. after two times 26-hours

| End point values                     | Dual-Hormone<br>Closed-Loop | Single-<br>Hormone<br>Closed-Loop |  |  |
|--------------------------------------|-----------------------------|-----------------------------------|--|--|
| Subject group type                   | Reporting group             | Reporting group                   |  |  |
| Number of subjects analysed          | 11                          | 11                                |  |  |
| Units: mmol/l                        |                             |                                   |  |  |
| arithmetic mean (standard deviation) | 8.7 ( $\pm$ 3.0)            | 8.1 ( $\pm$ 3.0)                  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Mean blood glucose value measured by YSI

|                 |  |
|-----------------|--|
| End point title | Mean blood glucose value measured by YSI |
|-----------------|--|

End point description:

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

End point timeframe:

Evaluation is performed after completion of the second study session, i.e. after two times 26-hours

| End point values                     | Dual-Hormone Closed-Loop | Single-Hormone Closed-Loop |  |  |
|--------------------------------------|--------------------------|----------------------------|--|--|
| Subject group type                   | Reporting group          | Reporting group            |  |  |
| Number of subjects analysed          | 11                       | 11                         |  |  |
| Units: mmol/L                        |                          |                            |  |  |
| arithmetic mean (standard deviation) | 8.43 (± 2.83)            | 7.51 (± 2.98)              |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of hypoglycemic episodes <3.9 mmol/L on CGM

|                 |  |
|-----------------|--|
| End point title | Number of hypoglycemic episodes <3.9 mmol/L on CGM |
|-----------------|--|

End point description:

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

End point timeframe:

Evaluation is performed after completion of the second study session, i.e. after two times 26-hours

| End point values            | Dual-Hormone Closed-Loop | Single-Hormone Closed-Loop |  |  |
|-----------------------------|--------------------------|----------------------------|--|--|
| Subject group type          | Reporting group          | Reporting group            |  |  |
| Number of subjects analysed | 11                       | 11                         |  |  |
| Units: number               | 14                       | 13                         |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of hypoglycemic episodes <3.9 mmol/L on YSI

|                 |  |
|-----------------|--|
| End point title | Number of hypoglycemic episodes <3.9 mmol/L on YSI |
|-----------------|--|

End point description:

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

End point timeframe:

Evaluation is performed after completion of the second study session, i.e. after two times 26-hours

| End point values            | Dual-Hormone Closed-Loop | Single-Hormone Closed-Loop |  |  |
|-----------------------------|--------------------------|----------------------------|--|--|
| Subject group type          | Reporting group          | Reporting group            |  |  |
| Number of subjects analysed | 11                       | 11                         |  |  |
| Units: Number               | 11                       | 17                         |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: CGM glycemic variability as SD

|                 |                                |
|-----------------|--------------------------------|
| End point title | CGM glycemic variability as SD |
|-----------------|--------------------------------|

End point description:

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

End point timeframe:

Evaluation is performed after completion of the second study session, i.e. after two times 26-hours

| End point values                     | Dual-Hormone Closed-Loop | Single-Hormone Closed-Loop |  |  |
|--------------------------------------|--------------------------|----------------------------|--|--|
| Subject group type                   | Reporting group          | Reporting group            |  |  |
| Number of subjects analysed          | 11                       | 11                         |  |  |
| Units: mmol/L                        |                          |                            |  |  |
| arithmetic mean (standard deviation) | 8.7 (± 3.0)              | 8.1 (± 3.0)                |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: CGM glycemic variability as CV

|                 |                                |
|-----------------|--------------------------------|
| End point title | CGM glycemic variability as CV |
|-----------------|--------------------------------|

End point description:

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

End point timeframe:

Evaluation is performed after completion of the second study session, i.e. after two times 26-hours

| End point values                     | Dual-Hormone Closed-Loop | Single-Hormone Closed-Loop |  |  |
|--------------------------------------|--------------------------|----------------------------|--|--|
| Subject group type                   | Reporting group          | Reporting group            |  |  |
| Number of subjects analysed          | 11                       | 11                         |  |  |
| Units: percent                       |                          |                            |  |  |
| arithmetic mean (standard deviation) | 34.7 (± 6.9)             | 37.3 (± 8.6)               |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Total insulin dose

|                        |                    |
|------------------------|--------------------|
| End point title        | Total insulin dose |
| End point description: |                    |

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

End point timeframe:

Evaluation is performed after completion of the second study session, i.e. after two times 26-hours

| End point values                     | Dual-Hormone Closed-Loop | Single-Hormone Closed-Loop |  |  |
|--------------------------------------|--------------------------|----------------------------|--|--|
| Subject group type                   | Reporting group          | Reporting group            |  |  |
| Number of subjects analysed          | 11                       | 11                         |  |  |
| Units: unit(s)                       |                          |                            |  |  |
| arithmetic mean (standard deviation) | 57.4 (± 20.1)            | 57.0 (± 16.1)              |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Total glucagon dose

|                        |                                    |
|------------------------|------------------------------------|
| End point title        | Total glucagon dose <sup>[2]</sup> |
| End point description: |                                    |

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

End point timeframe:

Evaluation is performed after completion of the second study session, i.e. after two times 26-hours

Notes:

[2] - 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: Glucagon was only provided in the one arm. Therefore no reporting in the other arm.

|                                       |                          |  |  |  |
|---------------------------------------|--------------------------|--|--|--|
| <b>End point values</b>               | Dual-Hormone Closed-Loop |  |  |  |
| Subject group type                    | Reporting group          |  |  |  |
| Number of subjects analysed           | 11                       |  |  |  |
| Units: unit(s)                        |                          |  |  |  |
| median (inter-quartile range (Q1-Q3)) | 548 (229.1 to 1348.6)    |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of manual insulin boluses

|                        |                                  |
|------------------------|----------------------------------|
| End point title        | Number of manual insulin boluses |
| End point description: |                                  |

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

End point timeframe:

Evaluation is performed after completion of the second study session, i.e. after two times 26-hours

|                             |                          |                            |  |  |
|-----------------------------|--------------------------|----------------------------|--|--|
| <b>End point values</b>     | Dual-Hormone Closed-Loop | Single-Hormone Closed-Loop |  |  |
| Subject group type          | Reporting group          | Reporting group            |  |  |
| Number of subjects analysed | 11                       | 11                         |  |  |
| Units: Number               | 1                        | 2                          |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of adverse events for nausea

|                        |                                     |
|------------------------|-------------------------------------|
| End point title        | Number of adverse events for nausea |
| End point description: |                                     |

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

End point timeframe:

Evaluation is performed after completion of the second study session, i.e. after two times 26-hours



| End point values            | Dual-Hormone Closed-Loop | Single-Hormone Closed-Loop |  |  |
|-----------------------------|--------------------------|----------------------------|--|--|
| Subject group type          | Reporting group          | Reporting group            |  |  |
| Number of subjects analysed | 11                       | 11                         |  |  |
| Units: percentage           | 27                       | 0                          |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of adverse events for headache

|   |                                       |
|---|---------------------------------------|
| End point title   | Number of adverse events for headache |
| End point description:  |                                       |
| End point type  | Secondary                             |
| End point timeframe:  |                                       |
| Evaluation is performed after completion of the second study session, i.e. after two times 26-hours |                                       |

| End point values            | Dual-Hormone Closed-Loop | Single-Hormone Closed-Loop |  |  |
|-----------------------------|--------------------------|----------------------------|--|--|
| Subject group type          | Reporting group          | Reporting group            |  |  |
| Number of subjects analysed | 11                       | 11                         |  |  |
| Units: percentage           | 36                       | 36                         |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of adverse events for stomach ache

|   |   |
|---|---|
| End point title   | Number of adverse events for stomach ache |
| End point description:  |   |
| End point type  | Secondary                                 |
| End point timeframe:  |   |
| Evaluation is performed after completion of the second study session, i.e. after two times 26-hours |   |

| End point values            | Dual-Hormone Closed-Loop | Single-Hormone Closed-Loop |  |  |
|-----------------------------|--------------------------|----------------------------|--|--|
| Subject group type          | Reporting group          | Reporting group            |  |  |
| Number of subjects analysed | 11                       | 11                         |  |  |
| Units: Percentage           | 18                       | 9                          |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of vomits

|                 |                  |
|-----------------|------------------|
| End point title | Number of vomits |
|-----------------|------------------|

End point description:

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

End point timeframe:

Evaluation is performed after completion of the second study session, i.e. after two times 26-hours

| End point values            | Dual-Hormone Closed-Loop | Single-Hormone Closed-Loop |  |  |
|-----------------------------|--------------------------|----------------------------|--|--|
| Subject group type          | Reporting group          | Reporting group            |  |  |
| Number of subjects analysed | 11                       | 11                         |  |  |
| Units: Number               | 0                        | 0                          |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Difference between actual and participant-estimated-CHO content in meals

|                 |  |
|-----------------|--|
| End point title | Difference between actual and participant-estimated-CHO content in meals |
|-----------------|--|

End point description:

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

End point timeframe:

Evaluation is performed after completion of the second study session, i.e. after two times 26-hours

| End point values                     | Dual-Hormone Closed-Loop | Single-Hormone Closed-Loop |  |  |
|--------------------------------------|--------------------------|----------------------------|--|--|
| Subject group type                   | Reporting group          | Reporting group            |  |  |
| Number of subjects analysed          | 11                       | 11                         |  |  |
| Units: percent                       |                          |                            |  |  |
| arithmetic mean (standard deviation) | 84.4 (± 12.6)            | 82.8 (± 13.8)              |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Composite outcome: Percentage of participants achieving (1) time in range (3.9-10) > 70 %, (2) time in alert hypoglycemia (<3.9 mmol/l) < 4 %, and (3) time in clinical hypoglycemia (<3.0 mmol) < 1% as measured by CGM

|                 |  |
|-----------------|--|
| End point title | Composite outcome: Percentage of participants achieving (1) time in range (3.9-10) > 70 %, (2) time in alert hypoglycemia (<3.9 mmol/l) < 4 %, and (3) time in clinical hypoglycemia (<3.0 mmol) < 1% as measured by CGM |
|-----------------|--|

End point description:

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

End point timeframe:

Evaluation is performed after completion of the second study session, i.e. after two times 26-hours

| End point values            | Dual-Hormone Closed-Loop | Single-Hormone Closed-Loop |  |  |
|-----------------------------|--------------------------|----------------------------|--|--|
| Subject group type          | Reporting group          | Reporting group            |  |  |
| Number of subjects analysed | 11                       | 11                         |  |  |
| Units: percent              |                          |                            |  |  |
| number (not applicable)     | 27                       | 72                         |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Composite outcome: Percentage of participants achieving (1) time in range (3.9-10) > 70 %, (2) time in alert hypoglycemia (<3.9 mmol/l) < 4 %, and (3) time in clinical hypoglycemia (<3.0 mmol) < 1% as measured by YSI

|                 |  |
|-----------------|--|
| End point title | Composite outcome: Percentage of participants achieving (1) time in range (3.9-10) > 70 %, (2) time in alert hypoglycemia (<3.9 mmol/l) < 4 %, and (3) time in clinical hypoglycemia (<3.0 mmol) < 1% as measured by YSI |
|-----------------|--|

End point description:

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

End point timeframe:

Evaluation is performed after completion of the second study session, i.e. after two times 26-hours

| End point values            | Dual-Hormone Closed-Loop | Single-Hormone Closed-Loop |  |  |
|-----------------------------|--------------------------|----------------------------|--|--|
| Subject group type          | Reporting group          | Reporting group            |  |  |
| Number of subjects analysed | 11                       | 11                         |  |  |
| Units: percent              |                          |                            |  |  |
| number (not applicable)     | 27                       | 36                         |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Physical activity intensity measured by ActiGraph GT9X Link

|                 |   |
|-----------------|---|
| End point title | Physical activity intensity measured by ActiGraph GT9X Link |
|-----------------|---|

End point description:

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

End point timeframe:

Evaluation is performed after completion of the second study session, i.e. after two times 26-hours

| End point values                     | Dual-Hormone Closed-Loop | Single-Hormone Closed-Loop |  |  |
|--------------------------------------|--------------------------|----------------------------|--|--|
| Subject group type                   | Reporting group          | Reporting group            |  |  |
| Number of subjects analysed          | 11                       | 11                         |  |  |
| Units: percent                       |                          |                            |  |  |
| arithmetic mean (standard deviation) | 2.8 ( $\pm$ 4.5)         | 1.5 ( $\pm$ 3.1)           |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Sleep efficiency measured by ActiGraph GT9X Link

|                 |  |
|-----------------|--|
| End point title | Sleep efficiency measured by ActiGraph GT9X Link |
|-----------------|--|

End point description:

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

End point timeframe:

Evaluation is performed after completion of the second study session, i.e. after two times 26-hours

| End point values                     | Dual-Hormone Closed-Loop | Single-Hormone Closed-Loop |  |  |
|--------------------------------------|--------------------------|----------------------------|--|--|
| Subject group type                   | Reporting group          | Reporting group            |  |  |
| Number of subjects analysed          | 11                       | 11                         |  |  |
| Units: percent                       |                          |                            |  |  |
| arithmetic mean (standard deviation) | 78.5 (± 9.2)             | 74.0 (± 10.5)              |  |  |

### Statistical analyses

No statistical analyses for this end point

### Post-hoc: Percentage of time with glucose values < 3.9 mmol/l as measured by CGM during sleep

|                 |   |
|-----------------|---|
| End point title | Percentage of time with glucose values < 3.9 mmol/l as measured by CGM during sleep |
|-----------------|---|

End point description:

|                |          |
|----------------|----------|
| End point type | Post-hoc |
|----------------|----------|

End point timeframe:

Evaluation is performed after completion of the second study session, i.e. after two times 26-hours

| End point values                      | Dual-Hormone Closed-Loop | Single-Hormone Closed-Loop |  |  |
|---------------------------------------|--------------------------|----------------------------|--|--|
| Subject group type                    | Reporting group          | Reporting group            |  |  |
| Number of subjects analysed           | 11                       | 11                         |  |  |
| Units: percent                        |                          |                            |  |  |
| median (inter-quartile range (Q1-Q3)) | 0 (0 to 0)               | 0 (0 to 3.48)              |  |  |

### Statistical analyses

No statistical analyses for this end point

### Post-hoc: Percentage of time with glucose values < 3.9 mmol/l as measured by YSI during sleep

|                 |   |
|-----------------|---|
| End point title | Percentage of time with glucose values < 3.9 mmol/l as measured by YSI during sleep |
|-----------------|---|

End point description:

|                |          |
|----------------|----------|
| End point type | Post-hoc |
|----------------|----------|

End point timeframe:

Evaluation is performed after completion of the second study session, i.e. after two times 26-hours

| End point values                      | Dual-Hormone Closed-Loop | Single-Hormone Closed-Loop |  |  |
|---------------------------------------|--------------------------|----------------------------|--|--|
| Subject group type                    | Reporting group          | Reporting group            |  |  |
| Number of subjects analysed           | 11                       | 11                         |  |  |
| Units: percent                        |                          |                            |  |  |
| median (inter-quartile range (Q1-Q3)) | 0 (0 to 0)               | 0 (0 to 5.22)              |  |  |

### Statistical analyses

No statistical analyses for this end point

### Post-hoc: Percentage of time with glucose values >10.0 mmol/l as measured by CGM during sleep

|                 |   |
|-----------------|---|
| End point title | Percentage of time with glucose values >10.0 mmol/l as measured by CGM during sleep |
|-----------------|---|

End point description:

|                |          |
|----------------|----------|
| End point type | Post-hoc |
|----------------|----------|

End point timeframe:

Evaluation is performed after completion of the second study session, i.e. after two times 26-hours

| End point values                      | Dual-Hormone Closed-Loop | Single-Hormone Closed-Loop |  |  |
|---------------------------------------|--------------------------|----------------------------|--|--|
| Subject group type                    | Reporting group          | Reporting group            |  |  |
| Number of subjects analysed           | 11                       | 11                         |  |  |
| Units: percent                        |                          |                            |  |  |
| median (inter-quartile range (Q1-Q3)) | 30.4 (13.5 to 43.9)      | 0 (0 to 10)                |  |  |

### Statistical analyses

No statistical analyses for this end point

### Post-hoc: Percentage of time with glucose values >10.0 mmol/l as measured by YSI

## during sleep

|                 |   |
|-----------------|---|
| End point title | Percentage of time with glucose values >10.0 mmol/l as measured by YSI during sleep |
|-----------------|---|

End point description:

|                |          |
|----------------|----------|
| End point type | Post-hoc |
|----------------|----------|

End point timeframe:

Evaluation is performed after completion of the second study session, i.e. after two times 26-hours

| End point values                      | Dual-Hormone Closed-Loop | Single-Hormone Closed-Loop |  |  |
|---------------------------------------|--------------------------|----------------------------|--|--|
| Subject group type                    | Reporting group          | Reporting group            |  |  |
| Number of subjects analysed           | 11                       | 11                         |  |  |
| Units: percent                        |                          |                            |  |  |
| median (inter-quartile range (Q1-Q3)) | 32.2 (5.22 to 37.8)      | 0 (0 to 5.22)              |  |  |

## Statistical analyses

No statistical analyses for this end point

## Post-hoc: Percentage of time with glucose values in range 3.9-10.0 mmol/L as measured by CGM during sleep

|                 |   |
|-----------------|---|
| End point title | Percentage of time with glucose values in range 3.9-10.0 mmol/L as measured by CGM during sleep |
|-----------------|---|

End point description:

|                |          |
|----------------|----------|
| End point type | Post-hoc |
|----------------|----------|

End point timeframe:

Evaluation is performed after completion of the second study session, i.e. after two times 26-hours

| End point values                      | Dual-Hormone Closed-Loop | Single-Hormone Closed-Loop |  |  |
|---------------------------------------|--------------------------|----------------------------|--|--|
| Subject group type                    | Reporting group          | Reporting group            |  |  |
| Number of subjects analysed           | 11                       | 11                         |  |  |
| Units: percent                        |                          |                            |  |  |
| median (inter-quartile range (Q1-Q3)) | 69.6 (52.6 to 86.5)      | 96.5 (84.3 to 100)         |  |  |

## Statistical analyses

No statistical analyses for this end point

### Post-hoc: percentage of time with glucose values in range 3.9-10.0 mmol/l as measured by YSI during sleep

|                 |   |
|-----------------|---|
| End point title | percentage of time with glucose values in range 3.9-10.0 mmol/l as measured by YSI during sleep |
|-----------------|---|

End point description:

|                |          |
|----------------|----------|
| End point type | Post-hoc |
|----------------|----------|

End point timeframe:

Evaluation is performed after completion of the second study session, i.e. after two times 26-hours

| End point values                      | Dual-Hormone Closed-Loop | Single-Hormone Closed-Loop |  |  |
|---------------------------------------|--------------------------|----------------------------|--|--|
| Subject group type                    | Reporting group          | Reporting group            |  |  |
| Number of subjects analysed           | 11                       | 11                         |  |  |
| Units: percent                        |                          |                            |  |  |
| median (inter-quartile range (Q1-Q3)) | 67.8 (60.4 to 89.6)      | 89.6 (82.6 to 100)         |  |  |

## Statistical analyses

No statistical analyses for this end point

### Post-hoc: Percentage of time with glucose values < 3.9 mmol/l as measured by CGM during and after exercise

|                 |  |
|-----------------|--|
| End point title | Percentage of time with glucose values < 3.9 mmol/l as measured by CGM during and after exercise |
|-----------------|--|

End point description:

|                |          |
|----------------|----------|
| End point type | Post-hoc |
|----------------|----------|

End point timeframe:

Evaluation is performed after completion of the second study session, i.e. after two times 26-hours

| End point values                      | Dual-Hormone Closed-Loop | Single-Hormone Closed-Loop |  |  |
|---------------------------------------|--------------------------|----------------------------|--|--|
| Subject group type                    | Reporting group          | Reporting group            |  |  |
| Number of subjects analysed           | 11                       | 11                         |  |  |
| Units: percent                        |                          |                            |  |  |
| median (inter-quartile range (Q1-Q3)) | 0 (0 to 0)               | 0 (0 to 0)                 |  |  |



## Statistical analyses

No statistical analyses for this end point

### Post-hoc: Percentage of time with glucose values < 3.9 mmol/l as measured by YSI during and after exercise

|                 |  |
|-----------------|--|
| End point title | Percentage of time with glucose values < 3.9 mmol/l as measured by YSI during and after exercise |
|-----------------|--|

End point description:

|                |          |
|----------------|----------|
| End point type | Post-hoc |
|----------------|----------|

End point timeframe:

Evaluation is performed after completion of the second study session, i.e. after two times 26-hours

| End point values                      | Dual-Hormone Closed-Loop | Single-Hormone Closed-Loop |  |  |
|---------------------------------------|--------------------------|----------------------------|--|--|
| Subject group type                    | Reporting group          | Reporting group            |  |  |
| Number of subjects analysed           | 11                       | 11                         |  |  |
| Units: percent                        |                          |                            |  |  |
| median (inter-quartile range (Q1-Q3)) | 0 (0 to 4.84)            | 0 (0 to 14.5)              |  |  |

## Statistical analyses

No statistical analyses for this end point

### Post-hoc: percentage of time with glucose values in range 3.9-10.0 mmol/L as measured by CGM during and after exercise

|                 |  |
|-----------------|--|
| End point title | percentage of time with glucose values in range 3.9-10.0 mmol/L as measured by CGM during and after exercise |
|-----------------|--|

End point description:

|                |          |
|----------------|----------|
| End point type | Post-hoc |
|----------------|----------|

End point timeframe:

Evaluation is performed after completion of the second study session, i.e. after two times 26-hours

| End point values                      | Dual-Hormone Closed-Loop | Single-Hormone Closed-Loop |  |  |
|---------------------------------------|--------------------------|----------------------------|--|--|
| Subject group type                    | Reporting group          | Reporting group            |  |  |
| Number of subjects analysed           | 11                       | 11                         |  |  |
| Units: percent                        |                          |                            |  |  |
| median (inter-quartile range (Q1-Q3)) | 64.5 (50 to 88.7)        | 83.9 (80.6 to 100)         |  |  |

### Statistical analyses

No statistical analyses for this end point

### Post-hoc: Percentage of time with glucose values 3.9-10.0 mmol/l as measured by YSI during and after exercise

|                 |   |
|-----------------|---|
| End point title | Percentage of time with glucose values 3.9-10.0 mmol/l as measured by YSI during and after exercise |
|-----------------|---|

End point description:

|                |          |
|----------------|----------|
| End point type | Post-hoc |
|----------------|----------|

End point timeframe:

Evaluation is performed after completion of the second study session, i.e. after two times 26-hours

| End point values                      | Dual-Hormone Closed-Loop | Single-Hormone Closed-Loop |  |  |
|---------------------------------------|--------------------------|----------------------------|--|--|
| Subject group type                    | Reporting group          | Reporting group            |  |  |
| Number of subjects analysed           | 11                       | 11                         |  |  |
| Units: percent                        |                          |                            |  |  |
| median (inter-quartile range (Q1-Q3)) | 67.7 (32.3 to 99.4)      | 93.5 (82.3 to 100)         |  |  |

### Statistical analyses

No statistical analyses for this end point

### Post-hoc: Percentage of time with glucose values >10.0 mmol/l as measured by CGM during and after exercise

|                 |  |
|-----------------|--|
| End point title | Percentage of time with glucose values >10.0 mmol/l as measured by CGM during and after exercise |
|-----------------|--|

End point description:

|                |          |
|----------------|----------|
| End point type | Post-hoc |
|----------------|----------|

End point timeframe:

Evaluation is performed after completion of the second study session, i.e. after two times 26-hours

| End point values                      | Dual-Hormone Closed-Loop | Single-Hormone Closed-Loop |  |  |
|---------------------------------------|--------------------------|----------------------------|--|--|
| Subject group type                    | Reporting group          | Reporting group            |  |  |
| Number of subjects analysed           | 11                       | 11                         |  |  |
| Units: perc                           |                          |                            |  |  |
| median (inter-quartile range (Q1-Q3)) | 22.6 (0 to 37.1)         | 12.9 (0 to 19.4)           |  |  |

### Statistical analyses

No statistical analyses for this end point

### Post-hoc: Percentage of time with glucose values >10.0 mmol/l as measured by YSI during and after exercise

|                 |  |
|-----------------|--|
| End point title | Percentage of time with glucose values >10.0 mmol/l as measured by YSI during and after exercise |
|-----------------|--|

End point description:

|                |          |
|----------------|----------|
| End point type | Post-hoc |
|----------------|----------|

End point timeframe:

Evaluation is performed after completion of the second study session, i.e. after two times 26-hours

| End point values                      | Dual-Hormone Closed-Loop | Single-Hormone Closed-Loop |  |  |
|---------------------------------------|--------------------------|----------------------------|--|--|
| Subject group type                    | Reporting group          | Reporting group            |  |  |
| Number of subjects analysed           | 11                       | 11                         |  |  |
| Units: percent                        |                          |                            |  |  |
| median (inter-quartile range (Q1-Q3)) | 1.18 (0 to 58.1)         | 0 (0 to 3.23)              |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Evaluation of adverse events were performed during study sessions, i.e., two times 26 hours per participant

Adverse event reporting additional description:

Adverse effects (nausea, headache, stomachache, palpitations, vomit, hunger and sweat) were scored using a 0-100 visual analog scale (VAS) seven times during each study session (at the start, before dinner, breakfast, lunch, snack and exercise session as well as at the end) to evaluate whether adverse events had occurred during the intervention.

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

### Dictionary used

|                 |      |
|-----------------|------|
| Dictionary name | None |
|-----------------|------|

|                    |   |
|--------------------|---|
| Dictionary version | 0 |
|--------------------|---|

### Reporting groups

|                       |                               |
|-----------------------|-------------------------------|
| Reporting group title | Dual-Hormone Closed-loop (DH) |
|-----------------------|-------------------------------|

Reporting group description:

Study session with insulin-glucagon in the system

|                       |                                 |
|-----------------------|---------------------------------|
| Reporting group title | Single-Hormone Closed-loop (SH) |
|-----------------------|---------------------------------|

Reporting group description:

Study session with insulin-saline in pumps

| Serious adverse events                            | Dual-Hormone Closed-loop (DH) | Single-Hormone Closed-loop (SH) |  |
|---|-------------------------------|---------------------------------|--|
| Total subjects affected by serious adverse events |                               |                                 |  |
| subjects affected / exposed                       | 0 / 11 (0.00%)                | 0 / 11 (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: 0 %

| Non-serious adverse events                            | Dual-Hormone Closed-loop (DH) | Single-Hormone Closed-loop (SH) |  |
|---|-------------------------------|---------------------------------|--|
| Total subjects affected by non-serious adverse events |                               |                                 |  |
| subjects affected / exposed                           | 4 / 11 (36.36%)               | 4 / 11 (36.36%)                 |  |
| General disorders and administration site conditions  |                               |                                 |  |
| Nausea  |                               |                                 |  |
| subjects affected / exposed                           | 3 / 11 (27.27%)               | 0 / 11 (0.00%)                  |  |
| occurrences (all)                                     | 3                             | 0                               |  |
| Headache  |                               |                                 |  |

|                             |                 |                 |  |
|-----------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 4 / 11 (36.36%) | 4 / 11 (36.36%) |  |
| occurrences (all)           | 4               | 4               |  |
| Stomachache                 |                 |                 |  |
| subjects affected / exposed | 1 / 11 (9.09%)  | 2 / 11 (18.18%) |  |
| occurrences (all)           | 1               | 2               |  |

## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported