



## Clinical trial results:

**A randomised, double-blind, placebo-controlled, parallel-group trial investigating the effect of 4 weeks bi-daily dosing of XEN-D0501 on blood glucose reduction as add-on to metformin in patients with diabetes type 2**

### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2018-001880-22   |
| Trial protocol           | LT               |
| Global end of trial date | 19 December 2019 |

### Results information

|                                |   |
|--------------------------------|---|
| Result version number          | v2 (current)  |
| This version publication date  | 14 January 2023   |
| First version publication date | 21 July 2022  |
| Version creation reason        | <ul style="list-style-type: none"><li>• Correction of full data set</li></ul> The data set has been corrected and aligned with the final clinical study report. |

### Trial information

#### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | PP-CT02 |
|-----------------------|---------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT05353686 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | PILA PHARMA AB   |
| Sponsor organisation address | Västergatan 1 , Malmö, Sweden, 211 21                              |
| Public contact               | Dorte X. Gram, PILA PHARMA AB, +46 73903 6969, info@pilapharma.com |
| Scientific contact           | Dorte X. Gram, PILA PHARMA AB, +46 73903 6969, info@pilapharma.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:

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**Results analysis stage**

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|  |                  |
|--|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 23 June 2022     |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 19 December 2019 |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 19 December 2019 |
| Was the trial ended prematurely?                     | No               |

Notes:

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**General information about the trial**

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Main objective of the trial:

To investigate the effects of four weeks of bi-daily dosing of XEN-D0501 (4 mg BID) as add-on to metformin on fasting blood glucose in patients with diabetes mellitus type 2

Protection of trial subjects:

None

Background therapy:

All subjects received metformin as background therapy.

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 15 February 2019 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | No               |

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

|                                      |               |
|--------------------------------------|---------------|
| Country: Number of subjects enrolled | Lithuania: 60 |
| Worldwide total number of subjects   | 60            |
| EEA total number of subjects         | 60            |

Notes:

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**Subjects enrolled per age group**

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|   |    |
|---|----|
| 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)                      | 38 |
| From 65 to 84 years                       | 22 |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

A total of 77 subjects gave informed consent and were screened. Of those, 60 subjects fulfilled the eligibility criteria and were randomised to treatment.

### Pre-assignment

Screening details: -

### Pre-assignment period milestones

|                              |                   |
|------------------------------|-------------------|
| Number of subjects started   | 77 <sup>[1]</sup> |
| Number of subjects completed | 60                |

### Pre-assignment subject non-completion reasons

|                            |                                 |
|----------------------------|---------------------------------|
| Reason: Number of subjects | Consent withdrawn by subject: 1 |
| Reason: Number of subjects | Screen failures: 16             |

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification:

77 subject gave informed consent and 60 of those fulfilled the eligibility criteria and were randomized to treatment.

### Period 1

|                              |                                       |
|------------------------------|---------------------------------------|
| Period 1 title               | Baseline                              |
| Is this the baseline period? | Yes                                   |
| Allocation method            | Randomised - controlled               |
| Blinding used                | Double blind                          |
| Roles blinded                | Subject, Investigator, Monitor, Carer |

### Arms

|                              |     |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

|                  |         |
|------------------|---------|
| <b>Arm title</b> | Placebo |
|------------------|---------|

Arm description:

1 tablet twice daily

|  |                               |
|--|-------------------------------|
| Arm type                               | Placebo                       |
| Investigational medicinal product name | Reference treatment (placebo) |
| Investigational medicinal product code |                               |
| Other name                             |                               |
| Pharmaceutical forms                   | Tablet                        |
| Routes of administration               | Oral use                      |

Dosage and administration details:

1 oral tablet twice daily

|                  |           |
|------------------|-----------|
| <b>Arm title</b> | XEN-D0501 |
|------------------|-----------|

Arm description:

1 tablet of 4 mg twice daily

|          |              |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

|  |           |
|--|-----------|
| Investigational medicinal product name | XEN-D0501 |
| Investigational medicinal product code |           |
| Other name                             |           |
| Pharmaceutical forms                   | Tablet    |
| Routes of administration               | Oral use  |
| Dosage and administration details:     |           |
| 1 oral tablet of 4 mg twice daily      |           |

| Number of subjects in period 1 | Placebo | XEN-D0501 |
|--------------------------------|---------|-----------|
| Started                        | 31      | 29        |
| Completed                      | 31      | 29        |

## Period 2

|                              |                                       |
|------------------------------|---------------------------------------|
| Period 2 title               | Treatment                             |
| Is this the baseline period? | No                                    |
| Allocation method            | Randomised - controlled               |
| Blinding used                | Double blind                          |
| Roles blinded                | Subject, Investigator, Monitor, Carer |

## Arms

|                              |         |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes     |
| <b>Arm title</b>             | Placebo |

Arm description:

1 tablet twice daily

|  |                               |
|--|-------------------------------|
| Arm type                               | Placebo                       |
| Investigational medicinal product name | Reference treatment (placebo) |
| Investigational medicinal product code |                               |
| Other name                             |                               |
| Pharmaceutical forms                   | Tablet                        |
| Routes of administration               | Oral use                      |

Dosage and administration details:

1 oral tablet twice daily

|                  |           |
|------------------|-----------|
| <b>Arm title</b> | XEN-D0501 |
|------------------|-----------|

Arm description:

1 tablet of 4 mg twice daily

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | XEN-D0501    |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

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**Dosage and administration details:**

1 oral tablet of 4 mg twice daily

| <b>Number of subjects in period 2</b> | Placebo | XEN-D0501 |
|---------------------------------------|---------|-----------|
| Started                               | 31      | 29        |
| Completed                             | 31      | 26        |
| Not completed                         | 0       | 3         |
| Consent withdrawn by subject          | -       | 1         |
| Adverse event, non-fatal              | -       | 1         |
| Protocol deviation                    | -       | 1         |

## Baseline characteristics

### Reporting groups

|  |           |
|--|-----------|
| Reporting group title  | Placebo   |
| Reporting group description:<br>1 tablet twice daily         |           |
| Reporting group title  | XEN-D0501 |
| Reporting group description:<br>1 tablet of 4 mg twice daily |           |

| Reporting group values                                | Placebo    | XEN-D0501  | Total |
|---|------------|------------|-------|
| Number of subjects                                    | 31         | 29         | 60    |
| Age categorical<br>Units: Subjects                    |            |            |       |
| In utero  |            |            | 0     |
| Preterm newborn infants<br>(gestational age < 37 wks) |            |            | 0     |
| Newborns (0-27 days)                                  |            |            | 0     |
| Infants and toddlers (28 days-23 months)              |            |            | 0     |
| Children (2-11 years)                                 |            |            | 0     |
| Adolescents (12-17 years)                             |            |            | 0     |
| Adults (18-64 years)                                  |            |            | 0     |
| From 65-84 years                                      |            |            | 0     |
| 85 years and over                                     |            |            | 0     |
| Age continuous<br>Units: years                        |            |            |       |
| geometric mean  | 60.6       | 62.1       |       |
| full range (min-max)                                  | 29 to 84   | 49 to 77   | -     |
| Gender categorical<br>Units: Subjects                 |            |            |       |
| Female  | 21         | 16         | 37    |
| Male  | 10         | 13         | 23    |
| Ethnic origin<br>Units: Subjects                      |            |            |       |
| White   | 31         | 29         | 60    |
| Diabetes duration<br>Units: Years                     |            |            |       |
| geometric mean  | 7.2        | 5.8        |       |
| standard deviation                                    | ± 5.9      | ± 3.6      | -     |
| Height<br>Units: cm                                   |            |            |       |
| geometric mean  | 167.3      | 170.2      |       |
| full range (min-max)                                  | 149 to 185 | 146 to 187 | -     |
| Weight<br>Units: kg                                   |            |            |       |
| geometric mean  | 92.3       | 99.2       |       |
| full range (min-max)                                  | 59 to 135  | 52 to 131  | -     |
| BMI   |            |            |       |

|  |                    |                    |   |
|--|--------------------|--------------------|---|
| Units: mg/kg*2<br>geometric mean<br>full range (min-max)                   | 33<br>23 to 46     | 34.3<br>19 to 46   | - |
| Waist circumference<br>Units: cm<br>geometric mean<br>full range (min-max) | 110.1<br>87 to 149 | 114.2<br>79 to 137 | - |
| Hip circumference<br>Units: cm<br>geometric mean<br>full range (min-max)   | 114.1<br>95 to 139 | 116.5<br>87 to 141 | - |
| Waist-hip ratio<br>Units: cm/cm<br>geometric mean<br>full range (min-max)  | 1<br>0.8 to 1.1    | 1<br>0.8 to 1.1    | - |
| HbA1c<br>Units: percent<br>geometric mean<br>standard deviation            | 7.3<br>± 0.92      | 7.5<br>± 0.99      | - |

## End points

### End points reporting groups

|   |                    |
|---|--------------------|
| Reporting group title   | Placebo            |
| Reporting group description:<br>1 tablet twice daily  |                    |
| Reporting group title   | XEN-D0501          |
| Reporting group description:<br>1 tablet of 4 mg twice daily  |                    |
| Reporting group title   | Placebo            |
| Reporting group description:<br>1 tablet twice daily  |                    |
| Reporting group title   | XEN-D0501          |
| Reporting group description:<br>1 tablet of 4 mg twice daily  |                    |
| Subject analysis set title  | PP                 |
| Subject analysis set type   | Per protocol       |
| Subject analysis set description:<br>All participants in the study who completed the study and had no major protocol deviations. The PP population also excluded 3 participants with a minor protocol deviation, i.e., those who took the last study medication dose > 1 day (24 hours) before V4 |                    |
| Subject analysis set title  | ITT                |
| Subject analysis set type   | Intention-to-treat |
| Subject analysis set description:<br>All randomized participants  |                    |

### Primary: Fasting blood glucose after 4 weeks of treatment, PP population

|  |   |
|--|---|
| End point title  | Fasting blood glucose after 4 weeks of treatment, PP population |
| End point description:<br>Measured after four weeks of treatment (visit 4) and at baseline (visit 3) for the PP population |   |
| End point type   | Primary   |
| End point timeframe:<br>At 4 weeks after treatment (visit 4)   |   |

| End point values                    | Placebo          | XEN-D0501        |  |  |
|-------------------------------------|------------------|------------------|--|--|
| Subject group type                  | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed         | 31               | 23               |  |  |
| Units: mmol/L                       |                  |                  |  |  |
| geometric mean (standard deviation) |                  |                  |  |  |
| Visit 4                             | 7.868 (± 1.798)  | 8.213 (± 2.034)  |  |  |
| Change from baseline                | -0.123 (± 1.114) | -0.272 (± 1.250) |  |  |
| Baseline (Visit 3)                  | 8.0 (± 1.9)      | 8.5 (± 2.2)      |  |  |



## Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Analysis of primary endpoint - visit 4 |
| Comparison groups                       | Placebo v XEN-D0501                    |
| Number of subjects included in analysis | 54                                     |
| Analysis specification                  | Post-hoc                               |
| Analysis type                           | equivalence                            |
| P-value                                 | = 0.5123                               |
| Method                                  | t-test, 2-sided                        |
| Parameter estimate                      | Mean difference (final values)         |
| Point estimate                          | -0.345                                 |
| Confidence interval                     |  |
| level                                   | 95 %                                   |
| sides                                   | 2-sided                                |
| lower limit                             | -1.395                                 |
| upper limit                             | 0.705                                  |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Analysis of primary endpoint - change from BL |
| Comparison groups                       | Placebo v XEN-D0501                           |
| Number of subjects included in analysis | 54  |
| Analysis specification                  | Post-hoc                                      |
| Analysis type                           | equivalence                                   |
| P-value                                 | = 0.6452                                      |
| Method                                  | t-test, 2-sided                               |
| Parameter estimate                      | Mean difference (final values)                |
| Point estimate                          | 0.15  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided                                       |
| lower limit                             | -0.4986                                       |
| upper limit                             | 0.7978  |

## Primary: Fasting blood glucose after 4 weeks of treatment, ITT population

|   |  |
|---|--|
| End point title   | Fasting blood glucose after 4 weeks of treatment, ITT population |
| End point description:  |  |
| Measured after 4 weeks of treatment (visit 4) and at baseline (visit 3) from the ITT population |  |
| End point type  | Primary  |
| End point timeframe:  |  |
| At 4 weeks after treatment (visit 4)  |  |

| <b>End point values</b>                 | Placebo         | XEN-D0501       |  |  |
|---|-----------------|-----------------|--|--|
| Subject group type                      | Reporting group | Reporting group |  |  |
| Number of subjects analysed             | 31              | 29              |  |  |
| Units: mmol/L                           |                 |                 |  |  |
| geometric mean (standard deviation)     |                 |                 |  |  |
| Baseline (visit 3)                      | 8.0 (± 1.9)     | 8.6 (± 2.1)     |  |  |
| Visit 4                                 | 7.9 (± 1.8)     | 8.4 (± 2.1)     |  |  |
| Change from baseline (visit 4- visit 3) | -0.1 (± 1.1)    | -0.2 (± 1.2)    |  |  |

### Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Analysis of primary endpoint - visit 4, ITT pop |
| Comparison groups                       | Placebo v XEN-D0501                             |
| Number of subjects included in analysis | 60  |
| Analysis specification                  | Post-hoc  |
| Analysis type                           | equivalence                                     |
| P-value                                 | = 0.3095  |
| Method                                  | t-test, 2-sided                                 |
| Parameter estimate                      | Mean difference (final values)                  |
| Point estimate                          | -0.525  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -1.5511   |
| upper limit                             | 0.5007  |

### Secondary: Self-monitored blood glucose after 2 and 4 weeks of treatment

|                                  |   |
|----------------------------------|---|
| End point title                  | Self-monitored blood glucose after 2 and 4 weeks of treatment |
| End point description:           |   |
| End point type                   | Secondary   |
| End point timeframe:             |   |
| At 2 and 4 weeks after treatment |   |

| End point values                    | Placebo         | XEN-D0501       |  |  |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type                  | Reporting group | Reporting group |  |  |
| Number of subjects analysed         | 31              | 23              |  |  |
| Units: mmol/L                       |                 |                 |  |  |
| geometric mean (standard deviation) |                 |                 |  |  |
| Wake-up, 2 wks                      | 8.4 (± 2.5)     | 8.7 (± 2.09)    |  |  |
| Before breakfast, 2 wks             | 8.8 (± 2.3)     | 9.1 (± 2.0)     |  |  |
| 2 hrs after breakfast, 2 wks        | 9.4 (± 3.1)     | 9.7 (± 3.2)     |  |  |
| Before lunch, 2 wks                 | 7.3 (± 2.1)     | 8.4 (± 2.7)     |  |  |
| 2 hrs after lunch, 2 wks            | 9.4 (± 2.4)     | 9.2 (± 2.3)     |  |  |
| 2 hrs after dinner, 2 wks           | 8.6 (± 2.2)     | 9.3 (± 2.2)     |  |  |
| Bedtime, 2 hrs                      | 8.8 (± 3.0)     | 9.0 (± 2.3)     |  |  |
| Wake-up, 4 wks                      | 8.3 (± 1.9)     | 8.6 (± 1.8)     |  |  |
| Before breakfast, 4 wks             | 8.4 (± 1.9)     | 8.9 (± 1.9)     |  |  |
| 2 hrs after breakfast, 4 wks        | 9.0 (± 2.3)     | 9.6 (± 3.3)     |  |  |
| Before lunch, 4 wks                 | 7.4 (± 1.8)     | 7.8 (± 2.7)     |  |  |
| 2 hrs after lunch, 4 wks            | 9.1 (± 3.0)     | 8.9 (± 2.0)     |  |  |
| 2 hrs after dinner, 4 wks           | 9.3 (± 2.6)     | 9.1 (± 2.2)     |  |  |
| Bedtime, 4 wks                      | 8.8 (± 2.6)     | 8.4 (± 2.5)     |  |  |
| Before dinner, 2 wks                | 8.2 (± 2.1)     | 8.6 (± 2.6)     |  |  |
| Before dinner, 4 wks                | 8.2 (± 2.5)     | 8.5 (± 2.2)     |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Plasma HbA1c after 4 weeks of treatment

|  |   |
|--|---|
| End point title  | Plasma HbA1c after 4 weeks of treatment |
| End point description:   |   |
| After 4 weeks of treatment (visit 4) and as change from baseline (visit 3) |   |
| End point type   | Secondary                               |
| End point timeframe:   |   |
| At 4 weeks of treatment  |   |

| End point values                    | Placebo         | XEN-D0501       |  |  |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type                  | Reporting group | Reporting group |  |  |
| Number of subjects analysed         | 31              | 23              |  |  |
| Units: percent                      |                 |                 |  |  |
| geometric mean (standard deviation) |                 |                 |  |  |
| Visit 4                             | 7.2 (± 0.95)    | 7.2 (± 0.93)    |  |  |
| Change from baseline (visit 3)      | -0.1 (± 0.33)   | -0.2 (± 0.3)    |  |  |
| Visit 3                             | 7.3 (± 0.92)    | 7.4 (± 0.98)    |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Glucose tolerance (OGTT) after 4 weeks of treatment

|                 |   |
|-----------------|---|
| End point title | Glucose tolerance (OGTT) after 4 weeks of treatment |
|-----------------|---|

End point description:

Measured after 4 weeks of treatment (visit 4) and compared to baseline (-60 min)

Change of the changes from baseline represents the change between 120 and 0 min at visit 4 minus the change between 120 and 0 min at visit 3

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

End point timeframe:

At 4 weeks after treatment

| End point values                        | Placebo         | XEN-D0501       |  |  |
|---|-----------------|-----------------|--|--|
| Subject group type                      | Reporting group | Reporting group |  |  |
| Number of subjects analysed             | 31              | 23              |  |  |
| Units: mmol/L                           |                 |                 |  |  |
| geometric mean (standard deviation)     |                 |                 |  |  |
| 4 weeks (visit 4), 120 min              | 15.18 (± 3.17)  | 13.42 (± 3.48)  |  |  |
| 4 weeks (visit 4), change from baseline | 7.3 (± 2.9)     | 5.2 (± 3.0)     |  |  |
| Change of the changes                   | 0.69 (± 2.68)   | -0.15 (± 2.4)   |  |  |

## Statistical analyses

|                            |  |
|----------------------------|--|
| Statistical analysis title | Plasma glucose at 120 min (V4 vs baseline -60 min) |
|----------------------------|--|

|                   |                     |
|-------------------|---------------------|
| Comparison groups | Placebo v XEN-D0501 |
|-------------------|---------------------|

|   |    |
|---|----|
| Number of subjects included in analysis | 54 |
|---|----|

|                        |          |
|------------------------|----------|
| Analysis specification | Post-hoc |
|------------------------|----------|

|               |             |
|---------------|-------------|
| Analysis type | equivalence |
|---------------|-------------|

|         |         |
|---------|---------|
| P-value | = 0.013 |
|---------|---------|

|        |                 |
|--------|-----------------|
| Method | t-test, 2-sided |
|--------|-----------------|

### Secondary: Insulin secretion during an OGTT

|                 |                                  |
|-----------------|----------------------------------|
| End point title | Insulin secretion during an OGTT |
|-----------------|----------------------------------|

End point description:

Measured after 4 weeks of treatment (visit 4) and compared to baseline (-60 min)

Change of the changes from baseline represents the change between 120 and 0 min at visit 4 minus the change between 120 and 0 min at visit 3

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

End point timeframe:

At 4 weeks after treatment

| <b>End point values</b>             | Placebo         | XEN-D0501       |  |  |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type                  | Reporting group | Reporting group |  |  |
| Number of subjects analysed         | 31              | 23              |  |  |
| Units: µU/mL                        |                 |                 |  |  |
| geometric mean (standard deviation) |                 |                 |  |  |
| Actual 120 min (V4)                 | 57.2 (± 42.4)   | 63.4 (± 42.3)   |  |  |
| Change from baseline, 30 min        | 20.1 (± 14.7)   | 33.7 (± 22.9)   |  |  |
| Change from baseline, 60 min        | 33.5 (± 24.1)   | 50.1 (± 34.9)   |  |  |
| Change from baseline, 90 min        | 43.3 (± 28.6)   | 57.3 (± 43.2)   |  |  |
| Change from baseline, 120 min       | 44.3 (± 37.5)   | 47.3 (± 35.8)   |  |  |
| Change of the changes, 120 min      | 2.9 (± 19.8)    | 2.0 (± 31.1)    |  |  |
| Actual 30 min (V4)                  | 33 (± 19.4)     | 49.8 (± 30.1)   |  |  |
| Actual 60 min (V4)                  | 46.3 (± 29.7)   | 66.2 (± 42.4)   |  |  |
| Actual 90 min (V4)                  | 56.5 (± 34.5)   | 73.4 (± 49.4)   |  |  |

### Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Insulin secretion at visit 4, 30 min (vs -60 min) |
| Comparison groups                       | Placebo v XEN-D0501                               |
| Number of subjects included in analysis | 54  |
| Analysis specification                  | Post-hoc  |
| Analysis type                           | equivalence                                       |
| P-value                                 | = 0.0178  |
| Method                                  | t-test, 2-sided                                   |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Insulin secretion at visit 4, 60 min (vs -60 min) |
| Comparison groups                       | Placebo v XEN-D0501                               |
| Number of subjects included in analysis | 54  |
| Analysis specification                  | Post-hoc  |
| Analysis type                           | equivalence                                       |
| P-value                                 | = 0.0429  |
| Method                                  | t-test, 2-sided                                   |

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Insulin secretion at visit 4, 90 min (vs -60 min) |
| Comparison groups                 | Placebo v XEN-D0501                               |

|   |                 |
|---|-----------------|
| Number of subjects included in analysis | 54              |
| Analysis specification                  | Post-hoc        |
| Analysis type                           | equivalence     |
| P-value                                 | = 0.1878        |
| Method                                  | t-test, 2-sided |

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Insulin secretion at visit 4, 120 min (vs -60 min) |
| Comparison groups                       | Placebo v XEN-D0501                                |
| Number of subjects included in analysis | 54   |
| Analysis specification                  | Post-hoc   |
| Analysis type                           | equivalence  |
| P-value                                 | = 0.7688   |
| Method                                  | t-test, 2-sided                                    |

### Secondary: HOMA insulin resistance and beta cell function

|                        |  |
|------------------------|--|
| End point title        | HOMA insulin resistance and beta cell function                                   |
| End point description: | Measured after 4 weeks of treatment (visit 4) and compared to baseline (visit 3) |
| End point type         | Secondary  |
| End point timeframe:   | At 4 weeks after treatment   |

| End point values                                 | Placebo         | XEN-D0501       |  |  |
|--|-----------------|-----------------|--|--|
| Subject group type                               | Reporting group | Reporting group |  |  |
| Number of subjects analysed                      | 31              | 23              |  |  |
| Units: pmol/L                                    |                 |                 |  |  |
| geometric mean (standard deviation)              |                 |                 |  |  |
| Insulin resistance, visit 4                      | 4.5 (± 3.1)     | 5.9 (± 4.5)     |  |  |
| Insulin resistance, change from baseline visit 4 | -0.8 (± 2.1)    | -1.0 (± 2.0)    |  |  |
| Beta cell function, visit 4                      | 67.1 (± 48.5)   | 85.2 (± 80.8)   |  |  |
| Beta cell function, change from baseline visit 4 | -9.9 (± 28.1)   | 8.0 (± 78.0)    |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Fasting insulin after 4 weeks of treatment

|                 |  |
|-----------------|--|
| End point title | Fasting insulin after 4 weeks of treatment |
|-----------------|--|

End point description:

Measured 4 weeks after treatment (visit 4) and compared to baseline (visit 3)

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

End point timeframe:

At 4 weeks of treatment (visit 4)

| End point values                    | Placebo           | XEN-D0501          |  |  |
|-------------------------------------|-------------------|--------------------|--|--|
| Subject group type                  | Reporting group   | Reporting group    |  |  |
| Number of subjects analysed         | 31                | 23                 |  |  |
| Units: $\mu\text{U/mL}$             |                   |                    |  |  |
| geometric mean (standard deviation) |                   |                    |  |  |
| Insulin, visit 4                    | 12.9 ( $\pm$ 8.0) | 16.1 ( $\pm$ 11.2) |  |  |
| Insulin, change from baseline       | -2.3 ( $\pm$ 4.8) | -1.6 ( $\pm$ 4.7)  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Body weight after 4 weeks of treatment

|                 |  |
|-----------------|--|
| End point title | Body weight after 4 weeks of treatment |
|-----------------|--|

End point description:

Measured at baseline (visit 3) and after 4 weeks of treatment (visit 4)

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

End point timeframe:

At 4 weeks after treatment (visit 4)

| End point values                         | Placebo            | XEN-D0501           |  |  |
|--|--------------------|---------------------|--|--|
| Subject group type                       | Reporting group    | Reporting group     |  |  |
| Number of subjects analysed              | 31                 | 23                  |  |  |
| Units: Kg                                |                    |                     |  |  |
| geometric mean (standard deviation)      |                    |                     |  |  |
| Baseline (visit 3)                       | 92.3 ( $\pm$ 20.4) | 103.4 ( $\pm$ 15.5) |  |  |
| Visit 4                                  | 91.8 ( $\pm$ 20.6) | 103.1 ( $\pm$ 15.3) |  |  |
| Change from baseline (visit 4 - visit 3) | -0.5 ( $\pm$ 1.4)  | -0.3 ( $\pm$ 1.2)   |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Waist circumference

|   |                     |
|---|---------------------|
| End point title   | Waist circumference |
| End point description:  |                     |
| Measured at baseline (visit 3) and after 4 weeks of treatment (visit 4) |                     |
| End point type  | Secondary           |
| End point timeframe:  |                     |
| At 4 weeks of treatment   |                     |

| End point values                         | Placebo         | XEN-D0501       |  |  |
|--|-----------------|-----------------|--|--|
| Subject group type                       | Reporting group | Reporting group |  |  |
| Number of subjects analysed              | 31              | 23              |  |  |
| Units: cm                                |                 |                 |  |  |
| geometric mean (standard deviation)      |                 |                 |  |  |
| Baseline (visit 3)                       | 109.7 (± 13.6)  | 116.7 (± 11.8)  |  |  |
| Visit 4                                  | 108.7 (± 13.4)  | 116.5 (± 11.6)  |  |  |
| Change from baseline (visit 4 - visit 3) | -0.9 (± 2.5)    | -0.2 (± 1.6)    |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Waist-hip ratio

|   |                 |
|---|-----------------|
| End point title   | Waist-hip ratio |
| End point description:  |                 |
| Measured at baseline (visit 3) and after 4 weeks of treatment (visit 4) |                 |
| End point type  | Secondary       |
| End point timeframe:  |                 |
| At 4 weeks after treatment (visit 4)                                    |                 |

| End point values                         | Placebo         | XEN-D0501       |  |  |
|--|-----------------|-----------------|--|--|
| Subject group type                       | Reporting group | Reporting group |  |  |
| Number of subjects analysed              | 31              | 23              |  |  |
| Units: cm/cm                             |                 |                 |  |  |
| geometric mean (standard deviation)      |                 |                 |  |  |
| Baseline (visit 3)                       | 1.0 (± 0.1)     | 1.0 (± 0.1)     |  |  |
| Visit 4                                  | 0.9 (± 0.1)     | 1.0 (± 0.1)     |  |  |
| Change from baseline (visit 4 - visit 3) | -0.006 (± 0.04) | -0.004 (± 0.02) |  |  |

### Statistical analyses



No statistical analyses for this end point

### Secondary: Fasting blood lipids after 4 weeks of treatment

|                 |   |
|-----------------|---|
| End point title | Fasting blood lipids after 4 weeks of treatment |
|-----------------|---|

End point description:

Measured after 4 weeks (visit 4) and as change from baseline (visit 4 - visit 3)

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

End point timeframe:

At 4 weeks of treatment (visit 4)

| End point values                    | Placebo         | XEN-D0501       |  |  |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type                  | Reporting group | Reporting group |  |  |
| Number of subjects analysed         | 31              | 23              |  |  |
| Units: mmol/L                       |                 |                 |  |  |
| geometric mean (standard deviation) |                 |                 |  |  |
| LDL, visit 4                        | 3.2 (± 0.9)     | 3.0 (± 1.17)    |  |  |
| LDL, change from baseline           | 0.05 (± 0.57)   | 0.08 (± 0.55)   |  |  |
| HDL, visit 4                        | 1.3 (± 0.27)    | 1.3 (± 0.35)    |  |  |
| HDL, change from baseline           | 0.007 (± 0.14)  | 0.012 (± 0.15)  |  |  |
| TAG, visit 4                        | 2.3 (± 1.21)    | 2.0 (± 0.7)     |  |  |
| TAG, change from baseline           | -0.051 (± 0.76) | -0.021 (± 0.48) |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Plasma CRP after 4 weeks of treatment

|                 |                                       |
|-----------------|---------------------------------------|
| End point title | Plasma CRP after 4 weeks of treatment |
|-----------------|---------------------------------------|

End point description:

Measured after 4 weeks of treatment (visit 4) and as change from baseline (visit 4 - visit 3)

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

End point timeframe:

At 4 weeks of treatment (visit 4)

| End point values                    | Placebo         | XEN-D0501       |  |  |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type                  | Reporting group | Reporting group |  |  |
| Number of subjects analysed         | 31              | 23              |  |  |
| Units: mg/L                         |                 |                 |  |  |
| geometric mean (standard deviation) |                 |                 |  |  |
| Visit 4                             | 4.0 (± 4.7)     | 5.1 (± 5.7)     |  |  |
| Change from baseline                | -1.33 (± 8.29)  | 0.90 (± 5.61)   |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Pro-BNP after 4 weeks of treatment

|                 |                                    |
|-----------------|------------------------------------|
| End point title | Pro-BNP after 4 weeks of treatment |
|-----------------|------------------------------------|

End point description:

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

End point timeframe:

At 4 weeks of treatment (visit 4)

| End point values                         | Placebo         | XEN-D0501       |  |  |
|--|-----------------|-----------------|--|--|
| Subject group type                       | Reporting group | Reporting group |  |  |
| Number of subjects analysed              | 24              | 18              |  |  |
| Units: pg/mL                             |                 |                 |  |  |
| geometric mean (standard deviation)      |                 |                 |  |  |
| Visit 4                                  | 475.8 (± 754.0) | 133.3 (± 85.0)  |  |  |
| Change from baseline (visit 4 - visit 3) | 43.3 (± 213.1)  | 13.1 (± 57.5)   |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Hyperthermia events

|                 |                     |
|-----------------|---------------------|
| End point title | Hyperthermia events |
|-----------------|---------------------|

End point description:

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

End point timeframe:

From start of treatment to follow-up, visit 5

| End point values            | Placebo         | XEN-D0501       |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 31              | 23              |  |  |
| Units: Events               | 0               | 0               |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Hypoglycemic events

|                 |                     |
|-----------------|---------------------|
| End point title | Hypoglycemic events |
|-----------------|---------------------|

End point description:

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

End point timeframe:

From start of treatment to follow-up (visit 5)

| End point values            | Placebo         | XEN-D0501       |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 31              | 23              |  |  |
| Units: Events               | 1               | 0               |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Plasma glucagon after four weeks of bi-daily doses of XEN-D0501

|                 |   |
|-----------------|---|
| End point title | Plasma glucagon after four weeks of bi-daily doses of XEN-D0501 |
|-----------------|---|

End point description:

Measured at baseline (visit 3) and after 4 weeks of treatment (visit 4)

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

End point timeframe:

After 4 weeks

| End point values                         | Placebo         | XEN-D0501       |  |  |
|--|-----------------|-----------------|--|--|
| Subject group type                       | Reporting group | Reporting group |  |  |
| Number of subjects analysed              | 28              | 22              |  |  |
| Units: pmol/L                            |                 |                 |  |  |
| geometric mean (standard deviation)      |                 |                 |  |  |
| Baseline (visit 3)                       | 6.2 (± 4.5)     | 5.4 (± 3.6)     |  |  |
| Visit 4                                  | 6.4 (± 3.8)     | 7.5 (± 5.5)     |  |  |
| Change from baseline (visit 4 - visit 3) | 0.3 (± 3.7)     | 3 (± 5.6)       |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Plasma concentration of XEN-D0501 after four weeks of bi-daily dosing of XEN-D0501

|                 |  |
|-----------------|--|
| End point title | Plasma concentration of XEN-D0501 after four weeks of bi-daily dosing of XEN-D0501 |
|-----------------|--|

End point description:

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

End point timeframe:

After 4 weeks

| End point values                       | XEN-D0501          |  |  |  |
|--|--------------------|--|--|--|
| Subject group type                     | Reporting group    |  |  |  |
| Number of subjects analysed            | 23                 |  |  |  |
| Units: ng/mL                           |                    |  |  |  |
| arithmetic mean (full range (min-max)) |                    |  |  |  |
| C <sub>max</sub>                       | 66.2 (14.1 to 159) |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Safety

|                 |        |
|-----------------|--------|
| End point title | Safety |
|-----------------|--------|

End point description:

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

End point timeframe:

From signing of informed content to end of trial participation

| End point values            | Placebo         | XEN-D0501       |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 31              | 29              |  |  |
| Units: Events               |                 |                 |  |  |
| Adverse events              | 13              | 57              |  |  |
| SAEs                        | 0               | 0               |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: ANP after 4 weeks of treatment

|  |                                |
|--|--------------------------------|
| End point title  | ANP after 4 weeks of treatment |
| End point description:   |                                |
| Measured 4 weeks after treatment and at baseline (visit 3) and as change from baseline |                                |
| End point type   | Secondary                      |
| End point timeframe:   |                                |
| At 4 weeks   |                                |

| End point values                    | Placebo         | XEN-D0501       |  |  |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type                  | Reporting group | Reporting group |  |  |
| Number of subjects analysed         | 31              | 23              |  |  |
| Units: pmol/L                       |                 |                 |  |  |
| geometric mean (standard deviation) |                 |                 |  |  |
| Visit 4                             | 83.2 (± 65.3)   | 58.9 (± 26.2)   |  |  |
| Visit 3                             | 78.2 (± 73.1)   | 66.4 (± 24.5)   |  |  |
| Change from baseline (visit 3)      | 3.9 (± 14.1)    | -7.5 (± 16.1)   |  |  |

## Statistical analyses

|   |                          |
|---|--------------------------|
| Statistical analysis title              | ANP change from baseline |
| Comparison groups                       | Placebo v XEN-D0501      |
| Number of subjects included in analysis | 54                       |
| Analysis specification                  | Post-hoc                 |
| Analysis type                           | equivalence              |
| P-value                                 | = 0.0097                 |
| Method                                  | t-test, 2-sided          |



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From signing of informed consent to end of trial participation

Adverse event reporting additional description:

Adverse events are collected at each visit.

The Investigator asked the subjects about AEs by asking: "Have you experienced any problems since the last contact?"

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

### Dictionary used

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

|                    |    |
|--------------------|----|
| Dictionary version | 22 |
|--------------------|----|

### Reporting groups

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description: -

|                       |           |
|-----------------------|-----------|
| Reporting group title | XEN-D0501 |
|-----------------------|-----------|

Reporting group description: -

| Serious adverse events                            | Placebo        | XEN-D0501      |  |
|---|----------------|----------------|--|
| Total subjects affected by serious adverse events |                |                |  |
| subjects affected / exposed                       | 0 / 31 (0.00%) | 0 / 29 (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: 1 %

| Non-serious adverse events  | Placebo         | XEN-D0501        |  |
|---|-----------------|------------------|--|
| Total subjects affected by non-serious adverse events               |                 |                  |  |
| subjects affected / exposed   | 9 / 31 (29.03%) | 17 / 29 (58.62%) |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                 |                  |  |
| Basal cell carcinoma  |                 |                  |  |
| subjects affected / exposed   | 0 / 31 (0.00%)  | 1 / 29 (3.45%)   |  |
| occurrences (all)   | 0               | 1                |  |
| Gastrointestinal polyp  |                 |                  |  |
| subjects affected / exposed   | 0 / 31 (0.00%)  | 1 / 29 (3.45%)   |  |
| occurrences (all)   | 0               | 1                |  |
| Vascular disorders  |                 |                  |  |

|  |                     |                      |  |
|--|---------------------|----------------------|--|
| Flushing<br>subjects affected / exposed<br>occurrences (all)   | 0 / 31 (0.00%)<br>0 | 2 / 29 (6.90%)<br>2  |  |
| Hot flush<br>subjects affected / exposed<br>occurrences (all)  | 0 / 31 (0.00%)<br>0 | 4 / 29 (13.79%)<br>4 |  |
| Hypertension<br>subjects affected / exposed<br>occurrences (all)   | 0 / 31 (0.00%)<br>0 | 1 / 29 (3.45%)<br>1  |  |
| Surgical and medical procedures<br>Skin neoplasm excision<br>subjects affected / exposed<br>occurrences (all)                | 0 / 31 (0.00%)<br>0 | 1 / 29 (3.45%)<br>1  |  |
| General disorders and administration<br>site conditions<br>Feeling cold<br>subjects affected / exposed<br>occurrences (all)  | 1 / 31 (3.23%)<br>1 | 3 / 29 (10.34%)<br>5 |  |
| Feeling hot<br>subjects affected / exposed<br>occurrences (all)  | 0 / 31 (0.00%)<br>0 | 3 / 29 (10.34%)<br>5 |  |
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)  | 2 / 31 (6.45%)<br>2 | 1 / 29 (3.45%)<br>1  |  |
| Respiratory, thoracic and mediastinal<br>disorders<br>Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all) | 1 / 31 (3.23%)<br>1 | 1 / 29 (3.45%)<br>1  |  |
| Psychiatric disorders<br>Insomnia<br>subjects affected / exposed<br>occurrences (all)  | 0 / 31 (0.00%)<br>0 | 1 / 29 (3.45%)<br>1  |  |
| Investigations<br>Body temperature increased<br>subjects affected / exposed<br>occurrences (all)                             | 3 / 31 (9.68%)<br>4 | 2 / 29 (6.90%)<br>2  |  |
| Heart rate increased   |                     |                      |  |



|  |  |  |  |
|--|--|--|--|
| subjects affected / exposed<br>occurrences (all)   | 0 / 31 (0.00%)<br>0  | 1 / 29 (3.45%)<br>3  |  |
| Injury, poisoning and procedural complications<br>Radius fracture<br>subjects affected / exposed<br>occurrences (all)  | 0 / 31 (0.00%)<br>0  | 1 / 29 (3.45%)<br>1  |  |
| Nervous system disorders<br>Dizziness<br>subjects affected / exposed<br>occurrences (all)<br><br>Headache<br>subjects affected / exposed<br>occurrences (all)<br><br>Hypoaesthesia<br>subjects affected / exposed<br>occurrences (all)<br><br>Hypogeusia<br>subjects affected / exposed<br>occurrences (all)<br><br>Paraesthesia<br>subjects affected / exposed<br>occurrences (all)<br><br>Taste disorder<br>subjects affected / exposed<br>occurrences (all) | 0 / 31 (0.00%)<br>0<br><br>0 / 31 (0.00%)<br>0<br><br>0 / 31 (0.00%)<br>0<br><br>0 / 31 (0.00%)<br>0<br><br>0 / 31 (0.00%)<br>0<br><br>0 / 31 (0.00%)<br>0 | 1 / 29 (3.45%)<br>1<br><br>2 / 29 (6.90%)<br>2<br><br>2 / 29 (6.90%)<br>3<br><br>1 / 29 (3.45%)<br>1<br><br>3 / 29 (10.34%)<br>3<br><br>3 / 29 (10.34%)<br>3 |  |
| Gastrointestinal disorders<br>Abdominal distension<br>subjects affected / exposed<br>occurrences (all)<br><br>Tongue oedema<br>subjects affected / exposed<br>occurrences (all)<br><br>Hypoaesthesia oral<br>subjects affected / exposed<br>occurrences (all)  | 1 / 31 (3.23%)<br>1<br><br>0 / 31 (0.00%)<br>0<br><br>0 / 31 (0.00%)<br>0  | 1 / 29 (3.45%)<br>1<br><br>1 / 29 (3.45%)<br>1<br><br>1 / 29 (3.45%)<br>1  |  |
| Skin and subcutaneous tissue disorders   |  |  |  |

|   |                     |                      |  |
|---|---------------------|----------------------|--|
| Hyperhidrosis<br>subjects affected / exposed<br>occurrences (all)   | 1 / 31 (3.23%)<br>1 | 3 / 29 (10.34%)<br>4 |  |
| Dermatitis<br>subjects affected / exposed<br>occurrences (all)  | 0 / 31 (0.00%)<br>0 | 1 / 29 (3.45%)<br>1  |  |
| Renal and urinary disorders<br>Polyuria<br>subjects affected / exposed<br>occurrences (all)                                   | 0 / 31 (0.00%)<br>0 | 1 / 29 (3.45%)<br>1  |  |
| Urinary incontinence<br>subjects affected / exposed<br>occurrences (all)  | 0 / 31 (0.00%)<br>0 | 1 / 29 (3.45%)<br>1  |  |
| Musculoskeletal and connective tissue disorders<br>Carpal tunnel syndrome<br>subjects affected / exposed<br>occurrences (all) | 0 / 31 (0.00%)<br>0 | 1 / 29 (3.45%)<br>2  |  |
| Meniscus injury<br>subjects affected / exposed<br>occurrences (all)   | 0 / 31 (0.00%)<br>0 | 1 / 29 (3.45%)<br>1  |  |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)   | 1 / 31 (3.23%)<br>1 | 0 / 29 (0.00%)<br>0  |  |
| Infections and infestations<br>Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)          | 0 / 31 (0.00%)<br>0 | 1 / 29 (3.45%)<br>1  |  |
| Metabolism and nutrition disorders<br>Increased appetite<br>subjects affected / exposed<br>occurrences (all)                  | 1 / 31 (3.23%)<br>2 | 0 / 29 (0.00%)<br>0  |  |
| Iron deficiency anaemia<br>subjects affected / exposed<br>occurrences (all)   | 0 / 31 (0.00%)<br>0 | 1 / 29 (3.45%)<br>1  |  |

## 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