



## Clinical trial results:

**A Phase III, multi-center, randomized, double-blind, 48 week study with an initial 12 week placebo-controlled period to evaluate the safety and efficacy of osilodrostat in patients with Cushing's disease**

### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2014-004092-23   |
| Trial protocol           | ES GR BE PL PT   |
| Global end of trial date | 31 December 2020 |

### Results information

|                                |                |
|--------------------------------|----------------|
| Result version number          | v1 (current)   |
| This version publication date  | 21 August 2021 |
| First version publication date | 21 August 2021 |

### Trial information

#### Trial identification

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | CLCI699C2302 |
|-----------------------|--------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02697734 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Novartis Pharma AG  |
| Sponsor organisation address | Novartis Campus, Basel, Switzerland,  |
| Public contact               | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@Novartis.com |
| Scientific contact           | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@Novartis.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**

|  |                  |
|--|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 31 December 2020 |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 31 December 2020 |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 31 December 2020 |
| Was the trial ended prematurely?                     | No               |

Notes:

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**General information about the trial**

Main objective of the trial:

Primary objective: To demonstrate the superiority of osilodrostat compared to placebo in achieving a complete response ( $mUFC \leq ULN$ ) at Week 12.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

|   |                 |
|---|-----------------|
| Actual start date of recruitment                          | 03 October 2016 |
| Long term follow-up planned                               | No              |
| Independent data monitoring committee (IDMC) involvement? | Yes             |

Notes:

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**Population of trial subjects****Subjects enrolled per country**

|                                      |                       |
|--------------------------------------|-----------------------|
| Country: Number of subjects enrolled | Belgium: 6            |
| Country: Number of subjects enrolled | Brazil: 9             |
| Country: Number of subjects enrolled | Canada: 3             |
| Country: Number of subjects enrolled | China: 12             |
| Country: Number of subjects enrolled | Costa Rica: 3         |
| Country: Number of subjects enrolled | Greece: 2             |
| Country: Number of subjects enrolled | Poland: 10            |
| Country: Number of subjects enrolled | Portugal: 1           |
| Country: Number of subjects enrolled | Russian Federation: 6 |
| Country: Number of subjects enrolled | Spain: 5              |
| Country: Number of subjects enrolled | Switzerland: 1        |
| Country: Number of subjects enrolled | Thailand: 5           |
| Country: Number of subjects enrolled | Turkey: 2             |
| Country: Number of subjects enrolled | United States: 9      |
| Worldwide total number of subjects   | 74                    |
| EEA total number of subjects         | 24                    |

Notes:

| <b>Subjects enrolled per age group</b>    |    |
|---|----|
| 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)                      | 72 |
| From 65 to 84 years                       | 2  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Number of subjects - enrolled: 74; analyzed: 73 (One patient was randomized but did not receive any study treatment as the patient experienced an SAE and discontinued the study)

### Pre-assignment

Screening details:

Full Analysis Set: comprises all randomized participants who received at least one dose of study drug (osilodrostat or placebo).

There are 73 participants in the FAS who were randomized and received treatment.

### Period 1

|                              |   |
|------------------------------|---|
| Period 1 title               | Core phase - up to week 48                                    |
| Is this the baseline period? | Yes   |
| Allocation method            | Randomised - controlled                                       |
| Blinding used                | Double blind  |
| Roles blinded                | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

### Arms

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

Arm description:

Participants in this arm were randomized to receive the study drug, osilodrostat, followed after Week 12 by open-label osilodrostat at the starting dose (with a second dose titration).

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Osilodrostat |
| Investigational medicinal product code | LCI699       |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

The starting dose in Period 1 was 2 mg b.i.d. osilodrostat. Osilodrostat dosing regimen included up-titration following a 5 mg b.i.d., 10 mg b.i.d. and 20 mg b.i.d. escalation sequence during Period 1.

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

Arm description:

Participants in this arm were randomized to receive osilodrostat placebo followed after Week 12 by open-label osilodrostat at the starting dose (with a dose titration).

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

Dosage and administration details:

Placebo tablet for oral use

| <b>Number of subjects in period 1</b> <sup>[1]</sup> | osilodrostat Group | osilodrostat Placebo Group |
|--|--------------------|----------------------------|
| Started  | 48                 | 25                         |
| Completed  | 42                 | 23                         |
| Not completed  | 6                  | 2                          |
| Consent withdrawn by subject                         | 4                  | -                          |
| Physician decision                                   | 1                  | -                          |
| Adverse event, non-fatal                             | 1                  | 2                          |

Notes:

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

Justification: 5 participants completed core phase and did not enter the optional extension phase.

## Period 2

|                              |                          |
|------------------------------|--------------------------|
| Period 2 title               | Optional Extension phase |
| Is this the baseline period? | No                       |
| Allocation method            | Not applicable           |
| Blinding used                | Not blinded              |

## Arms

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

Arm description:

Participants in this arm were randomized to receive the study drug, osilodrostat, followed after Week 12 by open-label osilodrostat at the starting dose (with a second dose titration).

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Osilodrostat |
| Investigational medicinal product code | LCI699       |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

In Period 2, the maximum starting dose of osilodrostat was 2 mg b.i.d., and could be <2 mg if they were receiving osilodrostat or placebo at a dose <2mg b.i.d. at the end of Period 1. Osilodrostat dosing regimen included up-titration following a 2 mg b.i.d., 5 mg b.i.d., 10 mg b.i.d., 20 mg b.i.d. and 30 mg b.i.d. escalation sequence during Period 2.

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

Arm description:

Participants in this arm were randomized to receive osilodrostat placebo followed after Week 12 by open-label osilodrostat at the starting dose (with a dose titration).

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

Dosage and administration details:

Placebo tablet for oral use

| Number of subjects in period<br>2 <sup>[2]</sup> | osilodrostat Group | osilodrostat Placebo<br>Group |
|--|--------------------|-------------------------------|
|  |                    |                               |
| Started  | 38                 | 22                            |
| Completed  | 33                 | 20                            |
| Not completed                                    | 5                  | 2                             |
| Physician decision                               | -                  | 1                             |
| Adverse event, non-fatal                         | 5                  | 1                             |

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Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Number of subjects; enrolled: 74; analyzed: 73 (One patient was randomized but did not receive any study treatment as the patient experienced an SAE and discontinued the study)

## Baseline characteristics

### Reporting groups

|  |                            |
|--|----------------------------|
| Reporting group title  | osilodrostat Group         |
| Reporting group description:   |                            |
| Participants in this arm were randomized to receive the study drug, osilodrostat, followed after Week 12 by open-label osilodrostat at the starting dose (with a second dose titration). |                            |
| Reporting group title  | osilodrostat Placebo Group |
| Reporting group description:   |                            |
| Participants in this arm were randomized to receive osilodrostat placebo followed after Week 12 by open-label osilodrostat at the starting dose (with a dose titration).                 |                            |

| Reporting group values                    | osilodrostat Group | osilodrostat Placebo Group | Total |
|---|--------------------|----------------------------|-------|
| Number of subjects                        | 48                 | 25                         | 73    |
| Age Categorical<br>Units: Participants    |                    |                            |       |
| <=18 years                                | 0                  | 0                          | 0     |
| Between 18 and 65 years                   | 46                 | 25                         | 71    |
| >=65 years                                | 2                  | 0                          | 2     |
| Age Continuous<br>Units: Years            |                    |                            |       |
| arithmetic mean                           | 42.3               | 38.9                       |       |
| standard deviation                        | ± 13.82            | ± 12.33                    | -     |
| Sex: Female, Male<br>Units: Participants  |                    |                            |       |
| Female                                    | 43                 | 18                         | 61    |
| Male                                      | 5                  | 7                          | 12    |
| Race (NIH/OMB)<br>Units: Subjects         |                    |                            |       |
| American Indian or Alaska Native          | 1                  | 0                          | 1     |
| Asian                                     | 9                  | 8                          | 17    |
| Native Hawaiian or Other Pacific Islander | 0                  | 0                          | 0     |
| Black or African American                 | 2                  | 0                          | 2     |
| White                                     | 34                 | 15                         | 49    |
| More than one race                        | 0                  | 1                          | 1     |
| Unknown or Not Reported                   | 2                  | 1                          | 3     |

### Subject analysis sets

|  |                                |
|--|--------------------------------|
| Subject analysis set title   | All participants combined      |
| Subject analysis set type  | Full analysis                  |
| Subject analysis set description:  |                                |
| Consisted of all randomized participants who received at least one dose of osilodrostat. |                                |
| Subject analysis set title   | All Participants               |
| Subject analysis set type  | Full analysis                  |
| Subject analysis set description:  |                                |
| All Participants   |                                |
| Subject analysis set title   | osilodrostat Incident Dose 1mg |

|   |                                |
|---|--------------------------------|
| Subject analysis set type   | Full analysis                  |
| Subject analysis set description:<br>Participants received 1mg of osilodrostat. |                                |
| Subject analysis set title  | osilodrostat Incident Dose 2mg |
| Subject analysis set type   | Full analysis                  |
| Subject analysis set description:<br>Participants received 2mg of osilodrostat. |                                |
| Subject analysis set title  | osilodrostat Incident Dose 5mg |
| Subject analysis set type   | Full analysis                  |
| Subject analysis set description:<br>Participants received 5mg of osilodrostat. |                                |

| Reporting group values                    | All participants combined | All Participants | osilodrostat Incident Dose 1mg |
|---|---------------------------|------------------|--------------------------------|
| Number of subjects                        | 73                        | 73               | 16                             |
| Age Categorical<br>Units: Participants    |                           |                  |                                |
| <=18 years                                |                           |                  |                                |
| Between 18 and 65 years                   |                           |                  |                                |
| >=65 years                                |                           |                  |                                |
| Age Continuous<br>Units: Years            |                           |                  |                                |
| arithmetic mean                           | 80.8                      | 2                |                                |
| standard deviation                        | ±                         | ±                | ±                              |
| Sex: Female, Male<br>Units: Participants  |                           |                  |                                |
| Female                                    |                           |                  |                                |
| Male                                      |                           |                  |                                |
| Race (NIH/OMB)<br>Units: Subjects         |                           |                  |                                |
| American Indian or Alaska Native          |                           |                  |                                |
| Asian                                     |                           |                  |                                |
| Native Hawaiian or Other Pacific Islander |                           |                  |                                |
| Black or African American                 |                           |                  |                                |
| White                                     |                           |                  |                                |
| More than one race                        |                           |                  |                                |
| Unknown or Not Reported                   |                           |                  |                                |

| Reporting group values                 | osilodrostat Incident Dose 2mg | osilodrostat Incident Dose 5mg |  |
|--|--------------------------------|--------------------------------|--|
| Number of subjects                     | 55                             | 29                             |  |
| Age Categorical<br>Units: Participants |                                |                                |  |
| <=18 years                             |                                |                                |  |
| Between 18 and 65 years                |                                |                                |  |
| >=65 years                             |                                |                                |  |
| Age Continuous<br>Units: Years         |                                |                                |  |
| arithmetic mean                        |                                |                                |  |
| standard deviation                     | ±                              | ±                              |  |



|  |  |  |  |
|--|--|--|--|
| Sex: Female, Male<br>Units: Participants   |  |  |  |
| Female<br>Male   |  |  |  |
| Race (NIH/OMB)<br>Units: Subjects  |  |  |  |
| American Indian or Alaska Native<br>Asian<br>Native Hawaiian or Other Pacific<br>Islander<br>Black or African American<br>White<br>More than one race<br>Unknown or Not Reported |  |  |  |

## End points

### End points reporting groups

|  |                                |
|--|--------------------------------|
| Reporting group title  | osilodrostat Group             |
| Reporting group description:<br>Participants in this arm were randomized to receive the study drug, osilodrostat, followed after Week 12 by open-label osilodrostat at the starting dose (with a second dose titration). |                                |
| Reporting group title  | osilodrostat Placebo Group     |
| Reporting group description:<br>Participants in this arm were randomized to receive osilodrostat placebo followed after Week 12 by open-label osilodrostat at the starting dose (with a dose titration).                 |                                |
| Reporting group title  | osilodrostat Group             |
| Reporting group description:<br>Participants in this arm were randomized to receive the study drug, osilodrostat, followed after Week 12 by open-label osilodrostat at the starting dose (with a second dose titration). |                                |
| Reporting group title  | osilodrostat Placebo Group     |
| Reporting group description:<br>Participants in this arm were randomized to receive osilodrostat placebo followed after Week 12 by open-label osilodrostat at the starting dose (with a dose titration).                 |                                |
| Subject analysis set title   | All participants combined      |
| Subject analysis set type  | Full analysis                  |
| Subject analysis set description:<br>Consisted of all randomized participants who received at least one dose of osilodrostat.  |                                |
| Subject analysis set title   | All Participants               |
| Subject analysis set type  | Full analysis                  |
| Subject analysis set description:<br>All Participants  |                                |
| Subject analysis set title   | osilodrostat Incident Dose 1mg |
| Subject analysis set type  | Full analysis                  |
| Subject analysis set description:<br>Participants received 1mg of osilodrostat.  |                                |
| Subject analysis set title   | osilodrostat Incident Dose 2mg |
| Subject analysis set type  | Full analysis                  |
| Subject analysis set description:<br>Participants received 2mg of osilodrostat.  |                                |
| Subject analysis set title   | osilodrostat Incident Dose 5mg |
| Subject analysis set type  | Full analysis                  |
| Subject analysis set description:<br>Participants received 5mg of osilodrostat.  |                                |

### Primary: Percentage of randomized participants with a complete response

|   |  |
|---|--|
| End point title   | Percentage of randomized participants with a complete response |
| End point description:<br>A complete responder at week 12 is defined as a participant who had a mean urine free cortisol $\leq$ upper limit of normal (mUFC $\leq$ ULN) at Week 12.<br><br>Participants who had a missing mUFC assessment at Week 12 were counted as non-responders for the primary endpoint. |  |
| End point type  | Primary  |
| End point timeframe:<br>at Week 12  |  |

| <b>End point values</b>     | osilodrostat Group | osilodrostat Placebo Group |  |  |
|-----------------------------|--------------------|----------------------------|--|--|
| Subject group type          | Reporting group    | Reporting group            |  |  |
| Number of subjects analysed | 48                 | 25                         |  |  |
| Units: Participants         | 37                 | 2                          |  |  |

## Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | osilodrostat Group v osilodrostat Placebo Group |
| Comparison groups                       | osilodrostat Group v osilodrostat Placebo Group |
| Number of subjects included in analysis | 73  |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           |   |
| P-value                                 | < 0.0001  |
| Method                                  | Cochran-Mantel-Haenszel                         |
| Parameter estimate                      | Odds ratio (OR)                                 |
| Point estimate                          | 43.4  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 7.06  |
| upper limit                             | 343.19  |

## Secondary: Time-to-first control of mUFC - number (%) of participants with mUFC ≤ULN

|  |   |
|--|---|
| End point title  | Time-to-first control of mUFC - number (%) of participants with mUFC ≤ULN |
| End point description:   |   |
| To assess time-to-first control of mUFC, (in days) from randomization to the first mUFC collection that was ≤ ULN before completion/discontinuation of placebo-controlled period.<br>Participants who did not achieve post-baseline mUFC control were censored at discontinuation or completion of placebo-controlled period, whichever was earlier. |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| up to 12 weeks   |   |

| End point values            | osilodrostat Group | osilodrostat Placebo Group |  |  |
|-----------------------------|--------------------|----------------------------|--|--|
| Subject group type          | Reporting group    | Reporting group            |  |  |
| Number of subjects analysed | 48                 | 25                         |  |  |
| Units: Participants         | 45                 | 8                          |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time-to-first control of mUFC - median time to first controlled mUFC response

|                 |   |
|-----------------|---|
| End point title | Time-to-first control of mUFC - median time to first controlled mUFC response |
|-----------------|---|

End point description:

To assess time-to-first control of mUFC, (in days) from randomization to the first mUFC collection that was  $\leq$  ULN before completion/discontinuation of placebo-controlled period.

Participants who did not achieve post-baseline mUFC control were censored at discontinuation or completion of placebo-controlled period, whichever was earlier.

The median time-to-first control and corresponding two-sided 95% Confidence Interval were calculated using Kaplan-Meier methodology of Brookmeyer and Crowley (1982).

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

End point timeframe:

up to 12 weeks

| End point values                 | osilodrostat Group | osilodrostat Placebo Group |  |  |
|----------------------------------|--------------------|----------------------------|--|--|
| Subject group type               | Reporting group    | Reporting group            |  |  |
| Number of subjects analysed      | 48                 | 25                         |  |  |
| Units: Days                      |                    |                            |  |  |
| number (confidence interval 95%) | 35 (34.0 to 52.0)  | 999 (87.0 to 999)          |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time-to-first control of mUFC - % event probability estimates

|                 |   |
|-----------------|---|
| End point title | Time-to-first control of mUFC - % event probability estimates |
|-----------------|---|

End point description:

To assess time-to-first control of mUFC, (in days) from randomization to the first mUFC collection that was  $\leq$  ULN before completion/discontinuation of placebo-controlled period.

Participants who did not achieve post-baseline mUFC control were censored at discontinuation or completion of placebo-controlled period, whichever was earlier.

% Event probability estimate is the estimated probability that a participant will have an event prior to

the specified time point. % Event probability estimates are obtained from the Kaplan-Meier survival estimates for all treatment groups; Greenwood formula is used for Confidence Interval (CI) of Kaplan-Meier (KM) estimates.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| up to 12 weeks       |           |

| End point values                 | osilodrostat Group  | osilodrostat Placebo Group |  |  |
|----------------------------------|---------------------|----------------------------|--|--|
| Subject group type               | Reporting group     | Reporting group            |  |  |
| Number of subjects analysed      | 48                  | 25                         |  |  |
| Units: Percentage                |                     |                            |  |  |
| number (confidence interval 95%) |                     |                            |  |  |
| 2 Weeks                          | 25.0 (15.0 to 39.8) | 16.0 (6.3 to 37.2)         |  |  |
| 5 Weeks                          | 60.4 (47.0 to 74.1) | 20.0 (8.9 to 41.6)         |  |  |
| 8 Weeks                          | 79.4 (67.0 to 89.4) | 28.0 (14.5 to 49.9)        |  |  |
| 12 Weeks                         | 99.9 (99.9 to 99.9) | 28.0 (14.5 to 49.9)        |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time-to-escape during osilodrostat treatment from collection of normal mUFC ( $\leq$ ULN) to the first mUFC $> 1.3 \times$ ULN - number (%) of participants

|                 |   |
|-----------------|---|
| End point title | Time-to-escape during osilodrostat treatment from collection of normal mUFC ( $\leq$ ULN) to the first mUFC $> 1.3 \times$ ULN - number (%) of participants |
|-----------------|---|

End point description:

To assess time-to-escape from the first collection of normal mUFC ( $\leq$  ULN) to the first mUFC  $> 1.3 \times$  ULN on two consecutive visits on the highest tolerated dose of osilodrostat and not related to a dose interruption or dose reduction due to safety reasons. Escape will not be assessed for participants during the first 26 weeks.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| up to 48 weeks       |           |

| End point values            | osilodrostat Group | osilodrostat Placebo Group | All Participants     |  |
|-----------------------------|--------------------|----------------------------|----------------------|--|
| Subject group type          | Reporting group    | Reporting group            | Subject analysis set |  |
| Number of subjects analysed | 48                 | 25                         | 73                   |  |
| Units: Participants         | 0                  | 2                          | 2                    |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Time-to-escape during osilodrostat treatment from collection of normal mUFC ( $\leq$ ULN) to the first mUFC $> 1.3 \times$ ULN - median time to escape from normal mUFC

|                 |   |
|-----------------|---|
| End point title | Time-to-escape during osilodrostat treatment from collection of normal mUFC ( $\leq$ ULN) to the first mUFC $> 1.3 \times$ ULN - median time to escape from normal mUFC |
|-----------------|---|

#### End point description:

To assess time-to-escape from the first collection of normal mUFC ( $\leq$  ULN) to the first mUFC  $> 1.3 \times$  ULN on two consecutive visits on the highest tolerated dose of osilodrostat and not related to a dose interruption or dose reduction due to safety reasons. Escape will not be assessed for participants during the first 26 weeks.

The median time-to-escape and corresponding two-sided 95% Confidence Interval were calculated using Kaplan-Meier methodology of Brookmeyer and Crowley (1982).

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

#### End point timeframe:

from week 26 to week 48

| End point values                 | osilodrostat Group | osilodrostat Placebo Group | All Participants     |  |
|----------------------------------|--------------------|----------------------------|----------------------|--|
| Subject group type               | Reporting group    | Reporting group            | Subject analysis set |  |
| Number of subjects analysed      | 48                 | 25                         | 73                   |  |
| Units: days                      |                    |                            |                      |  |
| number (confidence interval 95%) | 999 (999 to 999)   | 999 (116.0 to 999)         | 999 (999 to 999)     |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Time-to-escape during osilodrostat treatment from collection of normal mUFC ( $\leq$ ULN) to the first mUFC $> 1.3 \times$ ULN - % event probability estimates

|                 |  |
|-----------------|--|
| End point title | Time-to-escape during osilodrostat treatment from collection of normal mUFC ( $\leq$ ULN) to the first mUFC $> 1.3 \times$ ULN - % event probability estimates |
|-----------------|--|

#### End point description:

To assess time-to-escape from the first collection of normal mUFC ( $\leq$  ULN) to the first mUFC  $> 1.3 \times$  ULN on two consecutive visits on the highest tolerated dose of osilodrostat and not related to a dose interruption or dose reduction due to safety reasons. Escape will not be assessed for participants during the first 26 weeks.

% Event probability estimate is the estimated probability that a participant will have an event prior to the specified time point.

% Event probability estimates are obtained from the Kaplan-Meier survival estimates for all treatment groups; Greenwood formula is used for CI of KM estimates.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| week 26 to week 36   |           |

| End point values                 | osilodrostat Group | osilodrostat Placebo Group | All Participants     |  |
|----------------------------------|--------------------|----------------------------|----------------------|--|
| Subject group type               | Reporting group    | Reporting group            | Subject analysis set |  |
| Number of subjects analysed      | 48                 | 25                         | 73                   |  |
| Units: Percentage                |                    |                            |                      |  |
| number (confidence interval 95%) |                    |                            |                      |  |
| 26 Weeks                         | 0 (0 to 0)         | 21.3 (5.7 to 61.9)         | 15.6 (4.1 to 49.6)   |  |
| 36 Weeks                         | 0 (0 to 0)         | 999 (999 to 999)           | 15.6 (4.1 to 49.6)   |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Patients with a complete response (mUFC ≤ ULN) or a partial response (mUFC decrease ≥ 50% from baseline and >ULN) at week 12, 36 and 48

|                 |   |
|-----------------|---|
| End point title | Patients with a complete response (mUFC ≤ ULN) or a partial response (mUFC decrease ≥ 50% from baseline and >ULN) at week 12, 36 and 48 |
|-----------------|---|

End point description:

Overall response rate defined as percentage of complete responders (mUFC ≤ ULN) plus partial responders (≥ 50% reduction in mUFC from baseline and >ULN) at week 12, 36, 48 by treatment arms for all patients.

|                              |           |
|------------------------------|-----------|
| End point type               | Secondary |
| End point timeframe:         |           |
| baseline, week 12, 36 and 48 |           |

| End point values                                 | osilodrostat Group | osilodrostat Placebo Group |  |  |
|--|--------------------|----------------------------|--|--|
| Subject group type                               | Reporting group    | Reporting group            |  |  |
| Number of subjects analysed                      | 48                 | 25                         |  |  |
| Units: Participants                              |                    |                            |  |  |
| week 12 Complete responders                      | 37                 | 2                          |  |  |
| week 12 Partial responders                       | 2                  | 2                          |  |  |
| week 12 Overall responders (complete or partial) | 39                 | 4                          |  |  |
| week 12 Non-responders                           | 9                  | 21                         |  |  |
| week 36 Complete responders                      | 38                 | 21                         |  |  |

|  |    |    |  |  |
|--|----|----|--|--|
| week 36 Partial responders                       | 2  | 3  |  |  |
| week 36 Overall responders (complete or partial) | 40 | 24 |  |  |
| week 36 Non-responders                           | 8  | 1  |  |  |
| week 48 Complete responders                      | 34 | 16 |  |  |
| week 48 Partial responders                       | 5  | 3  |  |  |
| week 48 Overall responders (complete or partial) | 39 | 19 |  |  |
| week 48 Non-responders                           | 9  | 6  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from baseline to Week 12, Week 36, and Week 48 in clinical signs of Cushing's disease

|                 |  |
|-----------------|--|
| End point title | Change from baseline to Week 12, Week 36, and Week 48 in clinical signs of Cushing's disease |
|-----------------|--|

End point description:

Change from baseline to Week 12, Week 36, and Week 48 in each of the following clinical signs of Cushing's disease, captured by: a semi-quantitative Likert scale for facial rubor, striae, supraclavicular fat pad, dorsal fat pad, proximal muscle wasting (atrophy), central (abdominal) obesity, and ecchymoses (bruises) by randomized treatment arm. The number/proportion of participants with an improvement or no change compared to baseline are reported

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

End point timeframe:

baseline, Week 12, Week 36 and Week 48

| End point values                            | osilodrostat Group | osilodrostat Placebo Group |  |  |
|---|--------------------|----------------------------|--|--|
| Subject group type                          | Reporting group    | Reporting group            |  |  |
| Number of subjects analysed                 | 48                 | 25                         |  |  |
| Units: Participants                         |                    |                            |  |  |
| Facial Rubor - week 12 (n=42,20)            | 36                 | 19                         |  |  |
| Hirsutism - week 12 (n=36,16)               | 34                 | 15                         |  |  |
| Striae - week 12 (n=41,20)                  | 38                 | 19                         |  |  |
| Supraclavicular Fat Pad - week 12 (n=42,21) | 41                 | 19                         |  |  |
| Dorsal Fat Pad - week 12 (n=41,21)          | 35                 | 17                         |  |  |
| Proximal Muscle Atrophy - week 12 (n=42,21) | 38                 | 20                         |  |  |
| Central Obesity - week 12 (n=42,21)         | 37                 | 21                         |  |  |
| Ecchymoses - week 12 (n=42,20)              | 39                 | 19                         |  |  |
| Facial Rubor - week 36 (n=41,23)            | 39                 | 22                         |  |  |
| Hirsutism - week 36 (n=34,17)               | 28                 | 16                         |  |  |
| Striae - week 36 (n=40,23)                  | 38                 | 23                         |  |  |
| Supraclavicular Fat Pad - week 36 (n=41,24) | 40                 | 24                         |  |  |
| Dorsal Fat Pad - week 36 (n=40,24)          | 36                 | 22                         |  |  |



|   |    |    |  |  |
|---|----|----|--|--|
| Proximal Muscle Atrophy - week 36 (n=41,23) | 37 | 22 |  |  |
| Central Obesity - week 36 (n=41,24)         | 37 | 21 |  |  |
| Ecchymoses - week 36 (n=41,23)              | 39 | 22 |  |  |
| Facial Rubor - week 48 (n=39,21)            | 37 | 21 |  |  |
| Hirsutism - week 48 (n=33,15)               | 29 | 15 |  |  |
| Striae - week 48 (n=38,21)                  | 38 | 21 |  |  |
| Supraclavicular Fat Pad - week 48 (n=39,22) | 38 | 22 |  |  |
| Dorsal Fat Pad - week 48 (n=38,22)          | 36 | 20 |  |  |
| Proximal Muscle Atrophy - week 48 (n=39,22) | 35 | 21 |  |  |
| Central Obesity - week 48 (n=39,22)         | 35 | 21 |  |  |
| Ecchymoses - week 48 (n=39,21)              | 38 | 20 |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from baseline in EQ-5D-5L Utility Index

|  |  |
|--|--|
| End point title  | Change from baseline in EQ-5D-5L Utility Index |
| End point description:   |  |
| EQ-5D-5L Utility Index:  |  |
| The EQ-5D-5L questionnaire is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal. The EQ-5D-5L measures 5 items on mobility, self-care, usual activities, pain/discomfort, anxiety/depression, measured on 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. A utility index can be computed from the EQ 5D-5L descriptive system with utility scores ranging from -0.281 (worst imaginable health state) to 1 (best imaginable health state), with -0.281 representing an "unconscious" health state. A single index value is analyzed for the EQ-5D-5L score. An increase from baseline in the EQ-ED-5L utility index is indicative of an improvement. |  |
| End point type   | Secondary                                      |
| End point timeframe:   |  |
| Baseline to Week 12 and 48, Week 12 to Week 36, Week 36 to Week 48.  |  |

| End point values                                 | osilodrostat Group | osilodrostat Placebo Group |  |  |
|--|--------------------|----------------------------|--|--|
| Subject group type                               | Reporting group    | Reporting group            |  |  |
| Number of subjects analysed                      | 48                 | 25                         |  |  |
| Units: Scores on a scale                         |                    |                            |  |  |
| arithmetic mean (standard deviation)             |                    |                            |  |  |
| Actual - baseline (n=48,24)                      | 0.825 (± 0.1486)   | 0.903 (± 0.1125)           |  |  |
| Actual Change from Baseline at Week 12 (n=46,24) | -0.000 (± 0.1402)  | 0.021 (± 0.0771)           |  |  |
| Actual Change from Baseline at Week 48 (n=42,22) | 0.044 (± 0.1393)   | 0.033 (± 0.0826)           |  |  |
| Actual Change from Week 12 at Week 36 (n=44,23)  | 0.025 (± 0.1283)   | 0.010 (± 0.0487)           |  |  |
| Actual Change from Week 36 at Week 48 (n=42,22)  | 0.023 (± 0.0762)   | -0.008 (± 0.0367)          |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change from baseline in EQ-5D VAS

|                 |                                   |
|-----------------|-----------------------------------|
| End point title | Change from baseline in EQ-5D VAS |
|-----------------|-----------------------------------|

End point description:

The EQ-5D-5L also includes a 20 cm vertical, VAS (visual analogue scale) with a scale of 0-100, with endpoints labeled 100='the best health you can imagine' and 0='the worst health you can imagine'. A single index value is analyzed for the EQ-5D-5L VAS score. An increase from baseline in the EQ-ED-5L VAS is indicative of an improvement.

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

End point timeframe:

Baseline to Week 12 and 48, Week 12 to Week 36, Week 36 to Week 48.

| End point values                                 | osilodrostat Group | osilodrostat Placebo Group |  |  |
|--|--------------------|----------------------------|--|--|
| Subject group type                               | Reporting group    | Reporting group            |  |  |
| Number of subjects analysed                      | 48                 | 25                         |  |  |
| Units: Scores on a scale                         |                    |                            |  |  |
| arithmetic mean (standard deviation)             |                    |                            |  |  |
| Actual - baseline (n=48,23)                      | 70.3 (± 17.26)     | 76.7 (± 17.88)             |  |  |
| Actual Change from Baseline at week 12 (n=46,24) | 0.5 (± 13.57)      | -0.3 (± 10.52)             |  |  |
| Actual Change from Baseline at week 48 (n=42,22) | 9.4 (± 13.13)      | 5.8 (± 9.45)               |  |  |
| Actual Change from Week 12 at Week 36 (n=44,23)  | 6.0 (± 11.08)      | 3.7 (± 9.29)               |  |  |
| Actual Change from Week 36 at Week 48 (n=42,22)  | 3.2 (± 8.40)       | -0.8 (± 4.44)              |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change from baseline in Beck Depression Inventory-II - Total Score Derived

|                 |  |
|-----------------|--|
| End point title | Change from baseline in Beck Depression Inventory-II - Total Score Derived |
|-----------------|--|

End point description:

The Beck Depression Inventory II (BDI-II) is a patient reported instrument that consists of 21 items designed to assess the intensity of depression in clinical and normal patients in the preceding two weeks. Each item is a list of four statements arranged in increasing severity about a particular symptom of depression. A global score ranges from 0 to 63 and is calculated with a higher score representing a

greater level of depression. The following scoring guidelines for interpretation of BDI-II have been suggested (Smarr, 2011): Minimal range =0-13, Mild depression =14-19, Moderate depression =20-28 and Severe depression = 29-63. A reduction from baseline in BDI-II is indicative of an improvement.

|   |           |
|---|-----------|
| End point type  | Secondary |
| End point timeframe:  |           |
| Baseline to Week 12 and 48, Week 12 to Week 36, Week 36 to Week 48. |           |

| End point values                                 | osilodrostat Group | osilodrostat Placebo Group |  |  |
|--|--------------------|----------------------------|--|--|
| Subject group type                               | Reporting group    | Reporting group            |  |  |
| Number of subjects analysed                      | 48                 | 25                         |  |  |
| Units: Scores on a scale                         |                    |                            |  |  |
| arithmetic mean (standard deviation)             |                    |                            |  |  |
| Actual - baseline (n=48,25)                      | 12.2 (± 10.22)     | 8.4 (± 7.82)               |  |  |
| Actual Change from Baseline at Week 12 (n=46,24) | -1.4 (± 7.99)      | -3.9 (± 5.42)              |  |  |
| Actual Change from Baseline at Week 48 (n=42,22) | -4.3 (± 7.52)      | -4.0 (± 7.70)              |  |  |
| Actual Change from Week 12 at Week 36 (n=44,23)  | -2.0 (± 4.70)      | 0.6 (± 6.29)               |  |  |
| Actual Change from Week 36 at Week 48 (n=42,22)  | -1.1 (± 4.83)      | -0.4 (± 3.39)              |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Plasma osilodrostat concentrations (ng/mL)

|   |  |
|---|--|
| End point title   | Plasma osilodrostat concentrations (ng/mL) |
| End point description:  |  |
| Plasma osilodrostat concentrations (ng/mL)                        |  |
| End point type  | Secondary                                  |
| End point timeframe:  |  |
| pre-dose and 1-2hrs post dose at weeks 1, 2, 5, 8, 12, 14, 20, 26 |  |

| End point values                                    | osilodrostat Incident Dose 1mg | osilodrostat Incident Dose 2mg | osilodrostat Incident Dose 5mg |  |
|---|--------------------------------|--------------------------------|--------------------------------|--|
| Subject group type                                  | Subject analysis set           | Subject analysis set           | Subject analysis set           |  |
| Number of subjects analysed                         | 16                             | 55                             | 29                             |  |
| Units: ng/mL  |                                |                                |                                |  |
| geometric mean (geometric coefficient of variation) |                                |                                |                                |  |
| week 1 1-2 hrs post dose (n=1,43,0)                 | 3.85 (± 999)                   | 7.29 (± 101.0)                 | 999 (± 999)                    |  |
| week 2 0 hrs pre dose (n=0,41,0)                    | 999 (± 999)                    | 2.19 (± 107.5)                 | 999 (± 999)                    |  |
| week 2 1-2 hrs post dose (n=0,42,0)                 | 999 (± 999)                    | 9.76 (± 53.4)                  | 999 (± 999)                    |  |

|  |                 |               |                |  |
|--|-----------------|---------------|----------------|--|
| week 5 pre dose (n=2,18,17)            | 0.576 (± 141.9) | 2.07 (± 82.1) | 5.06 (± 109.6) |  |
| week 5 1-2 hrs post dose (n=2,9,29)    | 3.64 (± 60.5)   | 11.1 (± 31.5) | 25.8 (± 84.4)  |  |
| week 8 0 hrs pre dose (n=2,4,13)       | 0.971 (± 76.7)  | 2.64 (± 53.7) | 4.99 (± 55.6)  |  |
| week 8 1-2 hrs post dose (n=3,6,14)    | 3.70 (± 47.6)   | 8.31 (± 45.6) | 23.3 (± 68.1)  |  |
| week 12 0 hrs pre dose (n=2,8,11)      | 1.55 (± 3.7)    | 2.45 (± 39.2) | 5.03 (± 74.6)  |  |
| week 12 1-2 hrs post dose (n=4,34,0)   | 4.93 (± 32.0)   | 11.7 (± 78.9) | 999 (± 999)    |  |
| week 14 0 hrs pre dose (n=4,55,0)      | 0.974 (± 129.7) | 1.96 (± 74.9) | 999 (± 999)    |  |
| week 14 1-2 hrs post dose (n=6,49,6)   | 3.74 (± 161.4)  | 9.69 (± 35.8) | 22.6 (± 37.8)  |  |
| week 20 0 hrs pre dose (n=10,19,15)    | 1.63 (± 71.1)   | 1.95 (± 68.1) | 6.21 (± 74.3)  |  |
| week 20 1-2 hrs post dose (n=13,18,12) | 6.09 (± 27.3)   | 8.66 (± 94.0) | 26.0 (± 99.3)  |  |
| week 26 0 hrs pre dose (n=12,13,10)    | 1.77 (± 86.4)   | 2.12 (± 77.8) | 6.89 (± 85.1)  |  |
| week 26 1-2 hrs post dose (n=16,14,10) | 5.28 (± 31.5)   | 8.04 (± 50.7) | 33.1 (± 31.4)  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of participants with mUFC ≤ ULN at week 36

|  |   |
|--|---|
| End point title  | Percentage of participants with mUFC ≤ ULN at week 36 |
| End point description:   |   |
| The complete response rate in both arms combined at Week 36. A complete responder at Week 36 is defined as a participant who had mean urine free cortisol ≤ upper limit of normal (mUFC ≤ ULN) at Week 36. Participants with missing mUFC at Week 36 were counted as non-responders. |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| At Week 36   |   |

|                                   |                           |  |  |  |
|-----------------------------------|---------------------------|--|--|--|
| <b>End point values</b>           | All participants combined |  |  |  |
| Subject group type                | Subject analysis set      |  |  |  |
| Number of subjects analysed       | 73                        |  |  |  |
| Units: Percentage of participants |                           |  |  |  |
| number (confidence interval 95%)  | 80.8 (69.9 to 89.1)       |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from baseline in mUFC

|                 |                              |
|-----------------|------------------------------|
| End point title | Change from baseline in mUFC |
|-----------------|------------------------------|

End point description:

To assess the change in mean urinary free cortisol (mUFC) from baseline by treatment arm.

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

End point timeframe:

Baseline, weeks 2,5,8,12,14,17,20,23,26,29,32,36,40,48,60,72,84,96

| End point values                             | osilodrostat<br>Group | osilodrostat<br>Placebo Group |  |  |
|--|-----------------------|-------------------------------|--|--|
| Subject group type                           | Reporting group       | Reporting group               |  |  |
| Number of subjects analysed                  | 48                    | 25                            |  |  |
| Units: nmol/24hr                             |                       |                               |  |  |
| arithmetic mean (standard deviation)         |                       |                               |  |  |
| actual - baseline                            | 421.4 (±<br>291.25)   | 451.5 (±<br>535.09)           |  |  |
| change from baseline at week 2<br>(n=47,24)  | -139.3 (±<br>404.45)  | 164.9 (±<br>543.82)           |  |  |
| change from baseline at week 5<br>(n=46,25)  | -252.8 (±<br>338.48)  | -37.3 (±<br>280.84)           |  |  |
| change from baseline at week 8<br>(n=44,25)  | -330.2 (±<br>303.35)  | -35.0 (±<br>325.30)           |  |  |
| change from baseline at week 12<br>(n=44,24) | -332.7 (±<br>315.50)  | -49.1 (±<br>332.29)           |  |  |
| change from baseline at week 14<br>(n=45,25) | -191.7 (±<br>446.77)  | -209.5 (±<br>407.62)          |  |  |
| change from baseline at week 17<br>(n=45,25) | -238.8 (±<br>362.46)  | -284.5 (±<br>557.47)          |  |  |
| change from baseline at week 20<br>(n=44,24) | -294.5 (±<br>316.65)  | -355.1 (±<br>538.96)          |  |  |
| change from baseline at week 23<br>(n=44,25) | -314.1 (±<br>307.60)  | -387.8 (±<br>466.15)          |  |  |
| change from baseline at week 26<br>(n=43,25) | -345.2 (±<br>306.35)  | -365.4 (±<br>458.28)          |  |  |
| change from baseline at week 29<br>(n=43,25) | -331.4 (±<br>299.63)  | -391.4 (±<br>534.57)          |  |  |
| change from baseline at week 32<br>(n=44,25) | -341.3 (±<br>298.96)  | -298.0 (±<br>655.52)          |  |  |
| change from baseline at week 36<br>(n=43,25) | -349.6 (±<br>310.46)  | -372.9 (±<br>519.17)          |  |  |
| change from baseline at week 40<br>(n=43,23) | -333.4 (±<br>307.63)  | -364.7 (±<br>542.28)          |  |  |
| change from baseline at week 48<br>(n=42,22) | -325.1 (±<br>314.30)  | -367.5 (±<br>554.16)          |  |  |
| change from baseline at week 60<br>(n=33,19) | -364.4 (±<br>339.57)  | -335.2 (±<br>571.06)          |  |  |
| change from baseline at week 72<br>(n=31,17) | -381.2 (±<br>338.68)  | -372.4 (±<br>624.69)          |  |  |
| change from baseline at week 84<br>(n=23,17) | -398.6 (±<br>377.81)  | -196.0 (±<br>916.83)          |  |  |
| change from baseline at week 96<br>(n=6,7)   | -414.5 (±<br>347.83)  | -616.4 (±<br>881.92)          |  |  |

## Statistical analyses

**Secondary: Change from baseline in bone mineral density (BMD) by Dual-energy X-ray absorptiometry (DXA) scan at the femoral neck, hip and spinal cord - QC corrected**

|                 |   |
|-----------------|---|
| End point title | Change from baseline in bone mineral density (BMD) by Dual-energy X-ray absorptiometry (DXA) scan at the femoral neck, hip and spinal cord - QC corrected |
|-----------------|---|

## End point description:

The change from baseline in bone mineral density at the femoral neck, hip and spinal cord at Week 48 by treatment arm - QC corrected. An increase in bone mineral density is indicative of an improvement. CFB = change from baseline

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

## End point timeframe:

Baseline, week 48

| End point values                                   | osilodrostat Group | osilodrostat Placebo Group |  |  |
|--|--------------------|----------------------------|--|--|
| Subject group type                                 | Reporting group    | Reporting group            |  |  |
| Number of subjects analysed                        | 48                 | 25                         |  |  |
| Units: g/cm <sup>2</sup>                           |                    |                            |  |  |
| arithmetic mean (standard deviation)               |                    |                            |  |  |
| FEMORAL NECK QC CORRECTED- b/l - (n=43,24)         | 0.8 (± 0.16)       | 0.8 (± 0.14)               |  |  |
| FEMORAL NECK QC CORR - week 48 - CFB (n=28,19)     | 0.0 (± 0.04)       | 0.0 (± 0.03)               |  |  |
| HIP QC CORRECTED - b/l - (n=43,24)                 | 0.9 (± 0.14)       | 0.9 (± 0.11)               |  |  |
| HIP QC CORRECTED - week 48 - CFB (n=28,19)         | 0.0 (± 0.03)       | 0.0 (± 0.02)               |  |  |
| SPINAL CORD QC CORRECTED - b/l (n=42,23)           | 1.0 (± 0.15)       | 1.0 (± 0.18)               |  |  |
| SPINAL CORD QC CORRECTED - week 48 - CFB (n=28,18) | 0.0 (± 0.04)       | 0.0 (± 0.04)               |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Change from baseline in bone mineral density (BMD) T-score by Dual-energy X-ray absorptiometry (DXA) scan at the femoral neck, hip and spinal cord - QC corrected**

|                 |   |
|-----------------|---|
| End point title | Change from baseline in bone mineral density (BMD) T-score by Dual-energy X-ray absorptiometry (DXA) scan at the femoral neck, hip and spinal cord - QC corrected |
|-----------------|---|

## End point description:

The change from baseline in bone mineral density at the femoral neck, hip and spinal cord at Week 48 by treatment arm - QC corrected. An increase in bone mineral density is indicative of an improvement. T-score is the number of standard deviations above or below the mean for a healthy 30-year-old adult of the same sex and ethnicity as the patient. The WHO criteria are: Normal is a T-score of –1.0 or higher". CFB = change from baseline

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

End point timeframe:

Baseline, week 48

| End point values                                   | osilodrostat Group | osilodrostat Placebo Group |  |  |
|--|--------------------|----------------------------|--|--|
| Subject group type                                 | Reporting group    | Reporting group            |  |  |
| Number of subjects analysed                        | 48                 | 25                         |  |  |
| Units: scores on a scale                           |                    |                            |  |  |
| arithmetic mean (standard deviation)               |                    |                            |  |  |
| FEMORAL NECK QC CORRECTED - b/l (n=43,24)          | -1.2 (± 1.06)      | -1.3 (± 0.89)              |  |  |
| FEMORAL NECK QC CORRECTED - CFB at wk 48 (n=28,19) | 0.1 (± 0.30)       | 0.1 (± 0.21)               |  |  |
| HIP QC CORRECTED - b/l - Actual (n=43,24)          | -0.7 (± 1.08)      | -0.8 (± 0.84)              |  |  |
| HIP QC CORRECTED - CFB at wk 48 (n=28,19)          | 0.0 (± 0.27)       | 0.0 (± 0.16)               |  |  |
| SPINAL CORD QC CORRECTED - baseline - (n=42,23)    | -1.2 (± 1.10)      | -1.1 (± 1.40)              |  |  |
| SPINAL CORD QC CORRECTED - CFB at wk 48 (n=28,18)  | 0.1 (± 0.32)       | 0.1 (± 0.33)               |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change in fasting plasma glucose

|   |                                  |
|---|----------------------------------|
| End point title   | Change in fasting plasma glucose |
| End point description:<br>Change from baseline in fasting plasma glucose at Week 12, Week 36, and Week 48 by treatment arm.<br>CFB = change from baseline |                                  |
| End point type  | Secondary                        |
| End point timeframe:<br>Baseline, weeks 12, 36, and 48  |                                  |

| End point values                                   | osilodrostat Group | osilodrostat Placebo Group |  |  |
|--|--------------------|----------------------------|--|--|
| Subject group type                                 | Reporting group    | Reporting group            |  |  |
| Number of subjects analysed                        | 48                 | 25                         |  |  |
| Units: mg/dL                                       |                    |                            |  |  |
| arithmetic mean (standard deviation)               |                    |                            |  |  |
| Fasting glucose (mg/dL) - baseline - (n=47,24)     | 97.3 (± 18.14)     | 91.4 (± 15.15)             |  |  |
| Fasting glucose (mg/dL) - CFB at week 12 (n=44,23) | -4.3 (± 14.84)     | -1.7 (± 10.59)             |  |  |
| Fasting glucose (mg/dL) - CFB at week 36 (n=43,24) | -6.7 (± 12.48)     | -1.1 (± 12.93)             |  |  |

|  |                     |                    |  |  |
|--|---------------------|--------------------|--|--|
| Fasting glucose (mg/dL) - CFB at week 48 (n=41,21) | -5.6 ( $\pm$ 14.13) | 1.8 ( $\pm$ 13.92) |  |  |
|--|---------------------|--------------------|--|--|

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change in Hemoglobin A1C

|   |                          |
|---|--------------------------|
| End point title   | Change in Hemoglobin A1C |
| End point description:<br>Change from baseline in Hemoglobin A1C (%) at Week 12, Week 36, and Week 48 by treatment arm.<br>CFB = change from baseline |                          |
| End point type  | Secondary                |
| End point timeframe:<br>Baseline, weeks 12, 36, and 48  |                          |

| End point values   | osilodrostat Group | osilodrostat Placebo Group |  |  |
|--|--------------------|----------------------------|--|--|
| Subject group type   | Reporting group    | Reporting group            |  |  |
| Number of subjects analysed  | 48                 | 25                         |  |  |
| Units: percentage of Hemoglobin A1C arithmetic mean (standard deviation) |                    |                            |  |  |
| Hemoglobin A1C (%) - baseline  | 6.0 ( $\pm$ 0.92)  | 5.7 ( $\pm$ 0.56)          |  |  |
| Hemoglobin A1C (%) - CFB at week 12 (n=46,24)                            | -0.2 ( $\pm$ 0.44) | 0.0 ( $\pm$ 0.27)          |  |  |
| Hemoglobin A1C (%) CFB at week 36 (n=44,25)                              | -0.2 ( $\pm$ 0.54) | -0.1 ( $\pm$ 0.46)         |  |  |
| Hemoglobin A1C (%) CFB at week 48 (n=41,21)                              | -0.2 ( $\pm$ 0.58) | 0.1 ( $\pm$ 0.37)          |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change in Cholesterol

|   |                       |
|---|-----------------------|
| End point title   | Change in Cholesterol |
| End point description:<br>Change from baseline in Cholesterol (mmol/L) at Week 12, Week 36, and Week 48 by treatment arm.<br>CFB = change from baseline |                       |
| End point type  | Secondary             |
| End point timeframe:<br>Baseline, weeks 12, 36, and 48  |                       |



| End point values                                | osilodrostat Group | osilodrostat Placebo Group |  |  |
|---|--------------------|----------------------------|--|--|
| Subject group type                              | Reporting group    | Reporting group            |  |  |
| Number of subjects analysed                     | 48                 | 25                         |  |  |
| Units: mmol/L                                   |                    |                            |  |  |
| arithmetic mean (standard deviation)            |                    |                            |  |  |
| Cholesterol (mmol/L) - baseline (n=45,25)       | 5.7 ( $\pm$ 1.30)  | 5.3 ( $\pm$ 1.15)          |  |  |
| Cholesterol (mmol/L) - CFB at week 12 (n=44,24) | -0.8 ( $\pm$ 0.95) | 0.0 ( $\pm$ 0.65)          |  |  |
| Cholesterol (mmol/L) - CFB at week 36 (n=44,25) | -1.0 ( $\pm$ 1.28) | -0.4 ( $\pm$ 0.89)         |  |  |
| Cholesterol (mmol/L) - CFB at week 48 (n=42,22) | -0.6 ( $\pm$ 1.36) | -0.4 ( $\pm$ 1.18)         |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change in LDL Cholesterol

|   |                           |
|---|---------------------------|
| End point title   | Change in LDL Cholesterol |
| End point description:  |                           |
| Change from baseline in LDL Cholesterol (mmol/L) at Week 12, Week 36, and Week 48 by treatment arm. |                           |
| CFB = change from baseline  |                           |
| End point type  | Secondary                 |
| End point timeframe:  |                           |
| Baseline, weeks 12, 36, and 48  |                           |

| End point values                                  | osilodrostat Group | osilodrostat Placebo Group |  |  |
|---|--------------------|----------------------------|--|--|
| Subject group type                                | Reporting group    | Reporting group            |  |  |
| Number of subjects analysed                       | 48                 | 25                         |  |  |
| Units: mmol/L                                     |                    |                            |  |  |
| arithmetic mean (standard deviation)              |                    |                            |  |  |
| LDL Cholesterol (mmol/L) - baseline (n=45,24)     | 3.4 ( $\pm$ 1.12)  | 3.0 ( $\pm$ 1.07)          |  |  |
| LDL Cholesterol (mmol/L) - CBF at wk 12 (n=44,23) | -0.5 ( $\pm$ 0.80) | 0.1 ( $\pm$ 0.47)          |  |  |
| LDL Cholesterol (mmol/L) - CFB at wk 36 (n=44,24) | -0.6 ( $\pm$ 1.08) | -0.2 ( $\pm$ 0.70)         |  |  |
| LDL Cholesterol (mmol/L) - CFB at wk 48 (n=41,21) | -0.5 ( $\pm$ 0.99) | -0.2 ( $\pm$ 0.92)         |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change in HDL Cholesterol

|                 |                           |
|-----------------|---------------------------|
| End point title | Change in HDL Cholesterol |
|-----------------|---------------------------|

End point description:

Change from baseline in HDL Cholesterol (mmol/L) at Week 12, Week 36, and Week 48 by treatment arm.

CFB = change from baseline

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

End point timeframe:

Baseline, weeks 12, 36, and 48

| End point values                                  | osilodrostat Group | osilodrostat Placebo Group |  |  |
|---|--------------------|----------------------------|--|--|
| Subject group type                                | Reporting group    | Reporting group            |  |  |
| Number of subjects analysed                       | 48                 | 25                         |  |  |
| Units: mmol/L                                     |                    |                            |  |  |
| arithmetic mean (standard deviation)              |                    |                            |  |  |
| HDL Cholesterol (mmol/L) - baseline (n=45,25)     | 1.6 (± 0.35)       | 1.5 (± 0.38)               |  |  |
| HDL Cholesterol (mmol/L)-CFB at week 12 (n=44,24) | -0.3 (± 0.29)      | 0.0 (± 0.28)               |  |  |
| HDL Cholesterol (mmol/L)-CFB at week 36 (n=44,25) | -0.3 (± 0.27)      | -0.2 (± 0.25)              |  |  |
| HDL Cholesterol (mmol/L)-CFB at week 48 (n=42,22) | -0.2 (± 0.27)      | -0.1 (± 0.29)              |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change in Triglyceride

|                 |                        |
|-----------------|------------------------|
| End point title | Change in Triglyceride |
|-----------------|------------------------|

End point description:

Change from baseline in Triglyceride (mmol/L) at Week 12, Week 36, and Week 48 by treatment arm.

CFB = change from baseline

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

End point timeframe:

Baseline, weeks 12, 36, and 48

| End point values                               | osilodrostat Group | osilodrostat Placebo Group |  |  |
|--|--------------------|----------------------------|--|--|
| Subject group type                             | Reporting group    | Reporting group            |  |  |
| Number of subjects analysed                    | 48                 | 25                         |  |  |
| Units: mmol/L                                  |                    |                            |  |  |
| arithmetic mean (standard deviation)           |                    |                            |  |  |
| Triglyceride (mmol/L)- baseline (n=45,25)      | 1.5 (± 0.79)       | 1.7 (± 0.85)               |  |  |
| Triglyceride (mmol/L)-CFB at week 12(n=44,24)  | 0.0 (± 0.53)       | -0.2 (± 0.54)              |  |  |
| Triglyceride (mmol/L)-CFB at week 36 (n=44,25) | -0.1 (± 0.55)      | -0.1 (± 0.71)              |  |  |
| Triglyceride (mmol/L)-CFB at week 48 (n=42,22) | 0.1 (± 0.92)       | -0.2 (± 0.62)              |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change in Standing Systolic Blood Pressure

|   |  |
|---|--|
| End point title   | Change in Standing Systolic Blood Pressure |
| End point description:<br>Change from baseline in Standing Systolic Blood Pressure (mmHg) at Week 12, Week 36, and Week 48 by treatment arm.<br>CFB = change from baseline<br>BP = blood pressure |  |
| End point type  | Secondary                                  |
| End point timeframe:<br>Baseline, weeks 12, 36, and 48  |  |

| End point values                                | osilodrostat Group | osilodrostat Placebo Group |  |  |
|---|--------------------|----------------------------|--|--|
| Subject group type                              | Reporting group    | Reporting group            |  |  |
| Number of subjects analysed                     | 48                 | 25                         |  |  |
| Units: mmHg                                     |                    |                            |  |  |
| arithmetic mean (standard deviation)            |                    |                            |  |  |
| Standing Systolic Blood Pressure -b/l (n=46,25) | 132.4 (± 19.16)    | 130.0 (± 17.72)            |  |  |
| Standing Systolic BP - CFB at week 12 (n=44,24) | -7.1 (± 18.08)     | -0.9 (± 11.77)             |  |  |
| Standing Systolic BP - CFB at week 36 (n=42,25) | -9.3 (± 19.09)     | -7.0 (± 21.04)             |  |  |
| Standing Systolic BP - CFB at week 48 (n=41,22) | -9.1 (± 19.45)     | -11.0 (± 22.30)            |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change in Supine Systolic Blood Pressure

|                 |  |
|-----------------|--|
| End point title | Change in Supine Systolic Blood Pressure |
|-----------------|--|

End point description:

Change from baseline in Supine Systolic Blood Pressure (mmHg) at Week 12, Week 36, and Week 48 by treatment arm.

CFB = change from baseline

BP = blood pressure

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

End point timeframe:

Baseline, weeks 12, 36, and 48

| End point values                              | osilodrostat Group | osilodrostat Placebo Group |  |  |
|---|--------------------|----------------------------|--|--|
| Subject group type                            | Reporting group    | Reporting group            |  |  |
| Number of subjects analysed                   | 48                 | 25                         |  |  |
| Units: mmHg                                   |                    |                            |  |  |
| arithmetic mean (standard deviation)          |                    |                            |  |  |
| Supine Systolic BP - baseline (n=48,25)       | 131.7 (± 18.33)    | 127.8 (± 18.69)            |  |  |
| Supine Systolic BP - CFB at week 12 (n=46,24) | -8.0 (± 17.54)     | 2.3 (± 15.91)              |  |  |
| Supine Systolic BP - CFB at week 36 (n=42,25) | -9.7 (± 19.88)     | -4.4 (± 17.43)             |  |  |
| Supine Systolic BP - CFB at week 48 (n=42,22) | -7.4 (± 19.38)     | -7.5 (± 18.91)             |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in Standing Diastolic Blood Pressure

|                 |   |
|-----------------|---|
| End point title | Change in Standing Diastolic Blood Pressure |
|-----------------|---|

End point description:

Change from baseline in Standing Diastolic Blood Pressure (mmHg) at Week 12, Week 36, and Week 48 by treatment arm.

CFB = change from baseline

BP = blood pressure

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

End point timeframe:

Baseline, weeks 12, 36, and 48

| End point values                                 | osilodrostat Group | osilodrostat Placebo Group |  |  |
|--|--------------------|----------------------------|--|--|
| Subject group type                               | Reporting group    | Reporting group            |  |  |
| Number of subjects analysed                      | 48                 | 25                         |  |  |
| Units: mmHg                                      |                    |                            |  |  |
| arithmetic mean (standard deviation)             |                    |                            |  |  |
| Standing Diastolic BP - baseline (n=46,25)       | 87.2 (± 12.74)     | 88.2 (± 10.83)             |  |  |
| Standing Diastolic BP - CFB at week 12 (n=44,24) | -4.8 (± 11.14)     | -1.4 (± 9.84)              |  |  |
| Standing Diastolic BP - CFB at week 36 (n=42,25) | -6.0 (± 12.09)     | -4.4 (± 13.98)             |  |  |
| Standing Diastolic BP - CFB at week 48 (n=41,22) | -4.4 (± 11.64)     | -3.9 (± 13.36)             |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in Supine Diastolic Blood Pressure

|  |   |
|--|---|
| End point title  | Change in Supine Diastolic Blood Pressure |
| End point description:<br>Change from baseline in Supine Diastolic Blood Pressure (mmHg) at Week 12, Week 36, and Week 48 by treatment arm.<br>CFB = change from baseline<br>BP = blood pressure |   |
| End point type   | Secondary                                 |
| End point timeframe:<br>Baseline, weeks 12, 36, and 48   |   |

| End point values                               | osilodrostat Group | osilodrostat Placebo Group |  |  |
|--|--------------------|----------------------------|--|--|
| Subject group type                             | Reporting group    | Reporting group            |  |  |
| Number of subjects analysed                    | 48                 | 25                         |  |  |
| Units: mmHg                                    |                    |                            |  |  |
| arithmetic mean (standard deviation)           |                    |                            |  |  |
| Supine Diastolic BP - baseline (n=48,25)       | 83.9 (± 11.71)     | 81.4 (± 11.21)             |  |  |
| Supine Diastolic BP - CFB at week 12 (n=46,24) | -6.3 (± 11.05)     | -0.1 (± 8.31)              |  |  |
| Supine Diastolic BP - CFB at week 36 (n=44,25) | -7.7 (± 11.92)     | -3.4 (± 11.37)             |  |  |
| Supine Diastolic BP - CFB at week 48 (n=41,22) | -5.8 (± 11.60)     | -3.7 (± 10.92)             |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in Weight

|   |                  |
|---|------------------|
| End point title   | Change in Weight |
| End point description:<br>Change from baseline in Weight (kg) at Week 12, Week 36, and Week 48 by treatment arm |                  |
| End point type  | Secondary        |
| End point timeframe:<br>Baseline, weeks 12, 36, and 48  |                  |

| End point values                                 | osilodrostat Group | osilodrostat Placebo Group |  |  |
|--|--------------------|----------------------------|--|--|
| Subject group type                               | Reporting group    | Reporting group            |  |  |
| Number of subjects analysed                      | 48                 | 25                         |  |  |
| Units: kg  |                    |                            |  |  |
| arithmetic mean (standard deviation)             |                    |                            |  |  |
| Weight - baseline (n=48,25)                      | 78.8 (± 17.46)     | 77.3 (± 16.90)             |  |  |
| Weight - change from baseline at wk 12(n=46,24)  | -0.8 (± 3.09)      | -0.1 (± 2.12)              |  |  |
| Weight - change from baseline at wk 36 (n=44,25) | -3.0 (± 5.53)      | -4.8 (± 5.63)              |  |  |
| Weight - change from baseline at wk 48 (n=42,22) | -3.6 (± 6.53)      | -5.5 (± 6.38)              |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in Waist Circumference

|   |                               |
|---|-------------------------------|
| End point title   | Change in Waist Circumference |
| End point description:<br>Change from baseline in Waist Circumference (cm) at Week 12, Week 36, and Week 48 by treatment arm.<br>CFB = change from baseline |                               |
| End point type  | Secondary                     |
| End point timeframe:<br>Baseline, weeks 12, 36, and 48  |                               |

| End point values                     | osilodrostat Group | osilodrostat Placebo Group |  |  |
|--------------------------------------|--------------------|----------------------------|--|--|
| Subject group type                   | Reporting group    | Reporting group            |  |  |
| Number of subjects analysed          | 48                 | 25                         |  |  |
| Units: cm                            |                    |                            |  |  |
| arithmetic mean (standard deviation) |                    |                            |  |  |

|   |                 |                 |  |  |
|---|-----------------|-----------------|--|--|
| Waist Circumference - baseline<br>(n=48,25)       | 102.5 (± 17.01) | 103.4 (± 15.52) |  |  |
| Waist Circumference- CFB at week 12<br>(n=46,24)  | -1.0 (± 4.43)   | -0.5 (± 3.35)   |  |  |
| Waist Circumference- CFB at week 36<br>(n=44,25)  | -3.9 (± 6.36)   | -2.1 (± 8.60)   |  |  |
| Waist Circumference - CFB at week 48<br>(n=42,22) | -4.1 (± 6.10)   | -5.3 (± 5.68)   |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from baseline in Standardized Health Related Quality of Life score, using Cushing Disease-specific Quality of Life Patient Reported Outcome (PRO) Assessment

|                 |   |
|-----------------|---|
| End point title | Change from baseline in Standardized Health Related Quality of Life score, using Cushing Disease-specific Quality of Life Patient Reported Outcome (PRO) Assessment |
|-----------------|---|

End point description:

The CushingQoL is a valid and reliable disease-specific QoL questionnaire which assesses health-related quality of life (HRQoL) in patients with Cushing's syndrome and has been validated in patients with Cushing's disease. The CushingQoL consists of questions reflecting dimensions of HRQoL related to physical aspects (e.g. 'I bruise easily'), psychological aspects (e.g. 'I am more irritable, I have sudden mood swings and angry outbursts'), and social aspects (e.g. 'I have had to give up my social or leisure activities due to my illness').

The questionnaire consists of 12 items measured on a five point Likert-type scale assessing how often or how much each item has been related to the patient's Cushing's disease in the previous week. The raw score is calculated by summing the individual item scores prior to being standardized so that the total score ranges from 0 to 100. Increases from baseline are indicative of an improvement.

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

End point timeframe:

Baseline to Week 12 and 48, Week 12 to Week 36, Week 36 to Week 48.

| End point values                                    | osilodrostat Group | osilodrostat Placebo Group |  |  |
|---|--------------------|----------------------------|--|--|
| Subject group type                                  | Reporting group    | Reporting group            |  |  |
| Number of subjects analysed                         | 48                 | 25                         |  |  |
| Units: Scores on a scale                            |                    |                            |  |  |
| arithmetic mean (standard deviation)                |                    |                            |  |  |
| Actual - Baseline (n=48,25)                         | 49.1 (± 19.60)     | 56.9 (± 18.99)             |  |  |
| Actual Change from Baseline at Week 12<br>(n=46,24) | 6.2 (± 14.85)      | 8.6 (± 12.06)              |  |  |
| Actual Change from Baseline at Week 48<br>(n=42,22) | 11.7 (± 16.30)     | 12.8 (± 14.24)             |  |  |
| Actual Change from Week 12 at Week 36<br>(n=44,23)  | 4.7 (± 9.01)       | -0.5 (± 9.99)              |  |  |
| Actual Change from Week 36 at Week 48<br>(n=42,22)  | 0.1 (± 8.43)       | 2.5 (± 7.52)               |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change from baseline in Standardized Psychosocial issues score, using Cushing Disease-specific Quality of Life Patient Reported Outcome (PRO) Assessment

|                 |  |
|-----------------|--|
| End point title | Change from baseline in Standardized Psychosocial issues score, using Cushing Disease-specific Quality of Life Patient Reported Outcome (PRO) Assessment |
|-----------------|--|

#### End point description:

The CushingQoL is a valid and reliable disease-specific QoL questionnaire which assesses health-related quality of life (HRQoL) in patients with Cushing's syndrome and has been validated in patients with Cushing's disease. The CushingQoL consists of questions reflecting dimensions of HRQoL related to physical aspects (e.g. 'I bruise easily'), psychological aspects (e.g. 'I am more irritable, I have sudden mood swings and angry outbursts'), and social aspects (e.g. 'I have had to give up my social or leisure activities due to my illness').

The questionnaire consists of 12 items measured on a five point Likert-type scale assessing how often or how much each item has been related to the patient's Cushing's disease in the previous week. The raw score is calculated by summing the individual item scores prior to being standardized so that the total score ranges from 0 to 100. Increases from baseline are indicative of an improvement.

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

#### End point timeframe:

Baseline to Week 12 and 48, Week 12 to Week 36, Week 36 to Week 48.

| End point values                                 | osilodrostat Group | osilodrostat Placebo Group |  |  |
|--|--------------------|----------------------------|--|--|
| Subject group type                               | Reporting group    | Reporting group            |  |  |
| Number of subjects analysed                      | 48                 | 25                         |  |  |
| Units: Scores on a scale                         |                    |                            |  |  |
| arithmetic mean (standard deviation)             |                    |                            |  |  |
| Actual - baseline (n=48,25)                      | 49.9 (± 20.34)     | 56.7 (± 21.11)             |  |  |
| Actual Change from Baseline at Week 12 (n=46,24) | 6.1 (± 17.21)      | 9.6 (± 13.61)              |  |  |
| Actual Change from Baseline at Week 48 (n=42,22) | 11.1 (± 17.84)     | 13.0 (± 16.30)             |  |  |
| Actual Change from Week 12 at Week 36 (n=44,23)  | 4.1 (± 9.94)       | -1.3 (± 12.36)             |  |  |
| Actual Change from Week 36 at Week 48 (n=42,22)  | 0.1 (± 9.60)       | 2.4 (± 8.96)               |  |  |

## Statistical analyses



## Secondary: Change from baseline in Standardized Physical problems score, using Cushing Disease-specific Quality of Life Patient Reported Outcome (PRO) Assessment

|                 |  |
|-----------------|--|
| End point title | Change from baseline in Standardized Physical problems score, using Cushing Disease-specific Quality of Life Patient Reported Outcome (PRO) Assessment |
|-----------------|--|

### End point description:

The CushingQoL is a valid and reliable disease-specific QoL questionnaire which assesses health-related quality of life (HRQoL) in patients with Cushing's syndrome and has been validated in patients with Cushing's disease. The CushingQoL consists of questions reflecting dimensions of HRQoL related to physical aspects (e.g. 'I bruise easily'), psychological aspects (e.g. 'I am more irritable, I have sudden mood swings and angry outbursts'), and social aspects (e.g. 'I have had to give up my social or leisure activities due to my illness').

The questionnaire consists of 12 items measured on a five point Likert-type scale assessing how often or how much each item has been related to the patient's Cushing's disease in the previous week. The raw score is calculated by summing the individual item scores prior to being standardized so that the total score ranges from 0 to 100. Increases from baseline are indicative of an improvement.

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

### End point timeframe:

Baseline to Week 12 and 48, Week 12 to Week 36, Week 36 to Week 48.

| End point values                                 | osilodrostat Group | osilodrostat Placebo Group |  |  |
|--|--------------------|----------------------------|--|--|
| Subject group type                               | Reporting group    | Reporting group            |  |  |
| Number of subjects analysed                      | 48                 | 25                         |  |  |
| Units: Scores on a scale                         |                    |                            |  |  |
| arithmetic mean (standard deviation)             |                    |                            |  |  |
| Actual - baseline (n=48,25)                      | 46.9 (± 22.32)     | 57.7 (± 21.91)             |  |  |
| Actual Change from Baseline at Week 12 (n=46,24) | 6.3 (± 13.29)      | 5.6 (± 13.38)              |  |  |
| Actual Change from Baseline at Week 48 (n=42,22) | 13.3 (± 19.83)     | 12.1 (± 15.59)             |  |  |
| Actual Change from Week 12 at Week 36 (n=44,23)  | 6.6 (± 12.40)      | 2.2 (± 12.11)              |  |  |
| Actual Change from Week 36 at Week 48 (n=42,22)  | 23.59 (± 11.27)    | 2.7 (± 12.17)              |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from baseline in serum cortisol

|                 |  |
|-----------------|--|
| End point title | Change from baseline in serum cortisol |
|-----------------|--|

### End point description:

Change from baseline in serum cortisol

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

### End point timeframe:

Baseline, Week 12, Week 36, Week 48

| End point values                                 | osilodrostat Group | osilodrostat Placebo Group |  |  |
|--|--------------------|----------------------------|--|--|
| Subject group type                               | Reporting group    | Reporting group            |  |  |
| Number of subjects analysed                      | 48                 | 25                         |  |  |
| Units: nmol/L                                    |                    |                            |  |  |
| arithmetic mean (standard deviation)             |                    |                            |  |  |
| Baseline - actual (n=47,25)                      | 565.8 (± 169.01)   | 486.1 (± 198.12)           |  |  |
| Actual Change from Baseline at Week 12 (n=44,24) | -276.0 (± 178.43)  | 73.0 (± 185.29)            |  |  |
| Actual Change from Baseline at Week 36 (n=42,25) | -267.0 (± 174.18)  | -157.8 (± 225.56)          |  |  |
| Actual Change from Baseline at Week 48 (n=41,22) | -210.7 (± 161.07)  | -131.0 (± 236.88)          |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from baseline in late night saliva cortisol

|   |  |
|---|--|
| End point title   | Change from baseline in late night saliva cortisol |
| End point description:                                      |  |
| Change from baseline in late night saliva cortisol (nmol/L) |  |
| End point type  | Secondary  |
| End point timeframe:  |  |
| Baseline, Week 12, Week 36, Week 48                         |  |

| End point values                                 | osilodrostat Group | osilodrostat Placebo Group |  |  |
|--|--------------------|----------------------------|--|--|
| Subject group type                               | Reporting group    | Reporting group            |  |  |
| Number of subjects analysed                      | 48                 | 25                         |  |  |
| Units: nmol/L                                    |                    |                            |  |  |
| arithmetic mean (standard deviation)             |                    |                            |  |  |
| Baseline - actual (n=48,25)                      | 11.7 (± 28.68)     | 9.0 (± 6.74)               |  |  |
| Actual Change from Baseline at Week 12 (n=46,24) | -8.5 (± 29.60)     | 1.3 (± 8.87)               |  |  |
| Actual Change from Baseline at Week 36 (n=42,25) | -9.6 (± 30.82)     | -5.8 (± 6.84)              |  |  |
| Actual Change from Baseline at Week 48 (n=41,22) | -9.3 (± 29.05)     | -5.0 (± 5.75)              |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change from baseline in morning saliva cortisol

End point title Change from baseline in morning saliva cortisol

End point description:

Change from baseline in morning saliva cortisol (nmol/L)

End point type Secondary

End point timeframe:

Baseline, Week 12, Week 36, Week 48

| End point values                                 | osilodrostat Group | osilodrostat Placebo Group |  |  |
|--|--------------------|----------------------------|--|--|
| Subject group type                               | Reporting group    | Reporting group            |  |  |
| Number of subjects analysed                      | 48                 | 25                         |  |  |
| Units: nmol/L                                    |                    |                            |  |  |
| arithmetic mean (standard deviation)             |                    |                            |  |  |
| Baseline - actual (n=48,25)                      | 17.2 (± 30.00)     | 14.1 (± 12.29)             |  |  |
| Actual Change from Baseline at Week 12 (n=46,24) | -11.6 (± 30.05)    | -0.3 (± 11.21)             |  |  |
| Actual Change from Baseline at Week 36 (n=40,25) | -11.8 (± 30.74)    | -9.3 (± 11.82)             |  |  |
| Actual Change from Baseline at Week 48 (n=41,22) | -11.8 (± 31.74)    | -6.0 (± 10.97)             |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from baseline in hair cortisol levels

End point title Change from baseline in hair cortisol levels

End point description:

Change from baseline in hair cortisol levels

End point type Secondary

End point timeframe:

Baseline, Week 26, Week 48

| End point values                                | osilodrostat Group | osilodrostat Placebo Group |  |  |
|---|--------------------|----------------------------|--|--|
| Subject group type                              | Reporting group    | Reporting group            |  |  |
| Number of subjects analysed                     | 48                 | 25                         |  |  |
| Units: pg/mg                                    |                    |                            |  |  |
| arithmetic mean (standard deviation)            |                    |                            |  |  |
| Baseline - actual (n=19,9)                      | 38.9 (± 37.48)     | 10.5 (± 10.47)             |  |  |
| Actual Change from Baseline at Week 26 (n=16,7) | -15.8 (± 32.83)    | -1.1 (± 12.72)             |  |  |

|  |                 |               |  |  |
|--|-----------------|---------------|--|--|
| Actual Change from Baseline at Week 48<br>(n=14,6) | -17.8 (± 26.66) | -9.7 (± 8.90) |  |  |
|--|-----------------|---------------|--|--|

## Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events are reported from first dose of study treatment until end of study treatment plus 8 weeks post treatment, up to maximum duration of 116.7 weeks.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 23.1 |
|--------------------|------|

### Reporting groups

|                       |   |
|-----------------------|---|
| Reporting group title | Placebo controlled period@ Osilodrostat arm |
|-----------------------|---|

Reporting group description:

Placebo controlled period@ Osilodrostat arm

|                       |  |
|-----------------------|--|
| Reporting group title | Placebo controlled period@ Placebo arm |
|-----------------------|--|

Reporting group description:

Placebo controlled period@ Placebo arm

|                       |   |
|-----------------------|---|
| Reporting group title | Overall study period@ Osilodrostat@(Osilodrostat arm) |
|-----------------------|---|

Reporting group description:

Overall study period@ Osilodrostat@(Osilodrostat arm)

|                       |  |
|-----------------------|--|
| Reporting group title | Overall study period@ Osilodrostat@(Placebo arm) |
|-----------------------|--|

Reporting group description:

Overall study period@ Osilodrostat@(Placebo arm)

|                       |                                    |
|-----------------------|------------------------------------|
| Reporting group title | Overall study period@ All Patients |
|-----------------------|------------------------------------|

Reporting group description:

Overall study period@ All Patients

| <b>Serious adverse events</b>                     | Placebo controlled period@ Osilodrostat arm | Placebo controlled period@ Placebo arm | Overall study period@ Osilodrostat@(Osilodrostat arm) |
|---|---|--|---|
| Total subjects affected by serious adverse events |   |  |   |
| subjects affected / exposed                       | 2 / 48 (4.17%)                              | 1 / 25 (4.00%)                         | 10 / 48 (20.83%)                                      |
| number of deaths (all causes)                     | 0   | 0                                      | 0   |
| number of deaths resulting from adverse events    | 0   | 0                                      | 0   |
| Investigations                                    |   |  |   |
| Electrocardiogram QT prolonged                    |   |  |   |
| subjects affected / exposed                       | 0 / 48 (0.00%)                              | 0 / 25 (0.00%)                         | 1 / 48 (2.08%)  |
| occurrences causally related to treatment / all   | 0 / 0                                       | 0 / 0                                  | 1 / 1   |
| deaths causally related to treatment / all        | 0 / 0                                       | 0 / 0                                  | 0 / 0   |
| Electrocardiogram T wave inversion                |   |  |   |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed   | 1 / 48 (2.08%) | 0 / 25 (0.00%) | 1 / 48 (2.08%) |
| occurrences causally related to treatment / all                     | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          | 0 / 0          |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                |                |                |
| Uterine leiomyoma   |                |                |                |
| subjects affected / exposed   | 0 / 48 (0.00%) | 0 / 25 (0.00%) | 1 / 48 (2.08%) |
| occurrences causally related to treatment / all                     | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          | 0 / 0          |
| Injury, poisoning and procedural complications                      |                |                |                |
| Conjunctival laceration   |                |                |                |
| subjects affected / exposed   | 0 / 48 (0.00%) | 0 / 25 (0.00%) | 1 / 48 (2.08%) |
| occurrences causally related to treatment / all                     | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          | 0 / 0          |
| Eye injury  |                |                |                |
| subjects affected / exposed   | 0 / 48 (0.00%) | 0 / 25 (0.00%) | 1 / 48 (2.08%) |
| occurrences causally related to treatment / all                     | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          | 0 / 0          |
| Retinal injury  |                |                |                |
| subjects affected / exposed   | 0 / 48 (0.00%) | 0 / 25 (0.00%) | 1 / 48 (2.08%) |
| occurrences causally related to treatment / all                     | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          | 0 / 0          |
| Wrist fracture  |                |                |                |
| subjects affected / exposed   | 0 / 48 (0.00%) | 0 / 25 (0.00%) | 1 / 48 (2.08%) |
| occurrences causally related to treatment / all                     | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          | 0 / 0          |
| Vascular disorders  |                |                |                |
| Hypertension  |                |                |                |
| subjects affected / exposed   | 0 / 48 (0.00%) | 0 / 25 (0.00%) | 1 / 48 (2.08%) |
| occurrences causally related to treatment / all                     | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          | 0 / 0          |
| Hypotension   |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 48 (0.00%) | 0 / 25 (0.00%) | 1 / 48 (2.08%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Orthostatic hypotension                         |                |                |                |
| subjects affected / exposed                     | 0 / 48 (0.00%) | 0 / 25 (0.00%) | 1 / 48 (2.08%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Nervous system disorders                        |                |                |                |
| Cerebral vascular occlusion                     |                |                |                |
| subjects affected / exposed                     | 0 / 48 (0.00%) | 0 / 25 (0.00%) | 1 / 48 (2.08%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hemiparesis                                     |                |                |                |
| subjects affected / exposed                     | 0 / 48 (0.00%) | 0 / 25 (0.00%) | 1 / 48 (2.08%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastrointestinal disorders                      |                |                |                |
| Abdominal pain                                  |                |                |                |
| subjects affected / exposed                     | 0 / 48 (0.00%) | 0 / 25 (0.00%) | 1 / 48 (2.08%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Erosive duodenitis                              |                |                |                |
| subjects affected / exposed                     | 1 / 48 (2.08%) | 0 / 25 (0.00%) | 1 / 48 (2.08%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Nausea  |                |                |                |
| subjects affected / exposed                     | 0 / 48 (0.00%) | 0 / 25 (0.00%) | 1 / 48 (2.08%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Respiratory, thoracic and mediastinal disorders |                |                |                |
| Dyspnoea  |                |                |                |
| subjects affected / exposed                     | 0 / 48 (0.00%) | 0 / 25 (0.00%) | 1 / 48 (2.08%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Obstructive airways disorder                    |                |                |                |
| subjects affected / exposed                     | 0 / 48 (0.00%) | 0 / 25 (0.00%) | 1 / 48 (2.08%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Endocrine disorders                             |                |                |                |
| Adrenal insufficiency                           |                |                |                |
| subjects affected / exposed                     | 0 / 48 (0.00%) | 0 / 25 (0.00%) | 3 / 48 (6.25%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 3 / 3          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Musculoskeletal and connective tissue disorders |                |                |                |
| Myalgia   |                |                |                |
| subjects affected / exposed                     | 0 / 48 (0.00%) | 0 / 25 (0.00%) | 1 / 48 (2.08%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Periarthritis                                   |                |                |                |
| subjects affected / exposed                     | 0 / 48 (0.00%) | 0 / 25 (0.00%) | 1 / 48 (2.08%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Infections and infestations                     |                |                |                |
| Anal abscess                                    |                |                |                |
| subjects affected / exposed                     | 0 / 48 (0.00%) | 0 / 25 (0.00%) | 1 / 48 (2.08%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Dengue fever                                    |                |                |                |
| subjects affected / exposed                     | 1 / 48 (2.08%) | 0 / 25 (0.00%) | 1 / 48 (2.08%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pneumonia                                       |                |                |                |
| subjects affected / exposed                     | 0 / 48 (0.00%) | 1 / 25 (4.00%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pyelonephritis                                  |                |                |                |



|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 48 (0.00%) | 0 / 25 (0.00%) | 1 / 48 (2.08%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

| <b>Serious adverse events</b>                                       | Overall study period@<br>Osilodrostat@ (Placebo arm) | Overall study period@ All Patients |  |
|---|--|------------------------------------|--|
| Total subjects affected by serious adverse events                   |  |                                    |  |
| subjects affected / exposed   | 0 / 25 (0.00%)                                       | 10 / 73 (13.70%)                   |  |
| number of deaths (all causes)                                       | 0  | 0                                  |  |
| number of deaths resulting from adverse events                      | 0  | 0                                  |  |
| Investigations  |  |                                    |  |
| Electrocardiogram QT prolonged                                      |  |                                    |  |
| subjects affected / exposed   | 0 / 25 (0.00%)                                       | 1 / 73 (1.37%)                     |  |
| occurrences causally related to treatment / all                     | 0 / 0  | 1 / 1                              |  |
| deaths causally related to treatment / all                          | 0 / 0  | 0 / 0                              |  |
| Electrocardiogram T wave inversion                                  |  |                                    |  |
| subjects affected / exposed   | 0 / 25 (0.00%)                                       | 1 / 73 (1.37%)                     |  |
| occurrences causally related to treatment / all                     | 0 / 0  | 0 / 1                              |  |
| deaths causally related to treatment / all                          | 0 / 0  | 0 / 0                              |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |  |                                    |  |
| Uterine leiomyoma   |  |                                    |  |
| subjects affected / exposed   | 0 / 25 (0.00%)                                       | 1 / 73 (1.37%)                     |  |
| occurrences causally related to treatment / all                     | 0 / 0  | 0 / 1                              |  |
| deaths causally related to treatment / all                          | 0 / 0  | 0 / 0                              |  |
| Injury, poisoning and procedural complications                      |  |                                    |  |
| Conjunctival laceration   |  |                                    |  |
| subjects affected / exposed   | 0 / 25 (0.00%)                                       | 1 / 73 (1.37%)                     |  |
| occurrences causally related to treatment / all                     | 0 / 0  | 0 / 1                              |  |
| deaths causally related to treatment / all                          | 0 / 0  | 0 / 0                              |  |
| Eye injury  |  |                                    |  |
| subjects affected / exposed   | 0 / 25 (0.00%)                                       | 1 / 73 (1.37%)                     |  |
| occurrences causally related to treatment / all                     | 0 / 0  | 0 / 1                              |  |
| deaths causally related to treatment / all                          | 0 / 0  | 0 / 0                              |  |
| Retinal injury  |  |                                    |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 25 (0.00%) | 1 / 73 (1.37%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Wrist fracture                                  |                |                |  |
| subjects affected / exposed                     | 0 / 25 (0.00%) | 1 / 73 (1.37%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Vascular disorders                              |                |                |  |
| Hypertension                                    |                |                |  |
| subjects affected / exposed                     | 0 / 25 (0.00%) | 1 / 73 (1.37%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Hypotension                                     |                |                |  |
| subjects affected / exposed                     | 0 / 25 (0.00%) | 1 / 73 (1.37%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Orthostatic hypotension                         |                |                |  |
| subjects affected / exposed                     | 0 / 25 (0.00%) | 1 / 73 (1.37%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Nervous system disorders                        |                |                |  |
| Cerebral vascular occlusion                     |                |                |  |
| subjects affected / exposed                     | 0 / 25 (0.00%) | 1 / 73 (1.37%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Hemiparesis                                     |                |                |  |
| subjects affected / exposed                     | 0 / 25 (0.00%) | 1 / 73 (1.37%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Gastrointestinal disorders                      |                |                |  |
| Abdominal pain                                  |                |                |  |
| subjects affected / exposed                     | 0 / 25 (0.00%) | 1 / 73 (1.37%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

|   |                |                |  |
|---|----------------|----------------|--|
| Erosive duodenitis                              |                |                |  |
| subjects affected / exposed                     | 0 / 25 (0.00%) | 1 / 73 (1.37%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Nausea  |                |                |  |
| subjects affected / exposed                     | 0 / 25 (0.00%) | 1 / 73 (1.37%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Respiratory, thoracic and mediastinal disorders |                |                |  |
| Dyspnoea  |                |                |  |
| subjects affected / exposed                     | 0 / 25 (0.00%) | 1 / 73 (1.37%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Obstructive airways disorder                    |                |                |  |
| subjects affected / exposed                     | 0 / 25 (0.00%) | 1 / 73 (1.37%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Endocrine disorders                             |                |                |  |
| Adrenal insufficiency                           |                |                |  |
| subjects affected / exposed                     | 0 / 25 (0.00%) | 3 / 73 (4.11%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 3 / 3          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Musculoskeletal and connective tissue disorders |                |                |  |
| Myalgia   |                |                |  |
| subjects affected / exposed                     | 0 / 25 (0.00%) | 1 / 73 (1.37%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Periarthritis                                   |                |                |  |
| subjects affected / exposed                     | 0 / 25 (0.00%) | 1 / 73 (1.37%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Infections and infestations                     |                |                |  |
| Anal abscess                                    |                |                |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 25 (0.00%) | 1 / 73 (1.37%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Dengue fever                                    |                |                |  |
| subjects affected / exposed                     | 0 / 25 (0.00%) | 1 / 73 (1.37%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pneumonia                                       |                |                |  |
| subjects affected / exposed                     | 0 / 25 (0.00%) | 0 / 73 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pyelonephritis                                  |                |                |  |
| subjects affected / exposed                     | 0 / 25 (0.00%) | 1 / 73 (1.37%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

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

| <b>Non-serious adverse events</b>                     | Placebo controlled period@ Osilodrostat arm | Placebo controlled period@ Placebo arm | Overall study period@ Osilodrostat@ (Osilodrostat arm) |
|---|---|--|--|
| Total subjects affected by non-serious adverse events |   |  |  |
| subjects affected / exposed                           | 45 / 48 (93.75%)                            | 21 / 25 (84.00%)                       | 47 / 48 (97.92%)                                       |
| Vascular disorders                                    |   |  |  |
| Hypertension  |   |  |  |
| subjects affected / exposed                           | 7 / 48 (14.58%)                             | 7 / 25 (28.00%)                        | 12 / 48 (25.00%)                                       |
| occurrences (all)                                     | 7   | 7                                      | 18   |
| Hypotension   |   |  |  |
| subjects affected / exposed                           | 5 / 48 (10.42%)                             | 0 / 25 (0.00%)                         | 9 / 48 (18.75%)  |
| occurrences (all)                                     | 5   | 0                                      | 10   |
| Orthostatic hypotension                               |   |  |  |
| subjects affected / exposed                           | 4 / 48 (8.33%)                              | 0 / 25 (0.00%)                         | 7 / 48 (14.58%)  |
| occurrences (all)                                     | 4   | 0                                      | 8  |
| General disorders and administration site conditions  |   |  |  |

|   |                  |                 |                  |
|---|------------------|-----------------|------------------|
| Asthenia  |                  |                 |                  |
| subjects affected / exposed                     | 11 / 48 (22.92%) | 0 / 25 (0.00%)  | 15 / 48 (31.25%) |
| occurrences (all)                               | 11               | 0               | 18               |
| Fatigue   |                  |                 |                  |
| subjects affected / exposed                     | 12 / 48 (25.00%) | 4 / 25 (16.00%) | 23 / 48 (47.92%) |
| occurrences (all)                               | 13               | 4               | 36               |
| Oedema peripheral                               |                  |                 |                  |
| subjects affected / exposed                     | 5 / 48 (10.42%)  | 0 / 25 (0.00%)  | 12 / 48 (25.00%) |
| occurrences (all)                               | 6                | 0               | 13               |
| Pyrexia   |                  |                 |                  |
| subjects affected / exposed                     | 2 / 48 (4.17%)   | 0 / 25 (0.00%)  | 5 / 48 (10.42%)  |
| occurrences (all)                               | 2                | 0               | 5                |
| Respiratory, thoracic and mediastinal disorders |                  |                 |                  |
| Cough   |                  |                 |                  |
| subjects affected / exposed                     | 0 / 48 (0.00%)   | 0 / 25 (0.00%)  | 4 / 48 (8.33%)   |
| occurrences (all)                               | 0                | 0               | 4                |
| Dyspnoea  |                  |                 |                  |
| subjects affected / exposed                     | 1 / 48 (2.08%)   | 0 / 25 (0.00%)  | 2 / 48 (4.17%)   |
| occurrences (all)                               | 1                | 0               | 2                |
| Epistaxis                                       |                  |                 |                  |
| subjects affected / exposed                     | 0 / 48 (0.00%)   | 0 / 25 (0.00%)  | 0 / 48 (0.00%)   |
| occurrences (all)                               | 0                | 0               | 0                |
| Nasal congestion                                |                  |                 |                  |
| subjects affected / exposed                     | 1 / 48 (2.08%)   | 0 / 25 (0.00%)  | 3 / 48 (6.25%)   |
| occurrences (all)                               | 1                | 0               | 3                |
| Psychiatric disorders                           |                  |                 |                  |
| Anxiety   |                  |                 |                  |
| subjects affected / exposed                     | 0 / 48 (0.00%)   | 0 / 25 (0.00%)  | 2 / 48 (4.17%)   |
| occurrences (all)                               | 0                | 0               | 2                |
| Investigations                                  |                  |                 |                  |
| Alanine aminotransferase increased              |                  |                 |                  |
| subjects affected / exposed                     | 2 / 48 (4.17%)   | 2 / 25 (8.00%)  | 3 / 48 (6.25%)   |
| occurrences (all)                               | 2                | 2               | 3                |
| Aspartate aminotransferase increased            |                  |                 |                  |
| subjects affected / exposed                     | 1 / 48 (2.08%)   | 0 / 25 (0.00%)  | 2 / 48 (4.17%)   |
| occurrences (all)                               | 1                | 0               | 2                |

|  |                       |                      |                        |
|--|-----------------------|----------------------|------------------------|
| Blood cholesterol increased<br>subjects affected / exposed<br>occurrences (all)                            | 2 / 48 (4.17%)<br>2   | 1 / 25 (4.00%)<br>1  | 3 / 48 (6.25%)<br>8    |
| Blood potassium decreased<br>subjects affected / exposed<br>occurrences (all)                              | 1 / 48 (2.08%)<br>1   | 1 / 25 (4.00%)<br>1  | 2 / 48 (4.17%)<br>2    |
| Blood pressure increased<br>subjects affected / exposed<br>occurrences (all)                               | 1 / 48 (2.08%)<br>1   | 1 / 25 (4.00%)<br>1  | 3 / 48 (6.25%)<br>3    |
| Blood testosterone increased<br>subjects affected / exposed<br>occurrences (all)                           | 5 / 48 (10.42%)<br>5  | 0 / 25 (0.00%)<br>0  | 13 / 48 (27.08%)<br>13 |
| Electrocardiogram T wave inversion<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 48 (0.00%)<br>0   | 1 / 25 (4.00%)<br>1  | 0 / 48 (0.00%)<br>0    |
| Renin increased<br>subjects affected / exposed<br>occurrences (all)  | 1 / 48 (2.08%)<br>1   | 0 / 25 (0.00%)<br>0  | 1 / 48 (2.08%)<br>1    |
| Weight decreased<br>subjects affected / exposed<br>occurrences (all)                                       | 2 / 48 (4.17%)<br>2   | 0 / 25 (0.00%)<br>0  | 3 / 48 (6.25%)<br>3    |
| Injury, poisoning and procedural complications<br>Fall<br>subjects affected / exposed<br>occurrences (all) | 2 / 48 (4.17%)<br>2   | 0 / 25 (0.00%)<br>0  | 4 / 48 (8.33%)<br>4    |
| Cardiac disorders<br>Palpitations<br>subjects affected / exposed<br>occurrences (all)                      | 0 / 48 (0.00%)<br>0   | 2 / 25 (8.00%)<br>2  | 2 / 48 (4.17%)<br>2    |
| Tachycardia<br>subjects affected / exposed<br>occurrences (all)  | 6 / 48 (12.50%)<br>6  | 0 / 25 (0.00%)<br>0  | 8 / 48 (16.67%)<br>8   |
| Nervous system disorders<br>Dizziness<br>subjects affected / exposed<br>occurrences (all)                  | 9 / 48 (18.75%)<br>12 | 4 / 25 (16.00%)<br>4 | 19 / 48 (39.58%)<br>25 |

|  |                        |                      |                        |
|--|------------------------|----------------------|------------------------|
| Paraesthesia<br>subjects affected / exposed<br>occurrences (all)                                       | 0 / 48 (0.00%)<br>0    | 0 / 25 (0.00%)<br>0  | 4 / 48 (8.33%)<br>4    |
| Headache<br>subjects affected / exposed<br>occurrences (all)   | 7 / 48 (14.58%)<br>8   | 6 / 25 (24.00%)<br>8 | 17 / 48 (35.42%)<br>27 |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all)    | 2 / 48 (4.17%)<br>2    | 2 / 25 (8.00%)<br>2  | 2 / 48 (4.17%)<br>2    |
| Gastrointestinal disorders<br>Abdominal distension<br>subjects affected / exposed<br>occurrences (all) | 3 / 48 (6.25%)<br>3    | 1 / 25 (4.00%)<br>1  | 4 / 48 (8.33%)<br>4    |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)                                     | 4 / 48 (8.33%)<br>4    | 0 / 25 (0.00%)<br>0  | 10 / 48 (20.83%)<br>11 |
| Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all)                               | 1 / 48 (2.08%)<br>1    | 1 / 25 (4.00%)<br>1  | 3 / 48 (6.25%)<br>3    |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)  | 10 / 48 (20.83%)<br>11 | 0 / 25 (0.00%)<br>0  | 14 / 48 (29.17%)<br>20 |
| Nausea<br>subjects affected / exposed<br>occurrences (all)   | 15 / 48 (31.25%)<br>21 | 3 / 25 (12.00%)<br>5 | 22 / 48 (45.83%)<br>40 |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)   | 5 / 48 (10.42%)<br>5   | 0 / 25 (0.00%)<br>0  | 9 / 48 (18.75%)<br>9   |
| Skin and subcutaneous tissue disorders<br>Acne<br>subjects affected / exposed<br>occurrences (all)     | 2 / 48 (4.17%)<br>3    | 0 / 25 (0.00%)<br>0  | 9 / 48 (18.75%)<br>11  |
| Alopecia<br>subjects affected / exposed<br>occurrences (all)   | 1 / 48 (2.08%)<br>1    | 1 / 25 (4.00%)<br>1  | 4 / 48 (8.33%)<br>7    |
| Dry skin   |                        |                      |                        |

|   |                  |                 |                  |
|---|------------------|-----------------|------------------|
| subjects affected / exposed                     | 3 / 48 (6.25%)   | 0 / 25 (0.00%)  | 3 / 48 (6.25%)   |
| occurrences (all)                               | 3                | 0               | 6                |
| Eczema  |                  |                 |                  |
| subjects affected / exposed                     | 0 / 48 (0.00%)   | 0 / 25 (0.00%)  | 2 / 48 (4.17%)   |
| occurrences (all)                               | 0                | 0               | 3                |
| Pruritus  |                  |                 |                  |
| subjects affected / exposed                     | 6 / 48 (12.50%)  | 0 / 25 (0.00%)  | 7 / 48 (14.58%)  |
| occurrences (all)                               | 6                | 0               | 11               |
| Hirsutism                                       |                  |                 |                  |
| subjects affected / exposed                     | 0 / 48 (0.00%)   | 1 / 25 (4.00%)  | 6 / 48 (12.50%)  |
| occurrences (all)                               | 0                | 1               | 6                |
| Skin hyperpigmentation                          |                  |                 |                  |
| subjects affected / exposed                     | 2 / 48 (4.17%)   | 0 / 25 (0.00%)  | 3 / 48 (6.25%)   |
| occurrences (all)                               | 2                | 0               | 5                |
| Renal and urinary disorders                     |                  |                 |                  |
| Renal colic                                     |                  |                 |                  |
| subjects affected / exposed                     | 0 / 48 (0.00%)   | 1 / 25 (4.00%)  | 0 / 48 (0.00%)   |
| occurrences (all)                               | 0                | 1               | 0                |
| Endocrine disorders                             |                  |                 |                  |
| Adrenal insufficiency                           |                  |                 |                  |
| subjects affected / exposed                     | 7 / 48 (14.58%)  | 0 / 25 (0.00%)  | 12 / 48 (25.00%) |
| occurrences (all)                               | 8                | 0               | 18               |
| Musculoskeletal and connective tissue disorders |                  |                 |                  |
| Arthralgia                                      |                  |                 |                  |
| subjects affected / exposed                     | 17 / 48 (35.42%) | 3 / 25 (12.00%) | 26 / 48 (54.17%) |
| occurrences (all)                               | 20               | 3               | 48               |
| Back pain                                       |                  |                 |                  |
| subjects affected / exposed                     | 2 / 48 (4.17%)   | 0 / 25 (0.00%)  | 8 / 48 (16.67%)  |
| occurrences (all)                               | 2                | 0               | 9                |
| Muscle spasms                                   |                  |                 |                  |
| subjects affected / exposed                     | 2 / 48 (4.17%)   | 0 / 25 (0.00%)  | 3 / 48 (6.25%)   |
| occurrences (all)                               | 2                | 0               | 4                |
| Muscular weakness                               |                  |                 |                  |
| subjects affected / exposed                     | 2 / 48 (4.17%)   | 0 / 25 (0.00%)  | 4 / 48 (8.33%)   |
| occurrences (all)                               | 2                | 0               | 5                |
| Myalgia   |                  |                 |                  |



|                                    |                  |                 |                  |
|------------------------------------|------------------|-----------------|------------------|
| subjects affected / exposed        | 10 / 48 (20.83%) | 1 / 25 (4.00%)  | 15 / 48 (31.25%) |
| occurrences (all)                  | 11               | 2               | 26               |
| Pain in extremity                  |                  |                 |                  |
| subjects affected / exposed        | 2 / 48 (4.17%)   | 0 / 25 (0.00%)  | 3 / 48 (6.25%)   |
| occurrences (all)                  | 2                | 0               | 3                |
| Infections and infestations        |                  |                 |                  |
| Gastroenteritis                    |                  |                 |                  |
| subjects affected / exposed        | 1 / 48 (2.08%)   | 0 / 25 (0.00%)  | 4 / 48 (8.33%)   |
| occurrences (all)                  | 1                | 0               | 5                |
| Influenza                          |                  |                 |                  |
| subjects affected / exposed        | 2 / 48 (4.17%)   | 0 / 25 (0.00%)  | 4 / 48 (8.33%)   |
| occurrences (all)                  | 2                | 0               | 8                |
| Laryngitis                         |                  |                 |                  |
| subjects affected / exposed        | 0 / 48 (0.00%)   | 0 / 25 (0.00%)  | 3 / 48 (6.25%)   |
| occurrences (all)                  | 0                | 0               | 3                |
| Nasopharyngitis                    |                  |                 |                  |
| subjects affected / exposed        | 1 / 48 (2.08%)   | 1 / 25 (4.00%)  | 2 / 48 (4.17%)   |
| occurrences (all)                  | 2                | 1               | 4                |
| Oral herpes                        |                  |                 |                  |
| subjects affected / exposed        | 1 / 48 (2.08%)   | 0 / 25 (0.00%)  | 3 / 48 (6.25%)   |
| occurrences (all)                  | 1                | 0               | 3                |
| Pharyngitis                        |                  |                 |                  |
| subjects affected / exposed        | 1 / 48 (2.08%)   | 0 / 25 (0.00%)  | 5 / 48 (10.42%)  |
| occurrences (all)                  | 1                | 0               | 6                |
| Upper respiratory tract infection  |                  |                 |                  |
| subjects affected / exposed        | 5 / 48 (10.42%)  | 0 / 25 (0.00%)  | 12 / 48 (25.00%) |
| occurrences (all)                  | 5                | 0               | 20               |
| Urinary tract infection            |                  |                 |                  |
| subjects affected / exposed        | 4 / 48 (8.33%)   | 0 / 25 (0.00%)  | 8 / 48 (16.67%)  |
| occurrences (all)                  | 4                | 0               | 12               |
| Metabolism and nutrition disorders |                  |                 |                  |
| Decreased appetite                 |                  |                 |                  |
| subjects affected / exposed        | 18 / 48 (37.50%) | 4 / 25 (16.00%) | 24 / 48 (50.00%) |
| occurrences (all)                  | 21               | 4               | 37               |
| Hypercholesterolaemia              |                  |                 |                  |

|                             |                |                |                 |
|-----------------------------|----------------|----------------|-----------------|
| subjects affected / exposed | 3 / 48 (6.25%) | 1 / 25 (4.00%) | 6 / 48 (12.50%) |
| occurrences (all)           | 3              | 1              | 6               |
| Hypoglycaemia               |                |                |                 |
| subjects affected / exposed | 1 / 48 (2.08%) | 0 / 25 (0.00%) | 3 / 48 (6.25%)  |
| occurrences (all)           | 1              | 0              | 3               |
| Hypokalaemia                |                |                |                 |
| subjects affected / exposed | 1 / 48 (2.08%) | 0 / 25 (0.00%) | 6 / 48 (12.50%) |
| occurrences (all)           | 1              | 0              | 9               |

| <b>Non-serious adverse events</b>                     | Overall study period@<br>Osilodrostat@ (Placebo arm) | Overall study period@ All Patients |  |
|---|--|------------------------------------|--|
| Total subjects affected by non-serious adverse events |  |                                    |  |
| subjects affected / exposed                           | 24 / 25 (96.00%)                                     | 71 / 73 (97.26%)                   |  |
| Vascular disorders                                    |  |                                    |  |
| Hypertension  |  |                                    |  |
| subjects affected / exposed                           | 4 / 25 (16.00%)                                      | 16 / 73 (21.92%)                   |  |
| occurrences (all)                                     | 10   | 28                                 |  |
| Hypotension   |  |                                    |  |
| subjects affected / exposed                           | 3 / 25 (12.00%)                                      | 12 / 73 (16.44%)                   |  |
| occurrences (all)                                     | 4  | 14                                 |  |
| Orthostatic hypotension                               |  |                                    |  |
| subjects affected / exposed                           | 1 / 25 (4.00%)                                       | 8 / 73 (10.96%)                    |  |
| occurrences (all)                                     | 1  | 9                                  |  |
| General disorders and administration site conditions  |  |                                    |  |
| Asthenia  |  |                                    |  |
| subjects affected / exposed                           | 2 / 25 (8.00%)                                       | 17 / 73 (23.29%)                   |  |
| occurrences (all)                                     | 2  | 20                                 |  |
| Fatigue   |  |                                    |  |
| subjects affected / exposed                           | 6 / 25 (24.00%)                                      | 29 / 73 (39.73%)                   |  |
| occurrences (all)                                     | 10   | 46                                 |  |
| Oedema peripheral                                     |  |                                    |  |
| subjects affected / exposed                           | 0 / 25 (0.00%)                                       | 12 / 73 (16.44%)                   |  |
| occurrences (all)                                     | 0  | 13                                 |  |
| Pyrexia   |  |                                    |  |
| subjects affected / exposed                           | 0 / 25 (0.00%)                                       | 5 / 73 (6.85%)                     |  |
| occurrences (all)                                     | 0  | 5                                  |  |

|   |                 |                  |  |
|---|-----------------|------------------|--|
| Respiratory, thoracic and mediastinal disorders |                 |                  |  |
| Cough   |                 |                  |  |
| subjects affected / exposed                     | 0 / 25 (0.00%)  | 4 / 73 (5.48%)   |  |
| occurrences (all)                               | 0               | 4                |  |
| Dyspnoea  |                 |                  |  |
| subjects affected / exposed                     | 2 / 25 (8.00%)  | 4 / 73 (5.48%)   |  |
| occurrences (all)                               | 2               | 4                |  |
| Epistaxis                                       |                 |                  |  |
| subjects affected / exposed                     | 2 / 25 (8.00%)  | 2 / 73 (2.74%)   |  |
| occurrences (all)                               | 2               | 2                |  |
| Nasal congestion                                |                 |                  |  |
| subjects affected / exposed                     | 0 / 25 (0.00%)  | 3 / 73 (4.11%)   |  |
| occurrences (all)                               | 0               | 3                |  |
| Psychiatric disorders                           |                 |                  |  |
| Anxiety   |                 |                  |  |
| subjects affected / exposed                     | 2 / 25 (8.00%)  | 4 / 73 (5.48%)   |  |
| occurrences (all)                               | 3               | 5                |  |
| Investigations                                  |                 |                  |  |
| Alanine aminotransferase increased              |                 |                  |  |
| subjects affected / exposed                     | 3 / 25 (12.00%) | 6 / 73 (8.22%)   |  |
| occurrences (all)                               | 3               | 6                |  |
| Aspartate aminotransferase increased            |                 |                  |  |
| subjects affected / exposed                     | 3 / 25 (12.00%) | 5 / 73 (6.85%)   |  |
| occurrences (all)                               | 4               | 6                |  |
| Blood cholesterol increased                     |                 |                  |  |
| subjects affected / exposed                     | 0 / 25 (0.00%)  | 3 / 73 (4.11%)   |  |
| occurrences (all)                               | 0               | 8                |  |
| Blood potassium decreased                       |                 |                  |  |
| subjects affected / exposed                     | 2 / 25 (8.00%)  | 4 / 73 (5.48%)   |  |
| occurrences (all)                               | 3               | 5                |  |
| Blood pressure increased                        |                 |                  |  |
| subjects affected / exposed                     | 0 / 25 (0.00%)  | 3 / 73 (4.11%)   |  |
| occurrences (all)                               | 0               | 3                |  |
| Blood testosterone increased                    |                 |                  |  |
| subjects affected / exposed                     | 5 / 25 (20.00%) | 18 / 73 (24.66%) |  |
| occurrences (all)                               | 6               | 19               |  |

|  |                       |                        |  |
|--|-----------------------|------------------------|--|
| Electrocardiogram T wave inversion<br>subjects affected / exposed<br>occurrences (all)                     | 2 / 25 (8.00%)<br>2   | 2 / 73 (2.74%)<br>2    |  |
| Renin increased<br>subjects affected / exposed<br>occurrences (all)  | 4 / 25 (16.00%)<br>4  | 5 / 73 (6.85%)<br>5    |  |
| Weight decreased<br>subjects affected / exposed<br>occurrences (all)                                       | 1 / 25 (4.00%)<br>1   | 4 / 73 (5.48%)<br>4    |  |
| Injury, poisoning and procedural complications<br>Fall<br>subjects affected / exposed<br>occurrences (all) | 0 / 25 (0.00%)<br>0   | 4 / 73 (5.48%)<br>4    |  |
| Cardiac disorders<br>Palpitations<br>subjects affected / exposed<br>occurrences (all)                      | 0 / 25 (0.00%)<br>0   | 2 / 73 (2.74%)<br>2    |  |
| Tachycardia<br>subjects affected / exposed<br>occurrences (all)  | 1 / 25 (4.00%)<br>3   | 9 / 73 (12.33%)<br>11  |  |
| Nervous system disorders<br>Dizziness<br>subjects affected / exposed<br>occurrences (all)                  | 3 / 25 (12.00%)<br>3  | 22 / 73 (30.14%)<br>28 |  |
| Paraesthesia<br>subjects affected / exposed<br>occurrences (all)   | 0 / 25 (0.00%)<br>0   | 4 / 73 (5.48%)<br>4    |  |
| Headache<br>subjects affected / exposed<br>occurrences (all)   | 8 / 25 (32.00%)<br>13 | 25 / 73 (34.25%)<br>40 |  |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all)        | 1 / 25 (4.00%)<br>1   | 3 / 73 (4.11%)<br>3    |  |
| Gastrointestinal disorders   |                       |                        |  |

|  |                      |                        |  |
|--|----------------------|------------------------|--|
| Abdominal distension<br>subjects affected / exposed<br>occurrences (all) | 0 / 25 (0.00%)<br>0  | 4 / 73 (5.48%)<br>4    |  |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)       | 2 / 25 (8.00%)<br>9  | 12 / 73 (16.44%)<br>20 |  |
| Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all) | 0 / 25 (0.00%)<br>0  | 3 / 73 (4.11%)<br>3    |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)            | 3 / 25 (12.00%)<br>4 | 17 / 73 (23.29%)<br>24 |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)               | 5 / 25 (20.00%)<br>7 | 27 / 73 (36.99%)<br>47 |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)             | 0 / 25 (0.00%)<br>0  | 9 / 73 (12.33%)<br>9   |  |
| Skin and subcutaneous tissue disorders                                   |                      |                        |  |
| Acne<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 25 (4.00%)<br>1  | 10 / 73 (13.70%)<br>12 |  |
| Alopecia<br>subjects affected / exposed<br>occurrences (all)             | 1 / 25 (4.00%)<br>1  | 5 / 73 (6.85%)<br>8    |  |
| Dry skin<br>subjects affected / exposed<br>occurrences (all)             | 1 / 25 (4.00%)<br>1  | 4 / 73 (5.48%)<br>7    |  |
| Eczema<br>subjects affected / exposed<br>occurrences (all)               | 2 / 25 (8.00%)<br>2  | 4 / 73 (5.48%)<br>5    |  |
| Pruritus<br>subjects affected / exposed<br>occurrences (all)             | 2 / 25 (8.00%)<br>2  | 9 / 73 (12.33%)<br>13  |  |
| Hirsutism  |                      |                        |  |

|   |                      |                        |  |
|---|----------------------|------------------------|--|
| subjects affected / exposed<br>occurrences (all)  | 1 / 25 (4.00%)<br>1  | 7 / 73 (9.59%)<br>7    |  |
| Skin hyperpigmentation<br>subjects affected / exposed<br>occurrences (all)  | 1 / 25 (4.00%)<br>1  | 4 / 73 (5.48%)<br>6    |  |
| Renal and urinary disorders<br>Renal colic<br>subjects affected / exposed<br>occurrences (all)                    | 2 / 25 (8.00%)<br>3  | 2 / 73 (2.74%)<br>3    |  |
| Endocrine disorders<br>Adrenal insufficiency<br>subjects affected / exposed<br>occurrences (all)                  | 6 / 25 (24.00%)<br>9 | 18 / 73 (24.66%)<br>27 |  |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all) | 7 / 25 (28.00%)<br>8 | 33 / 73 (45.21%)<br>56 |  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)   | 2 / 25 (8.00%)<br>3  | 10 / 73 (13.70%)<br>12 |  |
| Muscle spasms<br>subjects affected / exposed<br>occurrences (all)   | 1 / 25 (4.00%)<br>1  | 4 / 73 (5.48%)<br>5    |  |
| Muscular weakness<br>subjects affected / exposed<br>occurrences (all)   | 2 / 25 (8.00%)<br>6  | 6 / 73 (8.22%)<br>11   |  |
| Myalgia<br>subjects affected / exposed<br>occurrences (all)   | 3 / 25 (12.00%)<br>4 | 18 / 73 (24.66%)<br>30 |  |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)   | 2 / 25 (8.00%)<br>2  | 5 / 73 (6.85%)<br>5    |  |
| Infections and infestations<br>Gastroenteritis<br>subjects affected / exposed<br>occurrences (all)                | 0 / 25 (0.00%)<br>0  | 4 / 73 (5.48%)<br>5    |  |

|                                    |                  |                  |  |
|------------------------------------|------------------|------------------|--|
| Influenza                          |                  |                  |  |
| subjects affected / exposed        | 0 / 25 (0.00%)   | 4 / 73 (5.48%)   |  |
| occurrences (all)                  | 0                | 8                |  |
| Laryngitis                         |                  |                  |  |
| subjects affected / exposed        | 0 / 25 (0.00%)   | 3 / 73 (4.11%)   |  |
| occurrences (all)                  | 0                | 3                |  |
| Nasopharyngitis                    |                  |                  |  |
| subjects affected / exposed        | 2 / 25 (8.00%)   | 4 / 73 (5.48%)   |  |
| occurrences (all)                  | 2                | 6                |  |
| Oral herpes                        |                  |                  |  |
| subjects affected / exposed        | 0 / 25 (0.00%)   | 3 / 73 (4.11%)   |  |
| occurrences (all)                  | 0                | 3                |  |
| Pharyngitis                        |                  |                  |  |
| subjects affected / exposed        | 1 / 25 (4.00%)   | 6 / 73 (8.22%)   |  |
| occurrences (all)                  | 1                | 7                |  |
| Upper respiratory tract infection  |                  |                  |  |
| subjects affected / exposed        | 4 / 25 (16.00%)  | 16 / 73 (21.92%) |  |
| occurrences (all)                  | 4                | 24               |  |
| Urinary tract infection            |                  |                  |  |
| subjects affected / exposed        | 4 / 25 (16.00%)  | 12 / 73 (16.44%) |  |
| occurrences (all)                  | 5                | 17               |  |
| Metabolism and nutrition disorders |                  |                  |  |
| Decreased appetite                 |                  |                  |  |
| subjects affected / exposed        | 10 / 25 (40.00%) | 34 / 73 (46.58%) |  |
| occurrences (all)                  | 11               | 48               |  |
| Hypercholesterolaemia              |                  |                  |  |
| subjects affected / exposed        | 0 / 25 (0.00%)   | 6 / 73 (8.22%)   |  |
| occurrences (all)                  | 0                | 6                |  |
| Hypoglycaemia                      |                  |                  |  |
| subjects affected / exposed        | 1 / 25 (4.00%)   | 4 / 73 (5.48%)   |  |
| occurrences (all)                  | 1                | 4                |  |
| Hypokalaemia                       |                  |                  |  |
| subjects affected / exposed        | 2 / 25 (8.00%)   | 8 / 73 (10.96%)  |  |
| occurrences (all)                  | 3                | 12               |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 20 November 2017 | <ul style="list-style-type: none"><li>- Issued when 18 patients had been enrolled in the study. The following key changes were made:</li><li>- The list of prohibited medications was revised to remove "all drugs known to prolong QT". The list of prohibited medications known to cause TdP, or with a possible risk to cause TdP, was reduced. This was based on evidence from the thorough QT study CLCI699C2105.</li><li>- The risks section was updated to include neutropenia.</li><li>- The duration of the optional extension period was increased in order to collect additional long-term safety and efficacy data and allow continued access to the study drug as required.</li><li>- Secondary objective endpoints were added: change from baseline in serum, salivary and hair cortisol levels, actual and percentage change in biomarkers of hypercortisolism.</li></ul> |
| 20 December 2019 | <p>Issued when all patients had been enrolled. The following key changes were made:</p> <ul style="list-style-type: none"><li>- Changed the end of study definition</li><li>- Removed Beck Depression Inventory (BDI) from Appendix 3 as Beck's Depression Inventory was not used in the study. For this study, the BDI-II was used</li><li>- Appendix 3 (Patient Quality of Life questionnaires) removed</li></ul>  |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported