



Clinical trial results:

A proof-of-concept (PoC), open-label, forced titration, multi-center study to assess the safety/tolerability and efficacy of 10-weeks treatment of LCI699 followed by a 12-week treatment period in patients with Cushing's disease.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use <https://www.novctrd.com/CtrdWeb/home.nov> for complete trial results.

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2010-022403-22 |
| Trial protocol | IT |
| Global end of trial date | 22 October 2019 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 06 November 2020 |
| First version publication date | 06 November 2020 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | CLCI699C2201 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01331239 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Novartis Pharma, AG |
| Sponsor organisation address | CH-4002, 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:

Results analysis stage

| | |
|--|-----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 22 October 2019 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 22 October 2019 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To assess the effect of 10-week treatment osilodrostat on 24 hour urine free cortisol (UFC) in patients with Cushing's disease

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 | 23 March 2011 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | France: 9 |
| Country: Number of subjects enrolled | Italy: 6 |
| Country: Number of subjects enrolled | Japan: 2 |
| Country: Number of subjects enrolled | United States: 10 |
| Worldwide total number of subjects | 27 |
| EEA total number of subjects | 15 |

Notes:

Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |

| | |
|---------------------------|----|
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 27 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

27 were enrolled in the study: 12 in Part I and 19 in Part II Core. Four of the participants in the Part II Core were previously enrolled in the Part I Core.

Pre-assignment

Screening details:

For overall study: 27 patients were planned; For Part I of the study, 12 - 15 patients were planned to be enrolled. For Part II Core 19 patients were planned to be enrolled.

Period 1

| | |
|------------------------------|--------------------|
| Period 1 title | Part I: Core Study |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|-----------|---------------------|
| Arm title | Part I: Core cohort |
|-----------|---------------------|

Arm description:

Participants took an ascending dose of LCI699 (osilodrostat) from 2mg bid or 5 mg bid, up to 30 mg bid and participated in Part I of this study. 4 patients in this cohort moved to Part II of the study

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

Dosage and administration details:

Starting dose of 2 mg b.i.d increasing to 50 mg b.i.d as detailed above.

| | |
|---|---------------------|
| Number of subjects in period 1^[1] | Part I: Core cohort |
| Started | 12 |
| Completed | 12 |

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: In this period there were fewer subjects were enrolled than in the whole study. More subjects joined in the next period.

Period 2

| | |
|------------------------------|-----------------------------|
| Period 2 title | Part II: Core Study |
| Is this the baseline period? | No |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|----|
| Are arms mutually exclusive? | No |
|------------------------------|----|

| | |
|------------------|--------------------------------|
| Arm title | Part II Core: Expansion cohort |
|------------------|--------------------------------|

Arm description:

Participants took an ascending dose from 2mg bid or 5 mg bid, up to 30 mg bid and participated in the Part II Core Expansion of this study. These patients were all newly enrolled into the phase II part of the study.

| | |
|--|------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | osilodrostat |
| Investigational medicinal product code | LCI699 |
| Other name | |
| Pharmaceutical forms | Capsule, soft, Coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Patients started the sequential dose- escalation treatment period at 2 mg bid of osilodrostat, or 5 mg bid if their UFC was greater than 3xULN on Day 1. This schedule of events continued every 2 weeks (i.e. Day 28, 42, 56) with potential interim dose escalation visits (on Days 35, 49, 63) during the dose escalation period, with the dose of LCI699 increasing. If at any time, the patient's UFC was less than ULN, dose escalation was to be halted and the patient remained on the current, efficacious dose through Week 10, with continued monitoring of UFC responses every 2 weeks to allow dose adjustments if necessary. If at any time the patient experienced side effects, which were either intolerable or met dose adjustment criteria, the prescribed dose was to be adjusted. The capsule formulation of osilodrostat was later changed to tablets and this change was implemented in the study with Protocol amendment 06.

| | |
|------------------|--------------------------------|
| Arm title | Part II Core: Follow-up cohort |
|------------------|--------------------------------|

Arm description:

Participants took an ascending dose from 2mg bid or 5 mg bid, up to 30 mg bid and participated in the Part II Core Follow-up of this study. These patients were patients who transferred from Part I Core phase of the study.

| | |
|--|------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | osilodrostat |
| Investigational medicinal product code | LCI699 |
| Other name | |
| Pharmaceutical forms | Capsule, soft, Coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Patients were to start at the penultimate osilodrostat dose that was efficacious and well tolerated during their previous treatment, with the possibility to up- titrate the dose within 1 week based on tolerability. The capsule formulation of osilodrostat was later changed to tablets and this change was implemented in the study with Protocol amendment 06.

| Number of subjects in period 2 | Part II Core: Expansion cohort | Part II Core: Follow-up cohort |
|--|---------------------------------------|---------------------------------------|
| Started | 15 | 4 |
| Completed | 7 | 3 |
| Not completed | 8 | 1 |
| Consent withdrawn by subject | 2 | - |
| Adverse event, non-fatal | 3 | - |
| Administrative problems | 1 | - |
| Subj's cond. no longer require treatment | 2 | 1 |

Baseline characteristics

Reporting groups

| | |
|--|---------------------|
| Reporting group title | Part I: Core cohort |
| Reporting group description: | |
| Participants took an ascending dose of LCI699 (osilodrostat) from 2mg bid or 5 mg bid, up to 30 mg bid and participated in Part I of this study. 4 patients in this cohort moved to Part II of the study | |

| Reporting group values | Part I: Core cohort | Total | |
|----------------------------|---------------------|-------|--|
| Number of subjects | 12 | 12 | |
| Age Categorical | | | |
| Units: years | | | |
| 18 - 64 years | 12 | 12 | |
| >65 years | 0 | 0 | |
| Sex: Female, Male | | | |
| Units: Participants | | | |
| Female | 8 | 8 | |
| Male | 4 | 4 | |
| Race/Ethnicity, Customized | | | |
| Units: Subjects | | | |
| White | 12 | 12 | |
| Black or African American | 0 | 0 | |
| Asian | 0 | 0 | |

Subject analysis sets

| | |
|--|--------------------|
| Subject analysis set title | 2mg bid |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| Participants in the Expansion cohort who took 2mg of osilodrostat | |
| Subject analysis set title | 5mg bid |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| Participants in the Expansion cohort who took 5mg of osilodrostat | |
| Subject analysis set title | 10mg bid |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| Participants in the Expansion cohort who took 10mg of osilodrostat | |
| Subject analysis set title | 20mg bid |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| Participants in the Expansion cohort who took 20mg of osilodrostat | |
| Subject analysis set title | 30mg bid |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| Participants in the Expansion cohort who took 30mg of osilodrostat | |
| Subject analysis set title | 2mg bid |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Participants in the Expansion cohort who took 2mg of osilodrostat

| | |
|----------------------------|--------------------|
| Subject analysis set title | 5mg bid |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Participants in the Expansion cohort who took 5mg of osilodrostat

| | |
|----------------------------|--------------------|
| Subject analysis set title | 10mg bid |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Participants in the Expansion cohort who took 10mg of osilodrostat

| | |
|----------------------------|--------------------|
| Subject analysis set title | 20mg bid |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Participants in the Expansion cohort who took 20mg of osilodrostat

| | |
|----------------------------|--------------------|
| Subject analysis set title | 2mg bid |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Participants in the Expansion cohort who took 2mg of osilodrostat

| | |
|----------------------------|--------------------|
| Subject analysis set title | 5mg bid |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Participants in the Expansion cohort who took 5mg of osilodrostat

| | |
|----------------------------|---------------------------------|
| Subject analysis set title | Phase II Core: Expansion cohort |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

Participants took an ascending dose from 2mg bid or 5 mg bid, up to 30 mg bid and participated in the Part II Core Expansion of this study. These patients were all newly enrolled into the phase II part of the study.

| Reporting group values | 2mg bid | 5mg bid | 10mg bid |
|---|---------|---------|----------|
| Number of subjects | 4 | 13 | 6 |
| Age Categorical Units: years | | | |
| 18 - 64 years | | | |
| >65 years | | | |
| Sex: Female, Male Units: Participants | | | |
| Female | | | |
| Male | | | |
| Race/Ethnicity, Customized Units: Subjects | | | |
| White | | | |
| Black or African American | | | |
| Asian | | | |

| Reporting group values | 20mg bid | 30mg bid | 2mg bid |
|---------------------------------|----------|----------|---------|
| Number of subjects | 1 | 1 | 6 |
| Age Categorical Units: years | | | |
| 18 - 64 years | | | |
| >65 years | | | |

| | | | |
|---|--|--|--|
| Sex: Female, Male Units: Participants | | | |
| Female Male | | | |
| Race/Ethnicity, Customized Units: Subjects | | | |
| White Black or African American Asian | | | |

| Reporting group values | 5mg bid | 10mg bid | 20mg bid |
|---|---------|----------|----------|
| Number of subjects | 14 | 8 | 2 |
| Age Categorical Units: years | | | |
| 18 - 64 years >65 years | | | |
| Sex: Female, Male Units: Participants | | | |
| Female Male | | | |
| Race/Ethnicity, Customized Units: Subjects | | | |
| White Black or African American Asian | | | |

| Reporting group values | 2mg bid | 5mg bid | Phase II Core: Expansion cohort |
|---|---------|---------|------------------------------------|
| Number of subjects | 2 | 11 | 15 |
| Age Categorical Units: years | | | |
| 18 - 64 years >65 years | | | 15 |
| Sex: Female, Male Units: Participants | | | |
| Female Male | | | 11 4 |
| Race/Ethnicity, Customized Units: Subjects | | | |
| White Black or African American Asian | | | 11 3 1 |

End points

End points reporting groups

| | |
|---|--------------------------------|
| Reporting group title | Part I: Core cohort |
| Reporting group description: Participants took an ascending dose of LCI699 (osilodrostat) from 2mg bid or 5 mg bid, up to 30 mg bid and participated in Part I of this study. 4 patients in this cohort moved to Part II of the study | |
| Reporting group title | Part II Core: Expansion cohort |
| Reporting group description: Participants took an ascending dose from 2mg bid or 5 mg bid, up to 30 mg bid and participated in the Part II Core Expansion of this study. These patients were all newly enrolled into the phase II part of the study. | |
| Reporting group title | Part II Core: Follow-up cohort |
| Reporting group description: Participants took an ascending dose from 2mg bid or 5 mg bid, up to 30 mg bid and participated in the Part II Core Follow-up of this study. These patients were patients who transferred from Part I Core phase of the study. | |
| Subject analysis set title | 2mg bid |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Participants in the Expansion cohort who took 2mg of osilodrostat | |
| Subject analysis set title | 5mg bid |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Participants in the Expansion cohort who took 5mg of osilodrostat | |
| Subject analysis set title | 10mg bid |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Participants in the Expansion cohort who took 10mg of osilodrostat | |
| Subject analysis set title | 20mg bid |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Participants in the Expansion cohort who took 20mg of osilodrostat | |
| Subject analysis set title | 30mg bid |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Participants in the Expansion cohort who took 30mg of osilodrostat | |
| Subject analysis set title | 2mg bid |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Participants in the Expansion cohort who took 2mg of osilodrostat | |
| Subject analysis set title | 5mg bid |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Participants in the Expansion cohort who took 5mg of osilodrostat | |
| Subject analysis set title | 10mg bid |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Participants in the Expansion cohort who took 10mg of osilodrostat | |
| Subject analysis set title | 20mg bid |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Participants in the Expansion cohort who took 20mg of osilodrostat

| | |
|----------------------------|--------------------|
| Subject analysis set title | 2mg bid |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Participants in the Expansion cohort who took 2mg of osilodrostat

| | |
|----------------------------|--------------------|
| Subject analysis set title | 5mg bid |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Participants in the Expansion cohort who took 5mg of osilodrostat

| | |
|----------------------------|---------------------------------|
| Subject analysis set title | Phase II Core: Expansion cohort |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

Participants took an ascending dose from 2mg bid or 5 mg bid, up to 30 mg bid and participated in the Part II Core Expansion of this study. These patients were all newly enrolled into the phase II part of the study.

Primary: Percentage of responders to LCI699 based on the change in mean urinary free cortisol (UFC) from baseline to Week 10

| | |
|-----------------|--|
| End point title | Percentage of responders to LCI699 based on the change in mean urinary free cortisol (UFC) from baseline to Week 10 ^[1] |
|-----------------|--|

End point description:

A patient was considered to be a responder if his/her mean UFC level from the three 24-hour urine samples collected at Week 10 was \leq ULN (as defined by the local laboratories) or represented a $\geq 50\%$ decrease from baseline. Patients who discontinued for a disease or treatment related reason (e.g. death, adverse event, clinical disease progression etc.), or whose mean Week 10 24-hour UFC levels were higher than the normal limit and experienced $< 50\%$ decrease in UFC were classified as non-responders.

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

End point timeframe:

10 weeks

Notes:

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

Justification: No statistical analysis was planned for this endpoint

| | | | | |
|-----------------------------------|---------------------|--|--|--|
| End point values | Part I: Core cohort | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 9 | | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 100.0 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Actual Change from baseline (BL) in steroid hormones of HPA-axis: 11-Deoxycorticosterone (Overall)

| | |
|-----------------|---|
| End point title | Actual Change from baseline (BL) in steroid hormones of HPA-axis: 11- Deoxycorticosterone (Overall) |
|-----------------|---|

End point description:

Change in Deoxycorticosterone over time.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| baseline, Week 22, Week 70, Last observed value (LOV) | |

| End point values | Part II Core: Expansion cohort | Part II Core: Follow-up cohort | | |
|--|--------------------------------------|--------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 15 | 4 | | |
| Units: pmol/L | | | | |
| arithmetic mean (standard deviation) | | | | |
| BL: 11-Deoxycorticosterone (n =12, 4) | 292.8 (± 371.54) | 188.0 (± 105.21) | | |
| WK 22: 11-Deoxycorticosterone (n= 10, 4) | 6957.8 (± 9627.77) | 3670.0 (± 2734.34) | | |
| WK 70: 11-Deoxycorticosterone (n= 7, 4) | 2523.1 (± 1597.39) | 1743.0 (± 1048.22) | | |
| LOV: 11-Deoxycorticosterone (n=12, 4) | 1640.8 (± 2097.16) | 1822.3 (± 1452.72) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Actual Change from baseline (BL) in steroid hormones of HPA-axis: 11-Deoxycortisol (Overall)

| | |
|---|--|
| End point title | Actual Change from baseline (BL) in steroid hormones of HPA-axis: 11-Deoxycortisol (Overall) |
| End point description: | |
| Change in Deoxycortisol over time. | |
| End point type | Secondary |
| End point timeframe: | |
| baseline, Week 22, Week 70, Last observed value (LOV) | |

| End point values | Part II Core: Expansion cohort | Part II Core: Follow-up cohort | | |
|--------------------------------------|--------------------------------------|--------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 15 | 4 | | |
| Units: nmol/L | | | | |
| arithmetic mean (standard deviation) | | | | |
| BL: 11-Deoxycortisol (n= 14, 4) | 4.21 (± 4.648) | 5.48 (± 6.549) | | |
| WK 22: 11-Deoxycortisol (n= 12, 4) | 45.48 (± 44.880) | 54.75 (± 60.676) | | |
| WK 70: 11-Deoxycortisol (n= 9, 4) | 15.32 (± 13.463) | 9.03 (± 7.934) | | |

| | | | | |
|-----------------------|----------------------|-----------------------|--|--|
| LOV: 11-Deoxycortisol | 8.60 (\pm 18.910) | 11.83 (\pm 19.101) | | |
|-----------------------|----------------------|-----------------------|--|--|

Statistical analyses

No statistical analyses for this end point

Secondary: Actual Change from baseline (BL) in steroid hormones of HPA-axis: Aldosterone, Thyroxine, free (T4)

| | |
|------------------------|---|
| End point title | Actual Change from baseline (BL) in steroid hormones of HPA-axis: Aldosterone, Thyroxine, free (T4) |
| End point description: | Change in aldosterone & thyroxine, free over time. |
| End point type | Secondary |
| End point timeframe: | baseline, Week 22, Week 70, Last observed value (LOV) |

| End point values | Part II Core: Expansion cohort | Part II Core: Follow-up cohort | | |
|--------------------------------------|--------------------------------|--------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 15 | 4 | | |
| Units: pmol/L | | | | |
| arithmetic mean (standard deviation) | | | | |
| BL: Aldosterone (n = 14, 4) | 165.5 (\pm 255.07) | 127.0 (\pm 177.04) | | |
| WK 22: Aldosterone (n =12, 4) | -151.1 (\pm 290.53) | -64.5 (\pm 247.93) | | |
| WK 70: Aldosterone (n = 9, 4) | -101.9 (\pm 153.82) | -120.0 (\pm 182.11) | | |
| LOV: Aldosterone (n =14, 4) | -135.1 (\pm 258.36) | -99.5 (\pm 149.06) | | |
| BL: Thyroxine, free (n = 14, 4) | 14.02 (\pm 3.233) | 18.40 (\pm 8.050) | | |
| WK 22: Thyroxine, free (n =11, 4) | -1.17 (\pm 3.254) | -3.63 (\pm 3.247) | | |
| WK 70: Thyroxine, free (n = 9, 4) | 0.46 (\pm 2.355) | -3.78 (\pm 7.951) | | |
| LOV: Thyroxine, free (n =14, 4) | 1.69 (\pm 3.281) | -2.33 (\pm 5.324) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Actual Change from baseline (BL) in steroid hormones of HPA-axis: Estradiol (Female)

| | |
|---|--|
| End point title | Actual Change from baseline (BL) in steroid hormones of HPA-axis: Estradiol (Female) |
| End point description: Change in Estradiol in females over time. | |
| End point type | Secondary |
| End point timeframe: baseline, Week 22, Week 70, Last observed value (LOV) | |

| End point values | Part II Core: Expansion cohort | Part II Core: Follow-up cohort | | |
|--------------------------------------|--------------------------------|--------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 11 | 3 | | |
| Units: pmol/L | | | | |
| arithmetic mean (standard deviation) | | | | |
| BL: Female Estradiol (n =10, 3) | 209.60 (± 282.423) | 307.23 (± 263.028) | | |
| WK 22: Female Estradiol (n =8, 3) | -42.19 (± 223.444) | -24.63 (± 234.288) | | |
| WK 70: Female Estradiol (n =6, 3) | 10.55 (± 187.443) | -141.00 (± 376.080) | | |
| LOV: Female Estradiol (n =10, 3) | -114.24 (± 305.334) | 666.93 (± 1108.794) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Actual Change from baseline (BL) in steroid hormones of HPA-axis: Estradiol (Male)

| | |
|---|--|
| End point title | Actual Change from baseline (BL) in steroid hormones of HPA-axis: Estradiol (Male) |
| End point description: Change in Estradiol in males over time. | |
| End point type | Secondary |
| End point timeframe: baseline, Week 22, Week 70, Last observed value (LOV) | |

| End point values | Part II Core: Expansion cohort | Part II Core: Follow-up cohort | | |
|--------------------------------------|--------------------------------|--------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 4 | 1 | | |
| Units: pmol/L | | | | |
| arithmetic mean (standard deviation) | | | | |
| BL: Male Estradiol | 55.00 (± 25.755) | 77.10 (± 999) | | |

| | | | | |
|---------------------------------|-----------------------|---------------------|--|--|
| WK 22: Male Estradiol | 35.00 (\pm 68.005) | 18.30 (\pm 999) | | |
| WK 70: Male Estradiol (n =3, 1) | -1.00 (\pm 16.523) | 110.10 (\pm 999) | | |
| LOV: Male Estradiol | 2.50 (\pm 55.729) | -33.10 (\pm 999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Actual Change from baseline (BL) in steroid hormones of HPA-axis: Follicle Stimulation Hormone (FSH) (Female)

| | |
|------------------------|---|
| End point title | Actual Change from baseline (BL) in steroid hormones of HPA-axis: Follicle Stimulation Hormone (FSH) (Female) |
| End point description: | Change in FSH in females over time. |
| End point type | Secondary |
| End point timeframe: | baseline, Week 22, Week 70, Last observed value (LOV) |

| End point values | Part II Core: Expansion cohort | Part II Core: Follow-up cohort | | |
|--------------------------------------|--------------------------------|--------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 11 | 3 | | |
| Units: U/L | | | | |
| arithmetic mean (standard deviation) | | | | |
| BL: Female FSH (n =10, 3) | 9.09 (\pm 13.277) | 2.43 (\pm 0.929) | | |
| WK 22: Female FSH (n =7, 3) | 14.89 (\pm 28.673) | 2.90 (\pm 2.476) | | |
| WK 70: Female FSH (n =6, 3) | 3.58 (\pm 14.021) | 3.20 (\pm 2.081) | | |
| LOV: Female FSH (n =10, 3) | 15.41 (\pm 23.613) | 3.70 (\pm 2.524) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Actual Change from baseline (BL) in steroid hormones of HPA-axis: Follicle Stimulation Hormone (Male)

| | |
|------------------------|---|
| End point title | Actual Change from baseline (BL) in steroid hormones of HPA-axis: Follicle Stimulation Hormone (Male) |
| End point description: | Change in FSH in males over time. |
| End point type | Secondary |

End point timeframe:

baseline, Week 22, Week 70, Last observed value (LOV)

| End point values | Part II Core: Expansion cohort | Part II Core: Follow-up cohort | | |
|--------------------------------------|--------------------------------------|--------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 4 | 1 | | |
| Units: U/L | | | | |
| arithmetic mean (standard deviation) | | | | |
| BL: Male FSH | 5.88 (± 3.241) | 5.80 (± 999) | | |
| WK 22: Male FSH | -1.20 (± 1.560) | -5.20 (± 999) | | |
| WK 70: Male FSH (n =3, 1) | -1.80 (± 1.735) | -5.80 (± 999) | | |
| LOV: Male FSH | -1.38 (± 5.660) | -2.90 (± 999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Actual Change from baseline (BL) in steroid hormones of HPA-axis: Renin, Insulin, Tyrotropin

| | |
|------------------------|--|
| End point title | Actual Change from baseline (BL) in steroid hormones of HPA-axis: Renin, Insulin, Tyrotropin |
| End point description: | Change in Renin, Insulin & Tyrotropin over time. |
| End point type | Secondary |
| End point timeframe: | baseline, Week 22, Week 70, Last observed value (LOV) |

| End point values | Part II Core: Expansion cohort | Part II Core: Follow-up cohort | | |
|--------------------------------------|--------------------------------------|--------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 15 | 4 | | |
| Units: mU/L | | | | |
| arithmetic mean (standard deviation) | | | | |
| BL: Renin (n =14, 4) | 23.706 (± 18.0642) | 73.973 (± 102.338) | | |
| WK 22: Renin (n= 12, 4) | 45.899 (± 144.9575) | -16.838 (± 145.6609) | | |
| WK 70: Renin (n= 9, 4) | 70.051 (± 117.9931) | -55.638 (± 88.9155) | | |
| LOV: Renin (n=14, 4) | 24.209 (± 52.0438) | -43.718 (± 70.5958) | | |

| | | | | |
|------------------------------|-------------------|------------------|--|--|
| BL: Insulin (n =14, 4) | 25.61 (± 27.166) | 22.38 (± 7.071) | | |
| WK 22: Insulin (n= 12, 4) | -10.63 (± 20.247) | -8.58 (± 4.456) | | |
| WK 70: Insulin (n= 9, 4) | -8.69 (± 24.132) | -12.53 (± 8.772) | | |
| LOV: Insulin (n=14, 4) | -8.11 (± 23.169) | -5.78 (± 11.771) | | |
| BL: Thyrotropin (n =14, 4) | 0.659 (± 0.6827) | 0.815 (± 0.8364) | | |
| WK 22: Thyrotropin(n= 11, 3) | 1.445 (± 2.3295) | 0.280 (± 0.3118) | | |
| WK 70: Thyrotropin (n= 9, 4) | 2.387 (± 4.0991) | 0.395 (± 0.4674) | | |
| LOV: Thyrotropin (n=14, 4) | 1.244 (± 3.4627) | 0.885 (± 0.5994) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Actual Change from baseline (BL) in steroid hormones of HPA-axis: Insulin-like Growth Factor-1

| | |
|------------------------|--|
| End point title | Actual Change from baseline (BL) in steroid hormones of HPA-axis: Insulin-like Growth Factor-1 |
| End point description: | Change in Insulin-like Growth Factor-1 over time. |
| End point type | Secondary |
| End point timeframe: | baseline, Week 22, Week 70, Last observed value (LOV) |

| End point values | Part II Core: Expansion cohort | Part II Core: Follow-up cohort | | |
|--|--------------------------------|--------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 15 | 4 | | |
| Units: ug/L | | | | |
| arithmetic mean (standard deviation) | | | | |
| BL: Insulin-like Growth Factor-1 (n =14, 3) | 157.56 (± 109.044) | 235.30 (± 110.249) | | |
| WK 22: Insulin-like Growth Factor-1 (n =12, 3) | -9.78 (± 67.387) | -35.20 (± 153.817) | | |
| WK 70: Insulin-like Growth Factor-1 (n= 9, 3) | -41.23 (± 76.969) | -113.43 (± 86.529) | | |
| LOV: Insulin-like Growth Factor-1 (n=14, 3) | -56.76 (± 105.936) | -46.07 (± 62.155) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Actual Change from baseline (BL) in steroid hormones of HPA-axis: Luteinising Hormone (LH) (Female)

| | |
|-----------------|---|
| End point title | Actual Change from baseline (BL) in steroid hormones of HPA-axis: Luteinising Hormone (LH) (Female) |
|-----------------|---|

End point description:

Change in LH in females over time.

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

End point timeframe:

baseline, Week 22, Week 70, Last observed value (LOV)

| End point values | Part II Core: Expansion cohort | Part II Core: Follow-up cohort | | |
|--------------------------------------|--------------------------------|--------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 11 | 3 | | |
| Units: U/L | | | | |
| arithmetic mean (standard deviation) | | | | |
| BL: Female LH (n =10, 3) | 2.78 (± 2.220) | 1.00 (± 1.000) | | |
| WK 22: Female LH (n =8, 2) | 7.45 (± 17.051) | 4.40 (± 0.990) | | |
| WK 70: Female LH (n =6, 3) | 7.47 (± 15.267) | 2.63 (± 3.235) | | |
| LOV: Female LH (n =10, 3) | 7.30 (± 10.885) | 3.37 (± 2.060) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Actual Change from baseline (BL) in steroid hormones of HPA-axis: LH (Male)

| | |
|-----------------|---|
| End point title | Actual Change from baseline (BL) in steroid hormones of HPA-axis: LH (Male) |
|-----------------|---|

End point description:

Change in LH in males over time.

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

End point timeframe:

baseline, Week 22, Week 70, Last observed value (LOV)

| End point values | Part II Core: Expansion cohort | Part II Core: Follow-up cohort | | |
|--------------------------------------|--------------------------------------|--------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 4 | 1 | | |
| Units: U/L | | | | |
| arithmetic mean (standard deviation) | | | | |
| BL: Male LH | 2.48 (± 1.328) | 5.90 (± 999) | | |
| WK 22: Male LH | 0.48 (± 1.081) | -5.70 (± 999) | | |
| WK 70: Male LH (n =3, 1) | -0.53 (± 1.021) | -5.90 (± 999) | | |
| LOV: Male LH | -0.05 (± 2.610) | -2.70 (± 999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Actual Change from baseline (BL) in steroid hormones of HPA-axis: Testosterone (Female)

| | |
|------------------------|---|
| End point title | Actual Change from baseline (BL) in steroid hormones of HPA-axis: Testosterone (Female) |
| End point description: | Change in Testosterone in females over time. |
| End point type | Secondary |
| End point timeframe: | baseline, Week 22, Week 70, Last observed value (LOV) |

| End point values | Part II Core: Expansion cohort | Part II Core: Follow-up cohort | | |
|--------------------------------------|--------------------------------------|--------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 11 | 3 | | |
| Units: nmol/L | | | | |
| arithmetic mean (standard deviation) | | | | |
| BL: Female Testosterone (n = 10, 3) | 1.18 (± 0.820) | 1.43 (± 0.404) | | |
| WK 22: Female Testosterone (n= 8, 3) | 1.85 (± 1.790) | 5.27 (± 5.353) | | |
| WK 70: Female Testosterone (n= 6, 3) | 0.53 (± 1.409) | 0.50 (± 1.400) | | |
| LOV: Female Testosterone (n=10, 3) | 0.25 (± 1.532) | 0.17 (± 1.266) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Actual Change from baseline (BL) in steroid hormones of HPA-axis: Testosterone (Male)

| | |
|---|---|
| End point title | Actual Change from baseline (BL) in steroid hormones of HPA-axis: Testosterone (Male) |
| End point description: Change in Testosterone in males over time. | |
| End point type | Secondary |
| End point timeframe: baseline, Week 22, Week 70, Last observed value (LOV) | |

| End point values | Part II Core: Expansion cohort | Part II Core: Follow-up cohort | | |
|--------------------------------------|--------------------------------------|--------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 4 | 1 | | |
| Units: nmol/L | | | | |
| arithmetic mean (standard deviation) | | | | |
| BL: Male Testosterone (n = 3, 1) | 7.53 (± 4.076) | 7.10 (± 999) | | |
| WK 22: Male Testosterone (n= 4, 1) | 6.55 (± 4.751) | 2.40 (± 999) | | |
| WK 70: Male Testosterone (n= 3, 1) | 5.17 (± 1.504) | 32.60 (± 999) | | |
| LOV: Male Testosterone (n=4, 1) | 8.15 (± 7.859) | 0.00 (± 999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Actual change from BL in Cardiovascular and other metabolic parameters: Fasting glucose

| | |
|---|---|
| End point title | Actual change from BL in Cardiovascular and other metabolic parameters: Fasting glucose |
| End point description: Improving metabolic abnormalities was assessed by descriptive statistics on the change from baseline. | |
| End point type | Secondary |
| End point timeframe: Baseline, Week 22, Week 70, Last observed value | |

| End point values | Part II Core: Expansion cohort | Part II Core: Follow-up cohort | | |
|--------------------------------------|--------------------------------------|--------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 15 | 4 | | |
| Units: mg/dL | | | | |
| arithmetic mean (standard deviation) | | | | |
| BL | 108.1 (± 55.12) | 96.3 (± 14.43) | | |
| WK 22 (n = 13, 4) | -14.5 (± 32.45) | -16.3 (± 14.93) | | |

| | | | | |
|-------------------|-----------------|-----------------|--|--|
| WK 70 (n = 10, 4) | -22.5 (± 36.87) | -20.8 (± 24.62) | | |
| LOV | -17.9 (± 35.99) | -13.8 (± 22.88) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Actual change from BL in Cardiovascular and other metabolic parameters: Hemoglobin A1C

| | |
|-----------------|--|
| End point title | Actual change from BL in Cardiovascular and other metabolic parameters: Hemoglobin A1C |
|-----------------|--|

End point description:

Improving metabolic abnormalities was assessed by descriptive statistics on the change from baseline.

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

End point timeframe:

Baseline, Week 22, Week 70, Last observed value

| End point values | Part II Core: Expansion cohort | Part II Core: Follow-up cohort | | |
|--------------------------------------|--------------------------------|--------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 15 | 4 | | |
| Units: Percentage | | | | |
| arithmetic mean (standard deviation) | | | | |
| BL (n =13, 4) | 5.7 (± 0.77) | 6.0 (± 0.61) | | |
| WK 22 (n = 11, 4) | -0.1 (± 0.27) | -0.3 (± 0.28) | | |
| WK 70 (n = 8, 4) | -0.1 (± 0.43) | -0.6 (± 0.74) | | |
| LOV (n = 11, 4) | -0.1 (± 0.56) | -0.4 (± 0.49) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Actual change from BL in Cardiovascular and other metabolic parameters: Cholesterol, LDL Cholesterol, HDL Cholesterol, Triglycerides

| | |
|-----------------|--|
| End point title | Actual change from BL in Cardiovascular and other metabolic parameters: Cholesterol, LDL Cholesterol, HDL Cholesterol, Triglycerides |
|-----------------|--|

End point description:

Improving metabolic abnormalities was assessed by descriptive statistics on the change from baseline.

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

End point timeframe:

Baseline, Week 22, Week 70, Last observed value

| End point values | Part II Core: Expansion cohort | Part II Core: Follow-up cohort | | |
|--------------------------------------|--------------------------------------|--------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 15 | 4 | | |
| Units: mmol/L | | | | |
| arithmetic mean (standard deviation) | | | | |
| BL Cholesterol (n =15, 4) | 5.2 (± 1.36) | 5.7 (± 1.44) | | |
| WK 22 Cholesterol (n = 13, 4) | -0.7 (± 1.58) | -0.5 (± 0.56) | | |
| WK 70 Cholesterol (n = 10, 4) | -0.1 (± 1.35) | -1.2 (± 1.74) | | |
| LOV Cholesterol (n = 15, 4) | 0.5 (± 2.39) | 1.5 (± 5.22) | | |
| BL LDL Cholesterol (n =15, 4) | 3.0 (± 1.32) | 4.8 (± 2.31) | | |
| WK 22 LDL Cholesterol (n = 13, 4) | -0.3 (± 1.35) | -1.5 (± 1.98) | | |
| WK 70 LDL Cholesterol (n = 10, 4) | 0.0 (± 1.17) | -2.2 (± 2.11) | | |
| LOV LDL Cholesterol (n = 15, 4) | 0.3 (± 1.58) | -0.7 (± 1.83) | | |
| BL HDL Cholesterol (n = 15, 4) | 1.6 (± 0.39) | 2.1 (± 1.85) | | |
| WK 22 HDL Cholesterol (n = 13, 4) | -0.3 (± 0.32) | -0.9 (± 1.58) | | |
| WK 70 HDL Cholesterol (n = 10, 4) | -0.3 (± 0.42) | -0.9 (± 1.60) | | |
| LOV HDL Cholesterol (n = 15, 4) | 0.1 (± 0.66) | -0.0 (± 0.49) | | |
| BL Triglycerides (n = 15, 4) | 1.5 (± 0.70) | 1.4 (± 0.32) | | |
| WK 22 Triglycerides (n = 13, 4) | -0.1 (± 0.42) | 0.1 (± 0.49) | | |
| WK 70 Triglycerides (n = 10, 4) | 0.3 (± 0.76) | -0.2 (± 0.25) | | |
| LOV Triglycerides (n = 15, 4) | 0.1 (± 0.64) | -0.1 (± 0.54) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Actual change from BL in Cardiovascular and other metabolic parameters: Sitting Diastolic Blood Pressure (DPB), Sitting Systolic Blood Pressure (SBP)

| | |
|---|---|
| End point title | Actual change from BL in Cardiovascular and other metabolic parameters: Sitting Diastolic Blood Pressure (DPB), Sitting Systolic Blood Pressure (SBP) |
| End point description: | |
| Improving metabolic abnormalities was assessed by descriptive statistics on the change from baseline. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 22, Week 70, Last observed value | |

| End point values | Part II Core: Expansion cohort | Part II Core: Follow-up cohort | | |
|--------------------------------------|--------------------------------------|--------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 15 | 4 | | |
| Units: mmHG | | | | |
| arithmetic mean (standard deviation) | | | | |
| BL DBP (n =15, 4) | 84.5 (± 7.01) | 87.3 (± 4.21) | | |
| WK 22 DPB (n = 13, 3) | 0.8 (± 9.59) | 2.6 (± 11.36) | | |
| WK 70 DPB (n = 10, 4) | -3.4 (± 11.65) | -5.8 (± 12.14) | | |
| LOV DPB (n = 15, 4) | -1.3 (± 9.23) | -3.2 (± 7.07) | | |
| BL SBP (n =15, 4) | 133.2 (± 12.51) | 130.3 (± 7.75) | | |
| WK 22 SPB (n = 13, 4) | -4.0 (± 12.46) | 8.8 (± 24.74) | | |
| WK 70 SPB (n = 10, 4) | -9.5 (± 15.78) | -4.7 (± 26.09) | | |
| LOV SPB (n = 15, 4) | -6.2 (± 16.50) | 0.3 (± 20.60) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Actual change from BL in Cardiovascular and other metabolic parameters: Weight

| | |
|---|--|
| End point title | Actual change from BL in Cardiovascular and other metabolic parameters: Weight |
| End point description: | |
| Improving metabolic abnormalities was assessed by descriptive statistics on the change from baseline. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 22, Week 70, Last observed value | |

| End point values | Part II Core: Expansion cohort | Part II Core: Follow-up cohort | | |
|--------------------------------------|--------------------------------------|--------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 15 | 4 | | |
| Units: Kg | | | | |
| arithmetic mean (standard deviation) | | | | |
| BL (n =15, 4) | 85.4 (± 23.52) | 84.0 (± 23.32) | | |
| WK 22 (n = 13, 4) | -2.1 (± 4.02) | 0.6 (± 2.64) | | |
| WK 70 (n = 10, 4) | -5.2 (± 4.56) | -3.2 (± 5.61) | | |
| LOV (n = 15, 4) | -4.5 (± 6.68) | -4.4 (± 7.00) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Actual change from BL in Cardiovascular and other metabolic parameters: Body Mass index (BMI)

| | |
|-----------------|---|
| End point title | Actual change from BL in Cardiovascular and other metabolic parameters: Body Mass index (BMI) |
|-----------------|---|

End point description:

Improving metabolic abnormalities was assessed by descriptive statistics on the change from baseline.

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

End point timeframe:

Baseline, Week 22, Week 70, Last observed value

| End point values | Part II Core: Expansion cohort | Part II Core: Follow-up cohort | | |
|--------------------------------------|--------------------------------------|--------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 15 | 4 | | |
| Units: Kg/m ² | | | | |
| arithmetic mean (standard deviation) | | | | |
| BL (n =15, 4) | 30.6 (± 7.46) | 31.3 (± 5.49) | | |
| WK 22 (n = 13, 4) | -0.7 (± 1.42) | 0.2 (± 1.09) | | |
| WK 70 (n = 10, 4) | -1.9 (± 1.93) | -1.4 (± 2.25) | | |
| LOV (n = 15, 4) | -1.6 (± 2.73) | -2.0 (± 2.73) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Actual change from BL in Cardiovascular and other metabolic parameters: Quantitative Insulin Sensitivity Check Index (QUICKI)

| | |
|-----------------|---|
| End point title | Actual change from BL in Cardiovascular and other metabolic parameters: Quantitative Insulin Sensitivity Check Index (QUICKI) |
|-----------------|---|

End point description:

Improving metabolic abnormalities was assessed by descriptive statistics on the change from baseline. QUICKI is the quantitative insulin sensitivity check index and is derived using the inverse of the sum of algorithms (base 10) of the fasting insulin and fasting glucose

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

End point timeframe:

Baseline, Week 22, Week 70, Last observed value

| End point values | Part II Core: Expansion cohort | Part II Core: Follow-up cohort | | |
|--------------------------------------|--------------------------------------|--------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 15 | 4 | | |
| Units: Kg/m ² | | | | |
| arithmetic mean (standard deviation) | | | | |
| BL (n =13, 4) | 0.3 (± 0.03) | 0.3 (± 0.02) | | |
| WK 22 (n = 11, 4) | 0.0 (± 0.02) | 0.0 (± 0.01) | | |
| WK 70 (n = 8, 4) | 0.0 (± 0.03) | 0.0 (± 0.06) | | |
| LOV (n = 13, 4) | 0.0 (± 0.04) | 0.0 (± 0.04) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: PK Parameters: AUC0-6h ss, AUC0-12h ss

| | |
|---|--|
| End point title | PK Parameters: AUC0-6h ss, AUC0-12h ss |
| End point description: | |
| Trough PK concentrations and PK profiles at steady-state were collected. | |
| End point type | Secondary |
| End point timeframe: | |
| pre-dose (0 hour), 1, 1.5, 2, 4 and 6 hours post AM dose for escalation dose or pre-dose (trough) for maintained dose | |

| End point values | 2mg bid | 5mg bid | 10mg bid | 20mg bid |
|---|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 4 | 13 | 6 | 1 |
| Units: hr•ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| AUC0-6h,ss | 37.79 (± 42.7) | 94.21 (± 37.0) | 236.83 (± 29.9) | 999 (± 999) |
| AUC0-12h,ss (n = 3,13,6,1,1) | 69.96 (± 32.6) | 140.65 (± 43.9) | 339.62 (± 37.6) | 999 (± 999) |

| End point values | 30mg bid | | | |
|---|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 1 | | | |
| Units: hr•ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| AUC0-6h,ss | 999 (± 999) | | | |
| AUC0-12h,ss (n = 3,13,6,1,1) | 999 (± 999) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: PK Parameters: Cmax ss, Ctrough ss

End point title PK Parameters: Cmax ss, Ctrough ss

End point description:

Trough PK concentrations and PK profiles at steady-state were collected.

End point type Secondary

End point timeframe:

pre-dose (0 hour), 1, 1.5, 2, 4 and 6 hours post AM dose for escalation dose or pre-dose (trough) for maintained dose

| End point values | 30mg bid | 2mg bid | 5mg bid | 10mg bid |
|---|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 1 | 6 | 14 | 8 |
| Units: ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Cmax,ss (n =4,13,6,1,1) | 999 (± 999) | 8.76 (± 46.1) | 23.09 (± 31.5) | 59.17 (± 25.5) |
| Ctrough, ss | 999 (± 999) | 2.73 (± 49.1) | 4.30 (± 112.9) | 10.60 (± 104.8) |

| End point values | 20mg bid | | | |
|---|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 2 | | | |
| Units: ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Cmax,ss (n =4,13,6,1,1) | 999 (± 999) | | | |
| Ctrough, ss | 19.69 (± 53.6) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: PK Parameters: Tmax ss,

End point title PK Parameters: Tmax ss,

End point description:

Trough PK concentrations and PK profiles at steady-state were collected.

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

End point timeframe:

pre-dose (0 hour), 1, 1.5, 2, 4 and 6 hours post AM dose for escalation dose or pre-dose (trough) for maintained dose

| End point values | 2mg bid | 5mg bid | 10mg bid | 20mg bid |
|-------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 4 | 13 | 6 | 1 |
| Units: hour (hr) | | | | |
| median (full range (min-max)) | 1.50 (1.0 to 4.1) | 1.50 (1.0 to 4.0) | 1.26 (1.0 to 2.0) | 999 (999 to 999) |

| End point values | 30mg bid | | | |
|-------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 1 | | | |
| Units: hour (hr) | | | | |
| median (full range (min-max)) | 999 (999 to 999) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: PK Parameters: T1/2 ss,

| | |
|-----------------|-------------------------|
| End point title | PK Parameters: T1/2 ss, |
|-----------------|-------------------------|

End point description:

Trough PK concentrations and PK profiles at steady-state were collected.

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

End point timeframe:

pre-dose (0 hour), 1, 1.5, 2, 4 and 6 hours post AM dose for escalation dose or pre-dose (trough) for maintained dose

| End point values | 10mg bid | 20mg bid | 30mg bid | 2mg bid |
|---|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 6 | 1 | 1 | 2 |
| Units: hour (hr) | | | | |
| geometric mean (geometric coefficient of variation) | 4.32 (± 47.8) | 999 (± 999) | 999 (± 999) | 6.39 (± 13.8) |

| | | | | |
|---|----------------------|--|--|--|
| End point values | 5mg bid | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 11 | | | |
| Units: hour (hr) | | | | |
| geometric mean (geometric coefficient of variation) | 3.54 (\pm 49.8) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who were responders on 24-hour urine free cortisol (UFC) at Week 22

| | |
|---|--|
| End point title | Percentage of participants who were responders on 24-hour urine free cortisol (UFC) at Week 22 |
| End point description: | |
| A patient was considered to be a responder if his/her mean UFC level from the three 24-hour urine samples collected at Week 22 was \leq ULN (as defined by the local laboratories) or represented a $\geq 50\%$ decrease from baseline. Participants with controlled or partially controlled UFC were defined as: Controlled UFC: mean UFC level \leq upper limit of normal (ULN). Partially controlled UFC: mean UFC level $>$ ULN but with $\geq 50\%$ reduction from baseline. | |
| End point type | Secondary |
| End point timeframe: | |
| Week 22 | |

| | | | | |
|-------------------------------------|--------------------------------|--------------------------------|--|--|
| End point values | Part II Core: Expansion cohort | Part II Core: Follow-up cohort | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 15 | 4 | | |
| Units: Percentage pf participants | | | | |
| number (confidence interval 95%) | | | | |
| Responders | 80.0 (51.91 to 95.67) | 75.0 (19.41 to 99.37) | | |
| Controlled UFC responders | 80.0 (51.91 to 95.67) | 75.0 (19.41 to 99.37) | | |
| Partially controlled UFC responders | 0 (0.00 to 21.80) | 0 (0.00 to 60.24) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with Escape

| | |
|-----------------|------------------------------------|
| End point title | Number of participants with Escape |
|-----------------|------------------------------------|

End point description:

Escape is defined as loss of UFC control (i.e. UFC > ULN) on at least 2 consecutive visits at the highest tolerated dose after previously attaining UFC normalization)

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

End point timeframe:

approx. 7 years

| End point values | Part II Core: Expansion cohort | Part II Core: Follow-up cohort | | |
|-----------------------------|--------------------------------------|--------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 15 | 4 | | |
| Units: Participants | 2 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Event (AE) timeframe: Adverse events were collected from first dose of study treatment until end of study treatment plus 28 days post treatment, up to maximum duration of 350.6 weeks.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 22.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------------------|
| Reporting group title | Part I: Core cohort |
|-----------------------|---------------------|

Reporting group description:

Participants took an ascending dose of LCI699 (osilodrostat) from 2mg bid or 5 mg bid, up to 30 mg bid and participated in Part I of this study. 4 patients in this cohort moved to Part II of the study

| | |
|-----------------------|--------------------------------|
| Reporting group title | Part II Core: Expansion cohort |
|-----------------------|--------------------------------|

Reporting group description:

Participants took an ascending dose from 2mg bid or 5 mg bid, up to 30 mg bid and participated in the Part II Core Expansion of this study. These patients were all newly enrolled into the phase II part of the study

| | |
|-----------------------|--------------------------------|
| Reporting group title | Part II Core: Follow-up cohort |
|-----------------------|--------------------------------|

Reporting group description:

Participants took an ascending dose from 2mg bid or 5 mg bid, up to 30 mg bid and participated in the Part II Core Follow-up of this study. These patients were patients who transferred from Part I Core phase of the study.

| Serious adverse events | Part I: Core cohort | Part II Core: Expansion cohort | Part II Core: Follow-up cohort |
|---|---------------------|--------------------------------|--------------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 5 / 15 (33.33%) | 1 / 4 (25.00%) |
| 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 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 15 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Neoplasm progression | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (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 |
| Pituitary tumour benign | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (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 |
| Vascular disorders | | | |
| Takayasu's arteritis | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 15 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Palpitations | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 15 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Supraventricular extrasystoles | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 15 (0.00%) | 1 / 4 (25.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tachycardia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 15 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ventricular extrasystoles | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 15 (0.00%) | 1 / 4 (25.00%) |
| 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 | | | |
| Headache | | | |

| | | | |
|--|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (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 |
| General disorders and administration site conditions | | | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 15 (0.00%) | 1 / 4 (25.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Food poisoning | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (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 |
| Endocrine disorders | | | |
| Adrenal insufficiency | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 1 / 4 (25.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pituitary-dependent Cushing's syndrome | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 2 / 15 (13.33%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (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 / 12 (0.00%) | 0 / 15 (0.00%) | 1 / 4 (25.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | Part I: Core cohort | Part II Core: Expansion cohort | Part II Core: Follow-up cohort |
|---|---------------------|--------------------------------|--------------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 12 / 12 (100.00%) | 15 / 15 (100.00%) | 4 / 4 (100.00%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Neoplasm progression | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pituitary tumour benign | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 15 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Vascular disorders | | | |
| Hot flush | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 15 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Hypertension | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 3 / 15 (20.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 4 | 1 |
| Hypotension | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 15 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 1 | 0 | 1 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 5 / 15 (33.33%) | 2 / 4 (50.00%) |
| occurrences (all) | 0 | 5 | 3 |
| Chest discomfort | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Chills | | | |

| | | | |
|--|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 15 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Fatigue | | | |
| subjects affected / exposed | 7 / 12 (58.33%) | 3 / 15 (20.00%) | 3 / 4 (75.00%) |
| occurrences (all) | 9 | 3 | 3 |
| Feeling drunk | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Generalised oedema | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Influenza like illness | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 15 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 1 | 0 | 2 |
| Malaise | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 4 / 15 (26.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 5 | 0 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 3 / 15 (20.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 1 | 3 | 1 |
| Peripheral swelling | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 15 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 2 / 15 (13.33%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Reproductive system and breast disorders | | | |
| Amenorrhoea | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 15 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Breast pain | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dysmenorrhoea | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Erectile dysfunction | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Menstruation delayed | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Menorrhagia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Oligomenorrhoea | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Vaginal haemorrhage | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 15 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 3 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 15 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Cough | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 2 / 15 (13.33%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Dysphonia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 15 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 2 |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 15 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Epistaxis | | | |

| | | | |
|------------------------------|----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 15 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Laryngeal oedema | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 15 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 2 |
| Nasal congestion | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Rhinitis allergic | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Sinus congestion | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 15 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Psychiatric disorders | | | |
| Abnormal sleep-related event | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 15 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Anxiety | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 2 / 15 (13.33%) | 0 / 4 (0.00%) |
| occurrences (all) | 3 | 2 | 0 |
| Depression | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 2 / 15 (13.33%) | 1 / 4 (25.00%) |
| occurrences (all) | 1 | 2 | 2 |
| Disorientation | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 15 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Insomnia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 1 | 1 |
| Libido decreased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| | | | |
|--|---------------------|----------------------|---------------------|
| Sleep disorder subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 1 / 15 (6.67%) 1 | 1 / 4 (25.00%) 2 |
| Investigations | | | |
| Aldosterone urine increased subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 1 / 15 (6.67%) 1 | 0 / 4 (0.00%) 0 |
| Amylase increased subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 0 / 15 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Blood aldosterone decreased subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 1 / 15 (6.67%) 1 | 0 / 4 (0.00%) 0 |
| Blood alkaline phosphatase increased subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 15 (0.00%) 0 | 1 / 4 (25.00%) 1 |
| Blood corticotrophin increased subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 5 / 15 (33.33%) 5 | 3 / 4 (75.00%) 3 |
| Blood creatine phosphokinase increased subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 4 / 15 (26.67%) 4 | 0 / 4 (0.00%) 0 |
| Blood creatinine increased subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 1 / 15 (6.67%) 1 | 0 / 4 (0.00%) 0 |
| Blood gonadotrophin abnormal subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 1 / 15 (6.67%) 1 | 0 / 4 (0.00%) 0 |
| Blood lactate dehydrogenase increased subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 1 / 15 (6.67%) 1 | 0 / 4 (0.00%) 0 |
| Blood luteinising hormone decreased subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 1 / 15 (6.67%) 1 | 0 / 4 (0.00%) 0 |
| Blood phosphorus | | | |

| | | | |
|-----------------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blood potassium decreased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 1 | 2 |
| Blood pressure decreased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blood pressure increased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 2 / 15 (13.33%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Blood prolactin increased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 15 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Blood testosterone free increased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 15 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Blood testosterone increased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 2 / 15 (13.33%) | 4 / 4 (100.00%) |
| occurrences (all) | 0 | 2 | 3 |
| Blood uric acid increased | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Cortisol decreased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 15 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Cortisol free urine decreased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 15 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 2 |
| Cortisol free urine increased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Electrocardiogram T wave abnormal | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 2 / 15 (13.33%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Gamma-glutamyltransferase | | | |

| | | | |
|------------------------------------|-----------------|-----------------|----------------|
| increased | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 15 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Gastric pH decreased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 15 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Heart rate increased | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| High density lipoprotein decreased | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 15 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hormone level abnormal | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 4 / 15 (26.67%) | 3 / 4 (75.00%) |
| occurrences (all) | 0 | 4 | 3 |
| Lipase increased | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 1 / 15 (6.67%) | 2 / 4 (50.00%) |
| occurrences (all) | 2 | 1 | 3 |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 15 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Neutrophil count increased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 15 (0.00%) | 2 / 4 (50.00%) |
| occurrences (all) | 0 | 0 | 2 |
| Oestradiol increased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 15 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Platelet count decreased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 15 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Protein total increased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| | | | |
|--|----------------------|----------------------|---------------------|
| Renin decreased subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 1 / 15 (6.67%) 1 | 0 / 4 (0.00%) 0 |
| Urine analysis abnormal subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 1 / 15 (6.67%) 1 | 0 / 4 (0.00%) 0 |
| Urine leukocyte esterase subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 1 / 15 (6.67%) 1 | 0 / 4 (0.00%) 0 |
| Vitamin D decreased subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 1 / 15 (6.67%) 1 | 1 / 4 (25.00%) 1 |
| Weight decreased subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 2 / 15 (13.33%) 3 | 0 / 4 (0.00%) 0 |
| Weight increased subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 2 / 15 (13.33%) 2 | 1 / 4 (25.00%) 1 |
| White blood cell count increased subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 15 (0.00%) 0 | 1 / 4 (25.00%) 1 |
| Injury, poisoning and procedural complications | | | |
| Accident subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 1 / 15 (6.67%) 1 | 0 / 4 (0.00%) 0 |
| Animal bite subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 1 / 15 (6.67%) 1 | 0 / 4 (0.00%) 0 |
| Arthropod bite subjects affected / exposed occurrences (all) | 2 / 12 (16.67%) 2 | 3 / 15 (20.00%) 3 | 0 / 4 (0.00%) 0 |
| Contusion subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 1 / 15 (6.67%) 3 | 0 / 4 (0.00%) 0 |
| Foot fracture | | | |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Heat illness | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Joint injury | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 15 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Ligament sprain | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Lumbar vertebral fracture | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Muscle injury | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Tooth fracture | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 15 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Cardiac disorders | | | |
| Bradycardia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 15 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Bundle branch block right | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Palpitations | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Sinus bradycardia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 15 (6.67%) | 1 / 4 (25.00%) |
| occurrences (all) | 1 | 1 | 1 |
| Tachycardia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| | | | |
|--------------------------------------|-----------------|-----------------|----------------|
| Nervous system disorders | | | |
| Cold-stimulus headache | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dizziness | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 3 / 15 (20.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 2 | 3 | 2 |
| Dizziness postural | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 15 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Headache | | | |
| subjects affected / exposed | 3 / 12 (25.00%) | 6 / 15 (40.00%) | 2 / 4 (50.00%) |
| occurrences (all) | 4 | 8 | 3 |
| Hypersomnia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 15 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Hypoaesthesia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 15 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hypogeusia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 15 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Paraesthesia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 15 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Presyncope | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 15 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Somnolence | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 15 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Syncope | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Blood and lymphatic system disorders | | | |

| | | | |
|--|----------------------|----------------------|---------------------|
| Anaemia subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 3 / 15 (20.00%) 3 | 0 / 4 (0.00%) 0 |
| Eosinophilia subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 0 / 15 (0.00%) 0 | 1 / 4 (25.00%) 1 |
| Iron deficiency anaemia subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 1 / 15 (6.67%) 2 | 1 / 4 (25.00%) 2 |
| Polycythaemia subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 1 / 15 (6.67%) 1 | 0 / 4 (0.00%) 0 |
| Ear and labyrinth disorders Inner ear disorder subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 15 (0.00%) 0 | 1 / 4 (25.00%) 1 |
| Middle ear effusion subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 15 (0.00%) 0 | 1 / 4 (25.00%) 1 |
| Vertigo subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 1 / 15 (6.67%) 1 | 2 / 4 (50.00%) 2 |
| Eye disorders Blepharospasm subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 3 | 0 / 15 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Conjunctival haemorrhage subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 1 / 15 (6.67%) 1 | 0 / 4 (0.00%) 0 |
| Visual impairment subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 1 / 15 (6.67%) 1 | 0 / 4 (0.00%) 0 |
| Gastrointestinal disorders Abdominal discomfort subjects affected / exposed occurrences (all) | 2 / 12 (16.67%) 4 | 0 / 15 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Abdominal distension | | | |

| | | | |
|----------------------------------|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 2 / 15 (13.33%) | 3 / 4 (75.00%) |
| occurrences (all) | 3 | 2 | 4 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Constipation | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 15 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 3 / 12 (25.00%) | 4 / 15 (26.67%) | 3 / 4 (75.00%) |
| occurrences (all) | 3 | 4 | 7 |
| Dry mouth | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 15 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 2 / 15 (13.33%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Dysphagia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 3 | 1 | 0 |
| Gastric disorder | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 15 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Gastrointestinal disorder | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Gastrointestinal pain | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 15 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 1 | 1 |
| Haemorrhoidal haemorrhage | | | |

| | | | |
|--|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Irritable bowel syndrome | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Nausea | | | |
| subjects affected / exposed | 5 / 12 (41.67%) | 8 / 15 (53.33%) | 2 / 4 (50.00%) |
| occurrences (all) | 6 | 10 | 3 |
| Tongue disorder | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 15 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Toothache | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 2 / 4 (50.00%) |
| occurrences (all) | 0 | 1 | 2 |
| Vomiting | | | |
| subjects affected / exposed | 3 / 12 (25.00%) | 1 / 15 (6.67%) | 2 / 4 (50.00%) |
| occurrences (all) | 4 | 1 | 4 |
| Hepatobiliary disorders | | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 15 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Hypertransaminaemia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Acanthosis nigricans | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Acne | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 3 / 15 (20.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 3 | 0 |
| Dermal cyst | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 15 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dermatitis contact | | | |

| | | | |
|-----------------------------|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 15 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dry skin | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Ecchymosis | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 15 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hair growth abnormal | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 15 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Hirsutism | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 2 / 15 (13.33%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Hyperhidrosis | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Hypertrichosis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 2 / 4 (50.00%) |
| occurrences (all) | 0 | 1 | 2 |
| Melanoderma | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Night sweats | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Papule | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pruritus | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 1 / 15 (6.67%) | 1 / 4 (25.00%) |
| occurrences (all) | 5 | 3 | 1 |
| Rash | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 3 / 15 (20.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Skin discolouration | | | |

| | | | |
|--|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Skin hyperpigmentation | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Urticaria | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 15 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Renal and urinary disorders | | | |
| Chromaturia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Haematuria | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 15 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Urinary incontinence | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Endocrine disorders | | | |
| Adrenal insufficiency | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 6 / 15 (40.00%) | 2 / 4 (50.00%) |
| occurrences (all) | 0 | 6 | 3 |
| Diabetes insipidus | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Glucocorticoid deficiency | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hypothyroidism | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pituitary-dependent Cushing's syndrome | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 12 (0.00%) | 2 / 15 (13.33%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 5 / 15 (33.33%) | 1 / 4 (25.00%) |
| occurrences (all) | 2 | 7 | 1 |
| Back pain | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 2 / 15 (13.33%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Bone pain | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 15 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Bursitis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Joint effusion | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 15 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Joint swelling | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Muscle spasms | | | |
| subjects affected / exposed | 3 / 12 (25.00%) | 1 / 15 (6.67%) | 1 / 4 (25.00%) |
| occurrences (all) | 3 | 1 | 1 |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 15 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 2 / 15 (13.33%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 2 | 1 |
| Musculoskeletal stiffness | | | |

| | | | |
|-------------------------------------|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 12 (0.00%) | 2 / 15 (13.33%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Myalgia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 1 | 1 |
| Neck pain | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 15 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Osteopenia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 2 / 15 (13.33%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 4 | 0 |
| Tendonitis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 15 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 15 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 6 |
| Cystitis | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 15 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Escherichia urinary tract infection | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Fungal infection | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 15 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 1 | 0 | 1 |
| Furuncle | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 15 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| | | | |
|-----------------------------------|----------------|-----------------|----------------|
| Gastroenteritis bacterial | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Groin abscess | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 15 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Helicobacter gastritis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 15 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Influenza | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 2 / 15 (13.33%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 3 | 1 |
| Laryngitis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 3 / 15 (20.00%) | 2 / 4 (50.00%) |
| occurrences (all) | 1 | 3 | 7 |
| Onychomycosis | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 15 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pharyngitis streptococcal | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 15 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 1 | 1 |
| Skin infection | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 15 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

| | | | |
|---|---------------------|----------------------|---------------------|
| Tongue fungal infection subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 15 (0.00%) 0 | 1 / 4 (25.00%) 1 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 2 / 15 (13.33%) 2 | 1 / 4 (25.00%) 1 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 3 / 15 (20.00%) 4 | 3 / 4 (75.00%) 5 |
| Viral rhinitis subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 1 / 15 (6.67%) 1 | 0 / 4 (0.00%) 0 |
| Vulvovaginal mycotic infection subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 15 (0.00%) 0 | 2 / 4 (50.00%) 2 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 1 / 15 (6.67%) 1 | 0 / 4 (0.00%) 0 |
| Folate deficiency subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 0 / 15 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Hypercalcaemia subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 15 (0.00%) 0 | 1 / 4 (25.00%) 1 |
| Hypercreatininaemia subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 15 (0.00%) 0 | 1 / 4 (25.00%) 1 |
| Hyperglycaemia subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 15 (0.00%) 0 | 1 / 4 (25.00%) 1 |
| Hyperkalaemia subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 1 / 15 (6.67%) 1 | 0 / 4 (0.00%) 0 |
| Hypernatraemia | | | |

| | | | |
|-----------------------------|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hypertriglyceridaemia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hyperuricaemia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 15 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Hypokalaemia | | | |
| subjects affected / exposed | 3 / 12 (25.00%) | 1 / 15 (6.67%) | 2 / 4 (50.00%) |
| occurrences (all) | 3 | 1 | 3 |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 1 | 1 |
| Hypoproteinaemia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hyposideraemia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 15 (6.67%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Vitamin B12 deficiency | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 15 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Vitamin D deficiency | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 15 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 17 December 2010 | Amended the inclusion criteria to ensure that only Cushing's disease patients are enrolled; Defined responders as having a normalization of UFC or a 50% decrease in UFC; Revised the assumptions and power calculations to support the study sample size were revised and remove the originally planned interim analysis; Amended stopping rules to minimize premature termination of a patient from the study for AEs that were expected in this population or were efficacy related |
| 31 January 2011 | Changed the blood volume required for PD assessments. |
| 16 March 2011 | Revised and clarify the statistical analysis; Removed the need for a UFC measurement at Screening |
| 26 March 2012 | Confirmed the preliminary observations from the PoC study by: - Enrolling a new cohort (Expansion cohort) of patients. - Reenrolling the patients from the first cohort (Core PoC Follow-up cohort). - Evaluated the long-term efficacy and safety of osilodrostat treatment at 22 weeks and up to 12 months. |
| 26 April 2013 | Intensified ECG monitoring for potential risk of QTc prolongation; Excluded patients with a history of pituitary irradiation within 5 years prior to study entry; Replaced the highest dosing regimen (50 mg bid) from the dose titration schedule with a dose of 30 mg bid for those patients who did not have normalization of UFC at 20 mg bid. |
| 14 March 2014 | The purpose of this protocol amendment was to continue the study to monitor patients for long-term safety and efficacy, and to provide continued access to osilodrostat to patients who have completed long term extension-1; Provided that the investigator's assessment was that the patient would benefit from continued treatment with osilodrostat, and did not meet the protocol's termination criteria, the patient had the option to enter a second-long term extension period (extension-2), which was to continue until osilodrostat was commercially available and reimbursed or through the availability of a local access program; In addition, the protocol was updated to indicate that the formulation of osilodrostat was changed from capsules to tablets during long term extension-2. |
| 16 February 2016 | The primary purpose of this protocol amendment was to ensure patient safety by adding specific criteria for the identification and management of patients with potential drug-induced liver injury (DILI). Although there are no known cases of suspected DILI in patients treated with osilodrostat to date, these criteria are added in the event that a case of suspected DILI arises in the future; Update to the requirement for contraception by male study participants. For male subjects participating in clinical trials, contraception was no longer required; Clarification of protocol language regarding withdrawal of consent, study treatment discontinuation, and discontinuation procedures. |

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| 11 July 2017 | The main purpose of this amendment was to provide continued access to the study treatment for those patients benefitting from the treatment into a separate long-term safety follow-up study (roll-over study). Based on this, the end of study (EOS) definition was updated. The EOS definition was changed throughout the protocol from "until osilodrostat is commercially available & reimbursed or through the availability of a local access program" to "patient treatment in Long Term Extension-2 will end at each site within 4 months after a separate roll-over study is opened at their site, or by 31 December 2018 (whichever occurred earlier). The roll-over study was to provide an opportunity of continued treatment for patients who were still ongoing at that time & were clinically benefitting from osilodrostat. For sites where a separate roll-over study was not an option, the patient had to be offered a local alternative treatment option. In addition, the option of an earlier End of Trial visit (i.e. earlier than the 6 month interval visits in Long Term Extension-2) was implemented to allow seamless transition of patients into the separate rollover study; The risks section was updated to include neutropenia, which is a known effect related to the decrease of cortisol in patients with Cushing's disease, in line with cases observed in clinical trials with osilodrostat. The QT-specific concomitant medication guidance for osilodrostat was revised to limit the list of prohibited drugs to medications with a 'Known risk to cause TdP' and 'Possible risk to cause TdP', instead of all drugs known to prolong QT. This change was also in alignment with the terminology used in the QT Drug Lists (CredibleMeds®); Interim Analysis was updated to allow for an additional database lock in support of future market authorization applications for osilodrostat |
| 03 May 2018 | The purpose of this amendment was to extend the study end date by a year from 31-Dec-2018 to 31-Dec-2019 to allow continued access to the study treatment for those patients benefitting from the treatment until a separate long-term safety follow-up study (roll-over study) was set up at participating sites; Additional updates were made to the Protocol glossary and withdrawal of informed consent section to align with the new Personal Data and Withdrawal of Consent language requirement. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use <https://www.novctrd.com/CtrdWeb/home.novforcomplete> trial results.

Notes: