



Clinical trial results:

Phase 2 Study of the Safety and Efficacy of CORT125134 in the Treatment of Endogenous Cushing's Syndrome

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2016-000899-23 |
| Trial protocol | GB HU NL IT |
| Global end of trial date | 24 September 2018 |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 (current) |
| This version publication date | 31 January 2020 |
| First version publication date | 31 January 2020 |

Trial information

Trial identification

| | |
|-----------------------|----------------|
| Sponsor protocol code | CORT125134-451 |
|-----------------------|----------------|

Additional study identifiers

| | |
|------------------------------------|--------------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02804750 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | 128625: IND Number |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Corcept Therapeutics |
| Sponsor organisation address | 149 Commonwealth Drive, Menlo Park, United States, 94025 |
| Public contact | Medical Director, Corcept Therapeutics, +1 650 327 3270, info@corcept.com |
| Scientific contact | Medical Director, Corcept Therapeutics, +1 650 327 3270, info@corcept.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 | 24 September 2018 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 24 September 2018 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to evaluate the safety and efficacy of CORT125134 for treatment of endogenous Cushing's syndrome. The multicenter study was conducted in the United States and in Europe.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 28 June 2016 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

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

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Netherlands: 2 |
| Country: Number of subjects enrolled | United Kingdom: 2 |
| Country: Number of subjects enrolled | Hungary: 5 |
| Country: Number of subjects enrolled | United States: 12 |
| Country: Number of subjects enrolled | Italy: 14 |
| Worldwide total number of subjects | 35 |
| EEA total number of subjects | 23 |

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) | 32 |
| From 65 to 84 years | 3 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants were screened up to 6 weeks before Day 1. A total of 67 participants were screened and 35 were enrolled.

Period 1

| | |
|------------------------------|----------------|
| Period 1 title | Period 1 |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|-------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Group 1: Low-dose Group |

Arm description:

100 mg/day for 4 weeks in Period 1, then 150 mg/day for 4 weeks in Period 2, then 200 mg/day for 4 weeks in Period 3. There was no washout between treatment periods. Period 3 was followed by a 4-week follow-up period. Per-protocol, Group 1 did not participate in treatment Period 4.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | CORT125134 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

CORT125134 50 mg capsules for oral administration

| | |
|------------------|--------------------------|
| Arm title | Group 2: High-dose Group |
|------------------|--------------------------|

Arm description:

250 mg/day for 4 weeks in Period 1, then 300 mg/day for 4 weeks in Period 2, then 350 mg/day for 4 weeks in Period 3, then 400 mg/day for 4 weeks in Period 4. There was no washout between treatment periods. Period 4 was followed by a 4-week follow-up period.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | CORT125134 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

CORT125134 50 mg capsules for oral administration

| Number of subjects in period 1 | Group 1: Low-dose Group | Group 2: High-dose Group |
|--------------------------------|-------------------------|--------------------------|
| Started | 17 | 18 |
| Completed | 17 | 15 |
| Not completed | 0 | 3 |
| Consent withdrawn by subject | - | 1 |
| Adverse event, non-fatal | - | 2 |

Period 2

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

Arms

| | |
|------------------------------|-------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Group 1: Low-dose Group |

Arm description:

100 mg/day for 4 weeks in Period 1, then 150 mg/day for 4 weeks in Period 2, then 200 mg/day for 4 weeks in Period 3. There was no washout between treatment periods. Period 3 was followed by a 4-week follow-up period. Per-protocol, Group 1 did not participate in treatment Period 4.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | CORT125134 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

CORT125134 50 mg capsules for oral administration

| | |
|------------------|--------------------------|
| Arm title | Group 2: High-dose Group |
|------------------|--------------------------|

Arm description:

250 mg/day for 4 weeks in Period 1, then 300 mg/day for 4 weeks in Period 2, then 350 mg/day for 4 weeks in Period 3, then 400 mg/day for 4 weeks in Period 4. There was no washout between treatment periods. Period 4 was followed by a 4-week follow-up period.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | CORT125134 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

CORT125134 50 mg capsules for oral administration

| Number of subjects in period 2 | Group 1: Low-dose Group | Group 2: High-dose Group |
|---------------------------------------|-------------------------|--------------------------|
| Started | 17 | 15 |
| Completed | 16 | 15 |
| Not completed | 1 | 0 |
| Adverse event, non-fatal | 1 | - |

Period 3

| | |
|------------------------------|----------------|
| Period 3 title | Period 3 |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|-------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Group 1: Low-dose Group |

Arm description:

100 mg/day for 4 weeks in Period 1, then 150 mg/day for 4 weeks in Period 2, then 200 mg/day for 4 weeks in Period 3. There was no washout between treatment periods. Period 3 was followed by a 4-week follow-up period. Per-protocol, Group 1 did not participate in treatment Period 4.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | CORT125134 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

CORT125134 50 mg capsules for oral administration

| | |
|------------------|--------------------------|
| Arm title | Group 2: High-dose Group |
|------------------|--------------------------|

Arm description:

250 mg/day for 4 weeks in Period 1, then 300 mg/day for 4 weeks in Period 2, then 350 mg/day for 4 weeks in Period 3, then 400 mg/day for 4 weeks in Period 4. There was no washout between treatment periods. Period 4 was followed by a 4-week follow-up period.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | CORT125134 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

CORT125134 50 mg capsules for oral administration

| Number of subjects in period 3 | Group 1: Low-dose Group | Group 2: High-dose Group |
|--------------------------------|-------------------------|--------------------------|
| Started | 16 | 15 |
| Completed | 16 | 13 |
| Not completed | 0 | 2 |
| Adverse event, non-fatal | - | 2 |

Period 4

| | |
|------------------------------|----------------|
| Period 4 title | Period 4 |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|-----------|--------------------------|
| Arm title | Group 2: High-dose Group |
|-----------|--------------------------|

Arm description:

250 mg/day for 4 weeks in Period 1, then 300 mg/day for 4 weeks in Period 2, then 350 mg/day for 4 weeks in Period 3, then 400 mg/day for 4 weeks in Period 4. There was no washout between treatment periods. Period 4 was followed by a 4-week follow-up period.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | CORT125134 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

CORT125134 50 mg capsules for oral administration

| Number of subjects in period 4 ^[1] | Group 2: High-dose Group |
|---|--------------------------|
| Started | 12 |
| Completed | 7 |
| Not completed | 5 |
| Adverse event, non-fatal | 5 |

Notes:

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

Justification: Per protocol, Group 1 did not participate in Period 4. One participant in Group 2 completed Period 3 but did not start Period 4 due to a pre-scheduled surgery. This participant is considered to have completed the study; this patient did not sign Protocol Version 7.0 allowing CORT125134 dosing at 400 mg.

Baseline characteristics

Reporting groups

| | |
|--|--------------------------|
| Reporting group title | Group 1: Low-dose Group |
| Reporting group description: 100 mg/day for 4 weeks in Period 1, then 150 mg/day for 4 weeks in Period 2, then 200 mg/day for 4 weeks in Period 3. There was no washout between treatment periods. Period 3 was followed by a 4-week follow-up period. Per-protocol, Group 1 did not participate in treatment Period 4. | |
| Reporting group title | Group 2: High-dose Group |
| Reporting group description: 250 mg/day for 4 weeks in Period 1, then 300 mg/day for 4 weeks in Period 2, then 350 mg/day for 4 weeks in Period 3, then 400 mg/day for 4 weeks in Period 4. There was no washout between treatment periods. Period 4 was followed by a 4-week follow-up period. | |

| Reporting group values | Group 1: Low-dose Group | Group 2: High-dose Group | Total |
|--|-------------------------|--------------------------|-------|
| Number of subjects | 17 | 18 | 35 |
| Age categorical Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 15 | 17 | 32 |
| From 65-84 years | 2 | 1 | 3 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous Units: years | | | |
| arithmetic mean | 47.6 | 49.5 | - |
| standard deviation | ± 13.62 | ± 13.46 | - |
| Gender categorical Units: Subjects | | | |
| Female | 9 | 16 | 25 |
| Male | 8 | 2 | 10 |
| Hypertension | | | |
| Confirmed with a mean systolic blood pressure (BP) of 130-170 mmHg and/or a mean diastolic BP of 85-110 mmHg based on the 24-hour ambulatory BP measurement. | | | |
| Units: Subjects | | | |
| Hypertension | 12 | 11 | 23 |
| No hypertension | 5 | 7 | 12 |
| Impaired Glucose Tolerance (IGT) / Type-2 Diabetes Mellitus (T2DM) | | | |
| Either a fasting glucose > 126 mg/dL and a 2-hour Oral Glucose Tolerance Test (oGTT) result for plasma glucose ≥ 200 mg/dL at 2 hours (for T2DM), or a 2-hour oGTT result for plasma glucose in the range of ≥ 140 mg/dL to < 200 mg/dL (for IGT). | | | |
| Units: Subjects | | | |
| IGT / T2DM | 13 | 15 | 28 |
| No IGT / T2DM | 4 | 3 | 7 |

End points

End points reporting groups

| | |
|--|--------------------------|
| Reporting group title | Group 1: Low-dose Group |
| Reporting group description: 100 mg/day for 4 weeks in Period 1, then 150 mg/day for 4 weeks in Period 2, then 200 mg/day for 4 weeks in Period 3. There was no washout between treatment periods. Period 3 was followed by a 4-week follow-up period. Per-protocol, Group 1 did not participate in treatment Period 4. | |
| Reporting group title | Group 2: High-dose Group |
| Reporting group description: 250 mg/day for 4 weeks in Period 1, then 300 mg/day for 4 weeks in Period 2, then 350 mg/day for 4 weeks in Period 3, then 400 mg/day for 4 weeks in Period 4. There was no washout between treatment periods. Period 4 was followed by a 4-week follow-up period. | |
| Reporting group title | Group 1: Low-dose Group |
| Reporting group description: 100 mg/day for 4 weeks in Period 1, then 150 mg/day for 4 weeks in Period 2, then 200 mg/day for 4 weeks in Period 3. There was no washout between treatment periods. Period 3 was followed by a 4-week follow-up period. Per-protocol, Group 1 did not participate in treatment Period 4. | |
| Reporting group title | Group 2: High-dose Group |
| Reporting group description: 250 mg/day for 4 weeks in Period 1, then 300 mg/day for 4 weeks in Period 2, then 350 mg/day for 4 weeks in Period 3, then 400 mg/day for 4 weeks in Period 4. There was no washout between treatment periods. Period 4 was followed by a 4-week follow-up period. | |
| Reporting group title | Group 1: Low-dose Group |
| Reporting group description: 100 mg/day for 4 weeks in Period 1, then 150 mg/day for 4 weeks in Period 2, then 200 mg/day for 4 weeks in Period 3. There was no washout between treatment periods. Period 3 was followed by a 4-week follow-up period. Per-protocol, Group 1 did not participate in treatment Period 4. | |
| Reporting group title | Group 2: High-dose Group |
| Reporting group description: 250 mg/day for 4 weeks in Period 1, then 300 mg/day for 4 weeks in Period 2, then 350 mg/day for 4 weeks in Period 3, then 400 mg/day for 4 weeks in Period 4. There was no washout between treatment periods. Period 4 was followed by a 4-week follow-up period. | |
| Reporting group title | Group 1: Low-dose Group |
| Reporting group description: 100 mg/day for 4 weeks in Period 1, then 150 mg/day for 4 weeks in Period 2, then 200 mg/day for 4 weeks in Period 3. There was no washout between treatment periods. Period 3 was followed by a 4-week follow-up period. Per-protocol, Group 1 did not participate in treatment Period 4. | |
| Reporting group title | Group 2: High-dose Group |
| Reporting group description: 250 mg/day for 4 weeks in Period 1, then 300 mg/day for 4 weeks in Period 2, then 350 mg/day for 4 weeks in Period 3, then 400 mg/day for 4 weeks in Period 4. There was no washout between treatment periods. Period 4 was followed by a 4-week follow-up period. | |

Primary: Percentage of Participants With One or More Adverse Events

| | |
|--|---|
| End point title | Percentage of Participants With One or More Adverse Events ^[1] |
| End point description: All treatment-emergent adverse events were recorded and summarized. | |
| End point type | Primary |
| End point timeframe: Group 1: up to Week 16; Group 2: up to Week 20 | |
| 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 between-group statistical comparisons were planned for safety and tolerability endpoints. | |

| End point values | Group 1: Low-dose Group | Group 2: High-dose Group | | |
|-----------------------------------|-------------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 17 | 18 | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 88.24 | 100 | | |

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants With One or More Severe (≥Grade 3) Adverse Events

| | |
|-----------------|---|
| End point title | Percentage of Participants With One or More Severe (≥Grade 3) Adverse Events ^[2] |
|-----------------|---|

End point description:

All treatment-emergent adverse events with Common Terminology Criteria for Adverse Events (CTCAE) ≥Grade 3 (severe) were recorded and summarized.

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

End point timeframe:

Group 1: up to Week 16; Group 2: up to Week 20

Notes:

[2] - 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 between-group statistical comparisons were planned for safety and tolerability endpoints.

| End point values | Group 1: Low-dose Group | Group 2: High-dose Group | | |
|-----------------------------------|-------------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 17 | 18 | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 17.65 | 38.89 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Hypertension Who Experience Improvement in Blood Pressure Following Treatment With CORT125134

| | |
|-----------------|---|
| End point title | Percentage of Participants With Hypertension Who Experience Improvement in Blood Pressure Following Treatment With CORT125134 |
|-----------------|---|

End point description:

Improvement in BP was defined as a participant who experiences at least a 5 mmHg decrease in mean diastolic or systolic BP from Baseline who has not taken an additional antihypertensive medication during the treatment period or increased the dosage of a concurrent antihypertensive medication. The population analyzed was all enrolled participants with hypertension at Baseline who received at least one dose of study drug and had at least one post-baseline assessment.

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

End point timeframe:

Group 1: Week 12 or last observation; Group 2: Week 16, or last observation

| End point values | Group 1: Low-dose Group | Group 2: High-dose Group | | |
|-----------------------------------|-------------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 12 | 11 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 41.67 (15.17 to 72.33) | 63.64 (30.79 to 89.07) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With IGT / T2DM Who Experienced a $\geq 25\%$ Reduction in AUCglucose Following Treatment With CORT125134

| | |
|-----------------|--|
| End point title | Percentage of Participants With IGT / T2DM Who Experienced a $\geq 25\%$ Reduction in AUCglucose Following Treatment With CORT125134 |
|-----------------|--|

End point description:

Improvement in glucose control was defined as a participant who experiences at least a 25% decrease from baseline in area under the concentration-time curve for blood glucose (AUCglucose) who has not taken an additional diabetes medication during the treatment period or increased the dosage of a concurrent diabetes medication. The population analyzed was all enrolled participants with IGT / T2DM at Baseline who received at least one dose of study drug and had at least one post-baseline assessment.

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

End point timeframe:

Before and 0.5, 1, 1.5, and 2 hours after a glucose drink at Week 12 or last observation (Group 1) or Week 16 or last observation (Group 2)

| End point values | Group 1: Low-dose Group | Group 2: High-dose Group | | |
|-----------------------------------|-------------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 13 | 14 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 23.08 (5.04 to 53.81) | 0 (0 to 23.16) | | |

Statistical analyses

No statistical analyses for this end point

Post-hoc: Percentage of Participants With IGT / T2DM Who Experience Improvement in Glucose Control Following Treatment With CORT125134: Responder

Definition Based on Response Criteria for Phase 3 Study NCT03697109 (2018-003096-35)

| | |
|-----------------|--|
| End point title | Percentage of Participants With IGT / T2DM Who Experience Improvement in Glucose Control Following Treatment With CORT125134: Responder Definition Based on Response Criteria for Phase 3 Study NCT03697109 (2018-003096-35) |
|-----------------|--|

End point description:

Improvement in glucose control was defined as a participant who experiences 1) a hemoglobin A1c (HbA1c) that is decreased by $\geq 0.5\%$ from baseline, 2) a 2-hour oGTT plasma glucose that is normalized (< 7.8 mmol/L) or decreased by ≥ 2.8 mmol/L from baseline, or 3) a total daily insulin dose that has decreased by $\geq 25\%$ or total daily sulfonylurea dose that has decreased by $\geq 50\%$ and an HbA1c that is unchanged or decreased from baseline. The population analyzed was all enrolled participants with IGT / T2DM at Baseline who received at least one dose of study drug and had non-missing post-baseline data collected, with exclusions based on clinical judgment and/or important protocol deviations applied on a visit and outcome level rather than a participant level.

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

End point timeframe:

Before and 0.5, 1, 1.5, and 2 hours after a glucose drink at Week 12 or last observation (Group 1) or Week 16 or last observation (Group 2)

| End point values | Group 1: Low-dose Group | Group 2: High-dose Group | | |
|-----------------------------------|-------------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 13 | 12 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 15.38 (1.92 to 45.45) | 50.00 (21.09 to 78.91) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Group 1: up to Week 16; Group 2: up to Week 20

Adverse event reporting additional description:

All enrolled participants who received at least 1 dose of study drug

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 19.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-------------------------|
| Reporting group title | Group 1: Low-dose Group |
|-----------------------|-------------------------|

Reporting group description:

100 mg/day for 4 weeks in Period 1, then 150 mg/day for 4 weeks in Period 2, then 200 mg/day for 4 weeks in Period 3. Period 3 was followed by a 4-week follow-up period.

| | |
|-----------------------|--------------------------|
| Reporting group title | Group 2: High-dose Group |
|-----------------------|--------------------------|

Reporting group description:

250 mg/day for 4 weeks in Period 1, then 300 mg/day for 4 weeks in Period 2, then 350 mg/day for 4 weeks in Period 3, then 400 mg/day for 4 weeks in Period 4.

| Serious adverse events | Group 1: Low-dose Group | Group 2: High-dose Group | |
|---|-------------------------|--------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 4 / 18 (22.22%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 18 (5.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 18 (5.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Polyneuropathy | | | |

| | | | |
|--|----------------|----------------|--|
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 18 (5.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Myopathy | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 18 (5.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Pilonidal cyst | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 18 (5.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events | Group 1: Low-dose Group | Group 2: High-dose Group | |
|---|-------------------------|--------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 15 / 17 (88.24%) | 18 / 18 (100.00%) | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 3 / 17 (17.65%) | 0 / 18 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Contusion | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 18 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Haematoma | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 18 (5.56%) | |
| occurrences (all) | 0 | 1 | |
| Peripheral venous disease | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 18 (5.56%) | |
| occurrences (all) | 0 | 1 | |
| Phlebitis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 18 (5.56%) | |
| occurrences (all) | 0 | 1 | |

| | | | |
|--|-----------------|-----------------|--|
| Surgical and medical procedures | | | |
| Medical device removal | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 18 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| General disorders and administration site conditions | | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 4 / 17 (23.53%) | 5 / 18 (27.78%) | |
| occurrences (all) | 6 | 10 | |
| Peripheral swelling | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 2 / 18 (11.11%) | |
| occurrences (all) | 2 | 2 | |
| Asthenia | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 1 / 18 (5.56%) | |
| occurrences (all) | 4 | 2 | |
| Fatigue | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 2 / 18 (11.11%) | |
| occurrences (all) | 2 | 2 | |
| Adverse drug reaction | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 18 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Fat tissue increased | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 18 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Flushing | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 18 (5.56%) | |
| occurrences (all) | 1 | 1 | |
| Influenza like illness | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 18 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Pain | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 18 (5.56%) | |
| occurrences (all) | 1 | 1 | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 2 / 18 (11.11%) | |
| occurrences (all) | 0 | 2 | |
| Application site bruise | | | |

| | | | |
|---|----------------------|----------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 18 (5.56%) 2 | |
| Application site irritation subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 18 (5.56%) 1 | |
| Pyrexia subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 18 (5.56%) 1 | |
| Dizziness subjects affected / exposed occurrences (all) | 3 / 17 (17.65%) 3 | 4 / 18 (22.22%) 5 | |
| Bronchitis subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 2 / 18 (11.11%) 2 | |
| Reproductive system and breast disorders Vaginal haemorrhage subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 2 / 18 (11.11%) 2 | |
| Respiratory, thoracic and mediastinal disorders Wheezing subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 18 (0.00%) 0 | |
| Cough subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 18 (5.56%) 1 | |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 18 (5.56%) 1 | |
| Pneumonia subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 18 (5.56%) 1 | |
| Respiratory failure subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 18 (5.56%) 1 | |
| Psychiatric disorders | | | |

| | | | |
|---|----------------------|----------------------|--|
| Drug withdrawal syndrome subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 18 (0.00%) 0 | |
| Emotional distress subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 18 (5.56%) 1 | |
| Sleep disorder subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 18 (5.56%) 1 | |
| Investigations | | | |
| Activated partial thromboplastin time prolonged subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 2 | 0 / 18 (0.00%) 0 | |
| C-reactive protein increased subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 2 / 18 (11.11%) 2 | |
| Body temperature increased subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 18 (5.56%) 2 | |
| Glucocorticoids abnormal subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 18 (5.56%) 1 | |
| Injury, poisoning and procedural complications | | | |
| Fall subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 18 (0.00%) 0 | |
| Spinal fracture subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 18 (5.56%) 1 | |
| Nervous system disorders | | | |
| Headache subjects affected / exposed occurrences (all) | 4 / 17 (23.53%) 5 | 5 / 18 (27.78%) 9 | |
| Somnolence subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 18 (0.00%) 0 | |

| | | | |
|---|---------------------|----------------------|--|
| Neuropathy peripheral subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 2 / 18 (11.11%) 2 | |
| Sciatica subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 2 / 18 (11.11%) 2 | |
| Cervicobrachial syndrome subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 18 (5.56%) 5 | |
| Diabetic neuropathy subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 18 (5.56%) 1 | |
| Hypoaesthesia subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 18 (5.56%) 1 | |
| Insomnia subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 18 (5.56%) 1 | |
| Migraine subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 18 (5.56%) 3 | |
| Nerve root compression subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 18 (5.56%) 1 | |
| Nystagmus subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 18 (5.56%) 1 | |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 3 / 18 (16.67%) 3 | |
| Ear and labyrinth disorders Deafness subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 18 (5.56%) 1 | |
| Ear pain | | | |

| | | | |
|--|----------------------|----------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 18 (5.56%) 1 | |
| Vertigo subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 2 / 18 (11.11%) 2 | |
| Eye disorders Astigmatism subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 18 (5.56%) 1 | |
| Cataract subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 18 (5.56%) 1 | |
| Conjunctival haemorrhage subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 18 (5.56%) 1 | |
| Photopsia subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 18 (5.56%) 1 | |
| Gastrointestinal disorders Abdominal distension subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 3 / 18 (16.67%) 3 | |
| Abdominal pain subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 4 / 18 (22.22%) 6 | |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 2 / 18 (11.11%) 4 | |
| Constipation subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 1 / 18 (5.56%) 1 | |
| Diarrhoea subjects affected / exposed occurrences (all) | 4 / 17 (23.53%) 7 | 3 / 18 (16.67%) 7 | |
| Dyspepsia | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 17 (5.88%) | 4 / 18 (22.22%) | |
| occurrences (all) | 1 | 5 | |
| Nausea | | | |
| subjects affected / exposed | 3 / 17 (17.65%) | 5 / 18 (27.78%) | |
| occurrences (all) | 5 | 7 | |
| Vomiting | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 1 / 18 (5.56%) | |
| occurrences (all) | 2 | 1 | |
| Flatulence | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 2 / 18 (11.11%) | |
| occurrences (all) | 1 | 4 | |
| Haemorrhoids | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 18 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Gingival hyperpigmentation | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 18 (5.56%) | |
| occurrences (all) | 0 | 1 | |
| Skin and subcutaneous tissue disorders | | | |
| Acne | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 1 / 18 (5.56%) | |
| occurrences (all) | 4 | 3 | |
| Dry skin | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 18 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hyperhidrosis | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 18 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Application site vesicles | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 18 (5.56%) | |
| occurrences (all) | 0 | 2 | |
| Dermatitis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 18 (5.56%) | |
| occurrences (all) | 0 | 2 | |
| Erythema | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 18 (5.56%) | |
| occurrences (all) | 0 | 1 | |

| | | | |
|---|----------------|----------------|--|
| Folliculitis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 18 (5.56%) | |
| occurrences (all) | 0 | 1 | |
| Hidradenitis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 18 (5.56%) | |
| occurrences (all) | 0 | 1 | |
| Hyperkeratosis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 18 (5.56%) | |
| occurrences (all) | 0 | 1 | |
| Night sweats | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 18 (5.56%) | |
| occurrences (all) | 0 | 1 | |
| Pigmentation disorder | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 18 (5.56%) | |
| occurrences (all) | 0 | 1 | |
| Pruritus | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 18 (5.56%) | |
| occurrences (all) | 0 | 1 | |
| Skin hyperpigmentation | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 18 (5.56%) | |
| occurrences (all) | 0 | 1 | |
| Renal and urinary disorders | | | |
| Polyuria | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 18 (5.56%) | |
| occurrences (all) | 0 | 1 | |
| Endocrine disorders | | | |
| Cushing's syndrome | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 18 (5.56%) | |
| occurrences (all) | 0 | 1 | |
| Diabetes mellitus inadequate control | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 18 (5.56%) | |
| occurrences (all) | 0 | 1 | |
| Hyperprolactinaemia | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 18 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Musculoskeletal and connective tissue disorders | | | |

| | | |
|----------------------------------|-----------------|-----------------|
| Back pain | | |
| subjects affected / exposed | 4 / 17 (23.53%) | 7 / 18 (38.89%) |
| occurrences (all) | 11 | 26 |
| Pain in extremity | | |
| subjects affected / exposed | 4 / 17 (23.53%) | 4 / 18 (22.22%) |
| occurrences (all) | 10 | 7 |
| Arthralgia | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 4 / 18 (22.22%) |
| occurrences (all) | 2 | 10 |
| Joint swelling | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 18 (5.56%) |
| occurrences (all) | 1 | 2 |
| Myalgia | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 4 / 18 (22.22%) |
| occurrences (all) | 1 | 7 |
| Musculoskeletal pain | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 3 / 18 (16.67%) |
| occurrences (all) | 0 | 8 |
| Intervertebral disc disorder | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 0 | 1 |
| Medial tibial stress syndrome | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 0 | 1 |
| Muscle fatigue | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 0 | 6 |
| Neck pain | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 0 | 1 |
| Pain in jaw | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 0 | 1 |
| Temporomandibular joint syndrome | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 0 | 1 |

| | | | |
|---|---------------------|---------------------|--|
| Muscular weakness subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 18 (5.56%) 1 | |
| Pilonidal cyst subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 18 (5.56%) 1 | |
| Infections and infestations | | | |
| Fungal infection subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 2 | 0 / 18 (0.00%) 0 | |
| Lower respiratory tract infection subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 18 (0.00%) 0 | |
| Lymphangitis subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 18 (0.00%) 0 | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 1 / 18 (5.56%) 1 | |
| Candida infection subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 18 (5.56%) 1 | |
| Enterobacter infection subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 18 (5.56%) 1 | |
| Escherichia urinary tract infection subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 18 (5.56%) 1 | |
| Herpes zoster subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 18 (5.56%) 1 | |
| Sinusitis subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 18 (5.56%) 1 | |
| Metabolism and nutrition disorders | | | |

| | | | |
|--|---------------------|---------------------|--|
| Decreased appetite subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 1 / 18 (5.56%) 1 | |
| Hypocalcaemia subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 18 (0.00%) 0 | |
| Hypoglycaemia subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 18 (0.00%) 0 | |
| Hypokalaemia subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 2 | 1 / 18 (5.56%) 1 | |
| Increased appetite subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 18 (0.00%) 0 | |
| Hypothyroidism subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 18 (5.56%) 1 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 11 May 2016 | Amendment 2 Version 4.0: 1) clarified details of urinary free cortisol and salivary cortisol sampling times; 2) clarified the timing of oGTTs and 24-hour ambulatory blood pressure monitoring; 3) changed dose levels; 4) added dose-escalation rule; 5) specified the timing of DRC review in the study design figure; 6) updated eligibility criteria; 7) clarified the number of capsules to use and capsule packaging; 8) detail added to the dose reduction and escalation options; 9) cautioned against foods known to inhibit CYP2C8 or CYP3A4; 10) added details and requirement for completion of Patient Diary Card; 11) defined the fasting time before oGTT test; 12) clarified timing of ambulatory blood pressure measurements; 13) specified time windows for PK samples; 14) clarified dose-escalation rule; 15) clarified visit windows; 16) clarified the screening tests to be performed if a washout period is needed for participants taking Cushing medications. |
| 16 November 2017 | Version 6.0: 1) added that participants who complete 12 weeks of dosing in Group 1, and on the recommendation of the Investigator and with agreement of the Medical Monitor may proceed into Group 2 and receive the Group 3 dose-escalation scheme; 2) made modifications and clarifications to the screening procedures and the inclusion and exclusion criteria; 3) made clarifications and updates to assessment procedures; 4) made clarifications to the Statistical Analysis Plan. |
| 15 January 2018 | Version 7.0: 1) the CORT125134 400 mg dose level was added to the Group 2 dose escalation scheme; 2) extended the age range from 75 to 80 years; 3) corrected the definition of impaired glucose tolerance; 4) clarified the assessments required for participants who proceed from Group 1 to Group 2 dose escalation. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported