



## Clinical trial results:

### A Phase III extension study of efficacy, safety and tolerability of Chronocort® in the treatment of congenital adrenal hyperplasia (CAH)

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2015-005448-32 |
| Trial protocol           | GB SE DE DK    |
| Global end of trial date | 13 July 2022   |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 29 July 2023 |
| First version publication date | 29 July 2023 |

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | DIUR-006 |
|-----------------------|----------|

##### Additional study identifiers

|                                    |                 |
|------------------------------------|-----------------|
| ISRCTN number                      | -               |
| ClinicalTrials.gov id (NCT number) | NCT03062280     |
| WHO universal trial number (UTN)   | -               |
| Other trial identifiers            | IND No. : 76485 |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Diurnal Ltd  |
| Sponsor organisation address | Cardiff Medicentre, Heath Park, Cardiff, United Kingdom, CF14 4UJ              |
| Public contact               | Clinical Trials Information, Diurnal Ltd, +44 2920 682 069, info@diurnal.co.uk |
| Scientific contact           | Clinical Trials Information, Diurnal Ltd, +44 2920 682 069, info@diurnal.co.uk |

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                       | 13 July 2022 |
| Is this the analysis of the primary completion data? | No           |
| Global end of trial reached?                         | Yes          |
| Global end of trial date                             | 13 July 2022 |
| Was the trial ended prematurely?                     | No           |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the safety and tolerability of Chronocort over time, as assessed by signs and symptoms of adrenal insufficiency or over-treatment, use of sick day rules, adrenal crisis, adverse events (AEs), laboratory measures and clinical observation.

Protection of trial subjects:

The study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki (1996 version for most countries except Sweden where the Regulatory Authority stipulated the 2013 version should be used), ICH and GCP requirements. The principles of informed consent in the Declaration of Helsinki, in the current requirements of GCP (published by the ICH) and local regulation, whichever afforded the greater participant protection, were implemented before any protocol-specified procedures or interventions were carried out. A signed and dated ICF was obtained from each participant prior to entering the study. The Investigator was responsible for obtaining written informed consent from the participant after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specified screening procedures or any study medications were administered. Information was given in both oral and written form whenever possible, and as deemed appropriate by the IECs/IRBs. Participants were also asked for consent to allow the Sponsor, Sponsor representative or external regulatory auditor to review their medical records to confirm compliance with GCP. All information sheets and consent forms were provided in the local language. The acquisition of informed consent was documented in the participant's medical record and the ICF was signed and personally dated by the participant or the participant's legally acceptable representative, as well as by the person who conducted the informed consent discussion. The original signed ICF was retained with the medical records at each site, a copy retained in the Investigator Site File and a further copy provided to the participant prior to the start of the study interventions. Representative written information for the participant and a sample ICF, designated as the master versions, were filed in the Trial Master File.

Background therapy:

Fludrocortisone dose adjustment was made if medically indicated and was based on blood pressure measurements and laboratory data (goal supine PRA  $<1.5 \times$  ULN).

Evidence for comparator:

Since all participants who took part in this study received Chronocort, there were no formal treatment comparisons. Summaries over time were produced for safety and efficacy parameters.

|   |                |
|---|----------------|
| Actual start date of recruitment                          | 30 August 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 | United States: 10  |
| Country: Number of subjects enrolled | Sweden: 13         |
| Country: Number of subjects enrolled | United Kingdom: 24 |
| Country: Number of subjects enrolled | France: 24         |

|                                      |             |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Germany: 20 |
| Worldwide total number of subjects   | 91          |
| EEA total number of subjects         | 57          |

Notes:

| <b>Subjects enrolled per age group</b>    |    |
|---|----|
| In utero                                  | 0  |
| Preterm newborn - gestational age < 37 wk | 0  |
| Newborns (0-27 days)                      | 0  |
| Infants and toddlers (28 days-23 months)  | 0  |
| Children (2-11 years)                     | 0  |
| Adolescents (12-17 years)                 | 0  |
| Adults (18-64 years)                      | 90 |
| From 65 to 84 years                       | 1  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Participants with CAH who successfully completed DIUR-003 and DIUR-005 have entered this study. The study centres in this study were the same centres that recruited the participants into the feeder study.

8 sites in 5 countries recruited participants: France 2, Germany 1, Sweden 1, UK 3, USA 1.

### Pre-assignment

Screening details:

Participants attended screening visit prior to baseline assessments to allow DIUR-006 to be fully explained and to give informed consent.

Participants from DIUR-003 and any participants from DIUR-005 who had a gap between completing DIUR-005 and starting DIUR-006 during which they received standard GC therapy screening included safety blood tests

### Pre-assignment period milestones

|                              |    |
|------------------------------|----|
| Number of subjects started   | 91 |
| Number of subjects completed | 91 |

### Period 1

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

Blinding implementation details:

Blinding was not applicable to the period

### Arms

|  |                                |
|--|--------------------------------|
| Arm title                              | Chronocort                     |
| Arm description: -                     |                                |
| Arm type                               | Experimental                   |
| Investigational medicinal product name | Chronocort                     |
| Investigational medicinal product code |                                |
| Other name                             |                                |
| Pharmaceutical forms                   | Modified-release capsule, hard |
| Routes of administration               | Oral use                       |

Dosage and administration details:

Participants who entered from DIUR-003, participants who received standard therapy in DIUR-005, and participants from DIUR-005 who had a gap between completing DIUR-005 and starting DIUR-006 during which they received standard GC therapy, had their initial dose of Chronocort determined using the hydrocortisone equivalent of the participant's previous treatment (immediately prior to the baseline visit). Participants from DIUR 005 who took Chronocort at the end of DIUR 005 and entered DIUR 006 immediately started DIUR 006 on the same dose as when they completed DIUR 005. Approximately 2/3rds of the daily dose was given in the evening, with the remainder given in the morning. The morning dose of Chronocort was to be taken at approximately 07:00 hours and the evening dose was to be taken at approximately 23:00 hours. It was recommended that the morning dose was taken on an empty stomach at least 1 hour before a meal, and the evening dose at least 2 hours after the last meal.

| <b>Number of subjects in period 1</b> | Chronocort |
|---------------------------------------|------------|
| Started                               | 91         |
| Completed                             | 69         |
| Not completed                         | 22         |
| Adverse event, serious fatal          | 1          |
| Physician decision                    | 2          |
| Consent withdrawn by subject          | 11         |
| Fertility treatment                   | 2          |
| Adverse event, non-fatal              | 1          |
| Pregnancy                             | 5          |

## Baseline characteristics

### Reporting groups

|                       |                                   |
|-----------------------|-----------------------------------|
| Reporting group title | Treatment Period (overall period) |
|-----------------------|-----------------------------------|

Reporting group description: -

| Reporting group values                                       | Treatment Period<br>(overall period) | Total |  |
|--|--------------------------------------|-------|--|
| Number of subjects   | 91                                   | 91    |  |
| Age categorical  |                                      |       |  |
| Units: Subjects  |                                      |       |  |
| In utero   | 0                                    | 0     |  |
| Preterm newborn infants<br>(gestational age < 37 wks)        | 0                                    | 0     |  |
| Newborns (0-27 days)   | 0                                    | 0     |  |
| Infants and toddlers (28 days-23<br>months)                  | 0                                    | 0     |  |
| Children (2-11 years)  | 0                                    | 0     |  |
| Adolescents (12-17 years)                                    | 0                                    | 0     |  |
| Adults (18-64 years)   | 0                                    | 0     |  |
| From 65-84 years   | 0                                    | 0     |  |
| 85 years and over  | 0                                    | 0     |  |
| Age between 18-30 years                                      | 30                                   | 30    |  |
| Age between 30-50 years                                      | 44                                   | 44    |  |
| Age between 50-70 years                                      | 17                                   | 17    |  |
| Not recorded   | 0                                    | 0     |  |
| Age continuous   |                                      |       |  |
| Units: years   |                                      |       |  |
| arithmetic mean  | 37.1                                 |       |  |
| full range (min-max)   | 20 to 67                             | -     |  |
| Gender categorical   |                                      |       |  |
| Units: Subjects  |                                      |       |  |
| Female   | 62                                   | 62    |  |
| Male   | 29                                   | 29    |  |
| Race/Ethnicity   |                                      |       |  |
| Units: Subjects  |                                      |       |  |
| White  | 89                                   | 89    |  |
| Other  | 2                                    | 2     |  |
| Hospitalised within the last 12 months<br>prior to enrolment |                                      |       |  |
| Units: Subjects  |                                      |       |  |
| Hospitalised in 12 months -Yes                               | 6                                    | 6     |  |
| Hospitalised in 12 months -No                                | 85                                   | 85    |  |
| Number of adrenal crisis in the last year                    |                                      |       |  |
| Units: Subjects  |                                      |       |  |
| Number of adrenal crisis in 12<br>months-None                | 86                                   | 86    |  |
| Number of adrenal crisis in 12<br>months-One                 | 5                                    | 5     |  |

|  |                   |   |  |
|--|-------------------|---|--|
| Body Mass Index (BMI)<br>Units: kg/m <sup>2</sup><br>arithmetic mean<br>standard deviation | 28.802<br>± 5.669 | - |  |
| Body Surface Area (BSA)<br>Units: m <sup>2</sup><br>arithmetic mean<br>standard deviation  | 1.798<br>± 0.2099 | - |  |
| Waist circumference<br>Units: cm<br>arithmetic mean<br>standard deviation                  | 91.54<br>± 14.810 | - |  |

## End points

### End points reporting groups

|  |  |
|--|--|
| Reporting group title  | Chronocort   |
| Reporting group description: -   |  |
| Subject analysis set title   | One or More Signs and Symptoms of Adrenal Insufficiency        |
| Subject analysis set type  | Per protocol   |
| Subject analysis set description:  |  |
| Number of participants had one or more signs of adrenal insufficiency or over-treatment.         |  |
| Subject analysis set title   | Signs and Symptoms of AI-due to Over Treatment                 |
| Subject analysis set type  | Per protocol   |
| Subject analysis set description:  |  |
| Number of participants having signs and symptoms of adrenal insufficiency due to over-treatment  |  |
| Subject analysis set title   | Signs and Symptoms of AI-due to Under Treatment                |
| Subject analysis set type  | Per protocol   |
| Subject analysis set description:  |  |
| Number of participants having signs and symptoms of adrenal insufficiency due to under treatment |  |
| Subject analysis set title   | Number of Participants Used Sick Day Medications               |
| Subject analysis set type  | Per protocol   |
| Subject analysis set description:  |  |
| Number of Participants Used Sick Day Medications and Steroids in Addition to IMP                 |  |
| Subject analysis set title   | Number of Participants Used Medication Not from Sick Day Packs |
| Subject analysis set type  | Per protocol   |
| Subject analysis set description:  |  |
| Number of participants used medication not from sick day packs                                   |  |
| Subject analysis set title   | Medication from Sick Day Pack- Injection                       |
| Subject analysis set type  | Per protocol   |
| Subject analysis set description:  |  |
| Number of participants used injections from the sick day pack.                                   |  |
| Subject analysis set title   | Medication from Sick Day Pack - Oral Hydrocortisone            |
| Subject analysis set type  | Per protocol   |
| Subject analysis set description:  |  |
| Number of participants used oral hydrocortisone from the sick day pack.                          |  |
|  |  |
| Subject analysis set title   | Number of Participants Experiencing Adrenal Crises             |
| Subject analysis set type  | Per protocol   |
| Subject analysis set description:  |  |
| Number of participants experiencing at least one adrenal crises through out the study            |  |
| Subject analysis set title   | Participants Experiencing Any AE                               |
| Subject analysis set type  | Per protocol   |
| Subject analysis set description:  |  |
| Number of participants experiencing any AE throughout the study.                                 |  |
| Subject analysis set title   | Participant Experiencing Any AE Causally Related to Chronocort |
| Subject analysis set type  | Per protocol   |
| Subject analysis set description:  |  |
| Number of participants experiencing any AE causally related to Chronocort throughout the study.  |  |
| Subject analysis set title   | Participants Experiencing Any AE Leading to Sick Day Rules     |
| Subject analysis set type  | Per protocol   |



Subject analysis set description:

Number of participants experiencing any AE leading to sick day rules throughout the study.

|                            |  |
|----------------------------|--|
| Subject analysis set title | Participant Experiencing AE Leading-Sick Day Rule-Chronocort |
| Subject analysis set type  | Per protocol   |

Subject analysis set description:

Number of participants experiencing any AE leading to sick day rules causally related to Chronocort throughout the study.

|                            |  |
|----------------------------|--|
| Subject analysis set title | Participants Experiencing Any AE Leading to Adrenal Crisis |
| Subject analysis set type  | Per protocol   |

Subject analysis set description:

Number of participants experiencing any AE relating to adrenal crisis throughout the study.

|                            |   |
|----------------------------|---|
| Subject analysis set title | Participants Experiencing AE-Unexpected Therapeutic Benefit |
| Subject analysis set type  | Per protocol  |

Subject analysis set description:

Number of participants experiencing any AE of unexpected therapeutic benefit throughout the study.

|                            |  |
|----------------------------|--|
| Subject analysis set title | AE of Unexpected Therapeutic Benefit-Related to Chronocort |
| Subject analysis set type  | Per protocol   |

Subject analysis set description:

Number of participants experiencing any AE of unexpected therapeutic benefit causally related to Chronocort throughout the study.

|                            |   |
|----------------------------|---|
| Subject analysis set title | Participants Experiencing Any AE Leading to Death |
| Subject analysis set type  | Per protocol                                      |

Subject analysis set description:

Number of participants experiencing any AE leading to death through out the study

|                            |   |
|----------------------------|---|
| Subject analysis set title | Participants Experiencing Any AE Leading to Discontinuation |
| Subject analysis set type  | Per protocol  |

Subject analysis set description:

Number of participants experiencing any AE leading to discontinuation throughout the study.

|                            |   |
|----------------------------|---|
| Subject analysis set title | Any AE Leading to Discontinuation-Related to Chronocort |
| Subject analysis set type  | Per protocol  |

Subject analysis set description:

Number of participants experiencing any AE leading to discontinuation causally related to Chronocort throughout the study.

|                            |  |
|----------------------------|--|
| Subject analysis set title | Participants Experiencing any Serious Adverse Events |
| Subject analysis set type  | Per protocol   |

Subject analysis set description:

Number of participants experiencing any Serious Adverse Events throughout the study.

|                            |  |
|----------------------------|--|
| Subject analysis set title | Participants with Any SAE Causally related to Chronocort |
| Subject analysis set type  | Per protocol   |

Subject analysis set description:

Number of participants experiencing any Serious Adverse Events causally related to Chronocort.

|                            |   |
|----------------------------|---|
| Subject analysis set title | Participants Experiencing Any Severe Adverse Events |
| Subject analysis set type  | Per protocol  |

Subject analysis set description:

Number of participants experiencing any severe adverse events throughout the study.

|                            |  |
|----------------------------|--|
| Subject analysis set title | Participants Experiencing Any AE Associated with Dose Increase |
| Subject analysis set type  | Per protocol   |

Subject analysis set description:

Number of participants experiencing any AE Associated with dose increase throughout the study.

|                            |  |
|----------------------------|--|
| Subject analysis set title | AE Associated with Dose Increase-Related to Chronocort |
| Subject analysis set type  | Per protocol   |

Subject analysis set description:

Number of participants experiencing any AE associated with a dose increase causally related to Chronocort throughout the study.

|                            |  |
|----------------------------|--|
| Subject analysis set title | Participants Experiencing Any AE Associated with Dose Decrease |
| Subject analysis set type  | Per protocol   |

Subject analysis set description:

Number of participants experiencing any AE Associated with dose decrease throughout the study.

|                            |  |
|----------------------------|--|
| Subject analysis set title | AE Associated with Dose Decrease-Related to Chronocort |
| Subject analysis set type  | Per protocol   |

Subject analysis set description:

Number of participants experiencing AE associated with dose decrease-Related to Chronocort throughout the study.

|                            |  |
|----------------------------|--|
| Subject analysis set title | Participants Experiencing Any AE - Dose Interruption |
| Subject analysis set type  | Per protocol   |

Subject analysis set description:

Number of participants experiencing Any AE associated with dose interruption throughout the study.

|                            |  |
|----------------------------|--|
| Subject analysis set title | Change from Pre-Chronocort Baseline - Sodium |
| Subject analysis set type  | Per protocol                                 |

Subject analysis set description:

Shifts in biochemistry variables from within the reference range (normal) at pre Chronocort baseline to maximum or minimum values on treatment throughout the study.

|                            |   |
|----------------------------|---|
| Subject analysis set title | Change from Pre-Chronocort Baseline - Potassium |
| Subject analysis set type  | Per protocol                                    |

Subject analysis set description:

Shifts in biochemistry variables from within the reference range (normal) at pre Chronocort baseline to maximum or minimum values on treatment throughout the study.

|                            |  |
|----------------------------|--|
| Subject analysis set title | Change from Pre-Chronocort Baseline - Chloride |
| Subject analysis set type  | Per protocol                                   |

Subject analysis set description:

Shifts in biochemistry variables from within the reference range (normal) at pre Chronocort baseline to maximum or minimum values on treatment throughout the study.

|                            |  |
|----------------------------|--|
| Subject analysis set title | Change from Pre-Chronocort Baseline-Total carbon dioxide |
| Subject analysis set type  | Per protocol   |

Subject analysis set description:

Shifts in biochemistry variables from within the reference range (normal) at pre Chronocort baseline to maximum or minimum values on treatment throughout the study.

|                            |   |
|----------------------------|---|
| Subject analysis set title | Change from Pre-Chronocort Baseline-Total Calcium |
| Subject analysis set type  | Per protocol                                      |

Subject analysis set description:

Shifts in biochemistry variables from within the reference range (normal) at pre Chronocort baseline to maximum or minimum values on treatment throughout the study.

|                            |  |
|----------------------------|--|
| Subject analysis set title | Change from Pre-Chronocort Baseline- Total Magnesium |
| Subject analysis set type  | Per protocol   |

Subject analysis set description:

Shifts in biochemistry variables from within the reference range (normal) at pre Chronocort baseline to maximum or minimum values on treatment throughout the study.

|                            |  |
|----------------------------|--|
| Subject analysis set title | Change from Pre-Chronocort Baseline-Inorganic phosphorus |
| Subject analysis set type  | Per protocol   |

Subject analysis set description:

Shifts in biochemistry variables from within the reference range (normal) at pre Chronocort baseline to maximum or minimum values on treatment throughout the study.

|                            |  |
|----------------------------|--|
| Subject analysis set title | Change from pre-Chronocort baseline-Creatinine |
|----------------------------|--|

|   |   |
|---|---|
| Subject analysis set type   | Per protocol  |
| Subject analysis set description:<br>Shifts in biochemistry variables from within the reference range (normal) at pre Chronocort baseline to maximum or minimum values on treatment throughout the study. |   |
| Subject analysis set title  | Change from Pre-Chronocort Baseline-Blood urea nitrogen   |
| Subject analysis set type   | Per protocol  |
| Subject analysis set description:<br>Shifts in biochemistry variables from within the reference range (normal) at pre Chronocort baseline to maximum or minimum values on treatment throughout the study. |   |
| Subject analysis set title  | Change from Pre-Chronocort Baseline-Fasting glucose       |
| Subject analysis set type   | Per protocol  |
| Subject analysis set description:<br>Shifts in biochemistry variables from within the reference range (normal) at pre Chronocort baseline to maximum or minimum values on treatment throughout the study. |   |
| Subject analysis set title  | Change from Pre-Chronocort Baseline-Uric Acid             |
| Subject analysis set type   | Per protocol  |
| Subject analysis set description:<br>Shifts in biochemistry variables from within the reference range (normal) at pre Chronocort baseline to maximum or minimum values on treatment throughout the study. |   |
| Subject analysis set title  | Change from pre-Chronocort baseline -Total protein        |
| Subject analysis set type   | Per protocol  |
| Subject analysis set description:<br>Shifts in biochemistry variables from within the reference range (normal) at pre Chronocort baseline to maximum or minimum values on treatment throughout the study. |   |
| Subject analysis set title  | Change from pre-Chronocort baseline-Albumin               |
| Subject analysis set type   | Per protocol  |
| Subject analysis set description:<br>Shifts in biochemistry variables from within the reference range (normal) at pre Chronocort baseline to maximum or minimum values on treatment throughout the study. |   |
| Subject analysis set title  | Change from pre-Chronocort baseline -ALP                  |
| Subject analysis set type   | Per protocol  |
| Subject analysis set description:<br>Shifts in biochemistry variables from within the reference range (normal) at pre Chronocort baseline to maximum or minimum values on treatment throughout the study. |   |
| Subject analysis set title  | Change from pre-Chronocort baseline-ALT/GPT               |
| Subject analysis set type   | Per protocol  |
| Subject analysis set description:<br>Shifts in biochemistry variables from within the reference range (normal) at pre Chronocort baseline to maximum or minimum values on treatment throughout the study. |   |
| Subject analysis set title  | Change from pre-Chronocort baseline-AST/GOT               |
| Subject analysis set type   | Per protocol  |
| Subject analysis set description:<br>Shifts in biochemistry variables from within the reference range (normal) at pre Chronocort baseline to maximum or minimum values on treatment throughout the study. |   |
| Subject analysis set title  | Change from pre-Chronocort baseline-Total creatine kinase |
| Subject analysis set type   | Per protocol  |
| Subject analysis set description:<br>Shifts in biochemistry variables from within the reference range (normal) at pre Chronocort baseline to maximum or minimum values on treatment throughout the study. |   |
| Subject analysis set title  | Change from pre-Chronocort baseline-Lactate dehydrogenase |
| Subject analysis set type   | Per protocol  |
| Subject analysis set description:<br>Shifts in biochemistry variables from within the reference range (normal) at pre Chronocort baseline to maximum or minimum values on treatment throughout the study. |   |

maximum or minimum values on treatment throughout the study.

|   |   |
|---|---|
| Subject analysis set title  | Change from pre-Chronocort baseline-Total bilirubin           |
| Subject analysis set type   | Per protocol  |
| Subject analysis set description:<br>Shifts in biochemistry variables from within the reference range (normal) at pre Chronocort baseline to maximum or minimum values on treatment throughout the study. |   |
| Subject analysis set title  | Change from pre-Chronocort baseline-Direct bilirubin          |
| Subject analysis set type   | Per protocol  |
| Subject analysis set description:<br>Shifts in biochemistry variables from within the reference range (normal) at pre Chronocort baseline to maximum or minimum values on treatment throughout the study. |   |
| Subject analysis set title  | Change from pre-Chronocort baseline-Total cholesterol         |
| Subject analysis set type   | Per protocol  |
| Subject analysis set description:<br>Shifts in biochemistry variables from within the reference range (normal) at pre Chronocort baseline to maximum or minimum values on treatment throughout the study. |   |
| Subject analysis set title  | Change from pre-Chronocort baseline-HDL cholesterol           |
| Subject analysis set type   | Per protocol  |
| Subject analysis set description:<br>Shifts in biochemistry variables from within the reference range (normal) at pre Chronocort baseline to maximum or minimum values on treatment throughout the study. |   |
| Subject analysis set title  | Change from pre-Chronocort baseline-LDL cholesterol           |
| Subject analysis set type   | Per protocol  |
| Subject analysis set description:<br>Shifts in biochemistry variables from within the reference range (normal) at pre Chronocort baseline to maximum or minimum values on treatment throughout the study. |   |
| Subject analysis set title  | Change from pre-Chronocort baseline-Triglycerides             |
| Subject analysis set type   | Per protocol  |
| Subject analysis set description:<br>Shifts in biochemistry variables from within the reference range (normal) at pre Chronocort baseline to maximum or minimum values on treatment throughout the study. |   |
| Subject analysis set title  | Mean Change-Pre-Chronocort Baseline- Systolic Blood Pressure  |
| Subject analysis set type   | Per protocol  |
| Subject analysis set description:<br>Mean Change from Pre-Chronocort Baseline to Month 30 in Systolic blood pressure (mmHg)   |   |
| Subject analysis set title  | Mean Change-Pre-Chronocort Baseline- Diastolic Blood Pressure |
| Subject analysis set type   | Per protocol  |
| Subject analysis set description:<br>Mean Change from Pre-Chronocort Baseline to Month 30 in Diastolic blood pressure (mmHg)  |   |
| Subject analysis set title  | Mean Change-Pre-Chronocort Baseline-Pulse rate                |
| Subject analysis set type   | Per protocol  |
| Subject analysis set description:<br>Mean Change from Pre-Chronocort Baseline to Month 30 in Pulse rate (beats/minute)  |   |
| Subject analysis set title  | Mean Change-Pre-Chronocort Baseline-Respiratory rate          |
| Subject analysis set type   | Per protocol  |
| Subject analysis set description:<br>Mean Change from Pre-Chronocort Baseline to Month 30 in Respiratory rate (breath/minute)   |   |
| Subject analysis set title  | Mean Change-Pre-Chronocort Baseline-Temperature               |
| Subject analysis set type   | Per protocol  |
| Subject analysis set description:<br>Mean Change from Pre-Chronocort Baseline to Month 30 in Temperature (Degree Celsius)   |   |
| Subject analysis set title  | Mean Change-Pre-Chronocort Baseline-Weight                    |

|   |   |
|---|---|
| Subject analysis set type   | Per protocol  |
| Subject analysis set description:   |   |
| Mean Change from Pre-Chronocort Baseline to Month 30 in Weight (kg)   |   |
| Subject analysis set title  | Mean Change-Pre-Chronocort Baseline-Body Mass Index     |
| Subject analysis set type   | Per protocol  |
| Subject analysis set description:   |   |
| Mean Change from Pre-Chronocort Baseline to Month 30 in Body Mass Index (kg/m2)   |   |
| Subject analysis set title  | Mean Change-Pre-Chronocort Baseline-Waist Circumference |
| Subject analysis set type   | Per protocol  |
| Subject analysis set description:   |   |
| Mean change from Pre-Chronocort Baseline to Month 30 in Waist circumference.  |   |
| Subject analysis set title  | Change from Pre-Chronocort Baseline-RBC Count           |
| Subject analysis set type   | Per protocol  |
| Subject analysis set description:   |   |
| Shifts in haematology variables from within the reference range (normal) at pre Chronocort baseline to maximum or minimum values on treatment throughout the study. |   |
| Subject analysis set title  | Change from pre-Chronocort baseline-Haemoglobin         |
| Subject analysis set type   | Per protocol  |
| Subject analysis set description:   |   |
| Shifts in haematology variables from within the reference range (normal) at pre Chronocort baseline to maximum or minimum values on treatment throughout the study. |   |
| Subject analysis set title  | Change from pre-Chronocort baseline-Haematocrit         |
| Subject analysis set type   | Per protocol  |
| Subject analysis set description:   |   |
| Shifts in haematology variables from within the reference range (normal) at pre Chronocort baseline to maximum or minimum values on treatment throughout the study. |   |
| Subject analysis set title  | Change from pre-Chronocort baseline-RDW                 |
| Subject analysis set type   | Per protocol  |
| Subject analysis set description:   |   |
| Shifts in haematology variables from within the reference range (normal) at pre Chronocort baseline to maximum or minimum values on treatment throughout the study. |   |
| Subject analysis set title  | Change from pre-Chronocort baseline-MCV                 |
| Subject analysis set type   | Per protocol  |
| Subject analysis set description:   |   |
| Shifts in haematology variables from within the reference range (normal) at pre Chronocort baseline to maximum or minimum values on treatment throughout the study. |   |
| Subject analysis set title  | Change from pre-Chronocort baseline-MCH                 |
| Subject analysis set type   | Per protocol  |
| Subject analysis set description:   |   |
| Shifts in haematology variables from within the reference range (normal) at pre Chronocort baseline to maximum or minimum values on treatment throughout the study. |   |
| Subject analysis set title  | Change from pre-Chronocort baseline-MCH concentration   |
| Subject analysis set type   | Per protocol  |
| Subject analysis set description:   |   |
| Shifts in haematology variables from within the reference range (normal) at pre Chronocort baseline to maximum or minimum values on treatment throughout the study. |   |
| Subject analysis set title  | Change from pre-Chronocort baseline-Platelet count      |
| Subject analysis set type   | Per protocol  |
| Subject analysis set description:   |   |
| Shifts in haematology variables from within the reference range (normal) at pre Chronocort baseline to maximum or minimum values on treatment throughout the study. |   |

|  |  |
|--|--|
| Subject analysis set title   | Change from pre-Chronocort baseline-Total WBC Count      |
| Subject analysis set type  | Per protocol   |
| Subject analysis set description:<br>Shifts in haematology variables from within the reference range (normal) at pre Chronocort baseline to maximum or minimum values on treatment throughout the study. |  |
| Subject analysis set title   | Change from pre-Chronocort baseline-Lymphocyte count abs |
| Subject analysis set type  | Per protocol   |
| Subject analysis set description:<br>Shifts in haematology variables from within the reference range (normal) at pre Chronocort baseline to maximum or minimum values on treatment throughout the study. |  |
| Subject analysis set title   | Change from pre-Chronocort baseline-Lymphocyte count %   |
| Subject analysis set type  | Per protocol   |
| Subject analysis set description:<br>Shifts in haematology variables from within the reference range (normal) at pre Chronocort baseline to maximum or minimum values on treatment throughout the study. |  |
| Subject analysis set title   | Change from pre-Chronocort baseline-Monocyte count abs   |
| Subject analysis set type  | Per protocol   |
| Subject analysis set description:<br>Shifts in haematology variables from within the reference range (normal) at pre Chronocort baseline to maximum or minimum values on treatment throughout the study. |  |
| Subject analysis set title   | Change from pre-Chronocort baseline-Monocyte count %     |
| Subject analysis set type  | Per protocol   |
| Subject analysis set description:<br>Shifts in haematology variables from within the reference range (normal) at pre Chronocort baseline to maximum or minimum values on treatment throughout the study. |  |
| Subject analysis set title   | Change from pre-Chronocort baseline-Neutrophil count abs |
| Subject analysis set type  | Per protocol   |
| Subject analysis set description:<br>Shifts in haematology variables from within the reference range (normal) at pre Chronocort baseline to maximum or minimum values on treatment throughout the study. |  |
| Subject analysis set title   | Change from pre-Chronocort baseline-Neutrophil count %   |
| Subject analysis set type  | Per protocol   |
| Subject analysis set description:<br>Shifts in haematology variables from within the reference range (normal) at pre Chronocort baseline to maximum or minimum values on treatment throughout the study. |  |
| Subject analysis set title   | Change from pre-Chronocort baseline-Basophil count abs   |
| Subject analysis set type  | Per protocol   |
| Subject analysis set description:<br>Shifts in haematology variables from within the reference range (normal) at pre Chronocort baseline to maximum or minimum values on treatment throughout the study. |  |
| Subject analysis set title   | Change from pre-Chronocort baseline-Basophil count %     |
| Subject analysis set type  | Per protocol   |
| Subject analysis set description:<br>Shifts in haematology variables from within the reference range (normal) at pre Chronocort baseline to maximum or minimum values on treatment throughout the study. |  |
| Subject analysis set title   | Change from pre-Chronocort baseline-Eosinophil count abs |
| Subject analysis set type  | Per protocol   |
| Subject analysis set description:<br>Shifts in haematology variables from within the reference range (normal) at pre Chronocort baseline to maximum or minimum values on treatment throughout the study. |  |
| Subject analysis set title   | Change from pre-Chronocort baseline-Eosinophil count %   |
| Subject analysis set type  | Per protocol   |

Subject analysis set description:

Shifts in haematology variables from within the reference range (normal) at pre Chronocort baseline to maximum or minimum values on treatment throughout the study.

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**Primary: Safety and Tolerability of Chronocort Over Time, as Assessed by Signs and symptoms of Adrenal Insufficiency.**

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|                 |   |
|-----------------|---|
| End point title | Safety and Tolerability of Chronocort Over Time, as Assessed by Signs and symptoms of Adrenal Insufficiency. <sup>[1]</sup> |
|-----------------|---|

End point description:

Safety and Tolerability of Chronocort Over Time, as Assessed by Signs and symptoms of Adrenal Insufficiency or over-treatment throughout the study.

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

End point timeframe:

5.5 years (Assessed at visits: Visit 2, Visit 3, Visit 4 then every 6 months and final visit)

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: The full analysis set was used for all data summaries. Summaries over time were produced for safety and efficacy parameters.

| End point values            | One or More Signs and Symptoms of Adrenal Insufficiency | Signs and Symptoms of AI-due to Over Treatment | Signs and Symptoms of AI-due to Under Treatment |  |
|-----------------------------|---|--|---|--|
| Subject group type          | Subject analysis set                                    | Subject analysis set                           | Subject analysis set                            |  |
| Number of subjects analysed | 91  | 91   | 91  |  |
| Units: Number of subjects   | 50  | 25   | 41  |  |

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**Statistical analyses**

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No statistical analyses for this end point

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**Primary: Safety and Tolerability of Chronocort as Assessed by Incidence of Use of Sick Day Rules.**

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|                 |   |
|-----------------|---|
| End point title | Safety and Tolerability of Chronocort as Assessed by Incidence of Use of Sick Day Rules. <sup>[2]</sup> |
|-----------------|---|

End point description:

Safety and yolerability of Chronocort as assessed by incidence of use of sick day rules throughout the study.

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

End point timeframe:

5.5 years (Assessed at visits: Visit 2, Visit 3, Visit 4 then every 6 months and final visit)

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: The full analysis set was used for all data summaries. Summaries over time were produced for safety and efficacy parameters.

| End point values            | Number of Participants Used Sick Day Medications | Number of Participants Used Medication Not from Sick Day Packs | Medication from Sick Day Pack- Injection | Medication from Sick Day Pack - Oral Hydrocortisone |
|-----------------------------|--|--|--|---|
| Subject group type          | Subject analysis set                             | Subject analysis set   | Subject analysis set                     | Subject analysis set                                |
| Number of subjects analysed | 91   | 91   | 91                                       | 91  |
| Units: Number of subjects   | 79   | 47   | 31                                       | 78  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Safety and Tolerability of Chronocort, as Assessed by the Occurrence of Adrenal Crises

|                 |   |
|-----------------|---|
| End point title | Safety and Tolerability of Chronocort, as Assessed by the Occurrence of Adrenal Crises <sup>[3]</sup> |
|-----------------|---|

End point description:

Safety and tolerability of Chronocort, as assessed by the occurrence of adrenal crises throughout the study.

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

End point timeframe:

5.5 years (Assessed at visits: Visit 2, Visit 3, Visit 4 then every 6 months and final visit)

Notes:

[3] - 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: The full analysis set was used for all data summaries. Summaries over time were produced for safety and efficacy parameters. Adverse Events leading to Adrenal Crises were summarised including an overall summary over the whole study treatment period. A total of 18 Adverse Events in 7 Participants (7.7%) were reported as Adverse Events considered indicative of Adrenal Crisis. None of these Adverse Events of Adrenal Crisis were considered causally related to Chronocort therapy.

| End point values            | Number of Participants Experiencing Adrenal Crises |  |  |  |
|-----------------------------|--|--|--|--|
| Subject group type          | Subject analysis set                               |  |  |  |
| Number of subjects analysed | 91   |  |  |  |
| Units: Number of subjects   | 7  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Safety and Tolerability of Chronocort, as Assessed by the Occurrence of AEs

|                 |  |
|-----------------|--|
| End point title | Safety and Tolerability of Chronocort, as Assessed by the Occurrence of AEs <sup>[4]</sup> |
|-----------------|--|

End point description:

Number of participants with at least 1 AE. Includes AEs with onset date on or after the date of first dose of DIUR-006 Chronocort (in the evening of the baseline visit) and up to and including 30 days following



EOS visit (or at the time they entered the follow-on study participants in France and USA).

|                      |         |
|----------------------|---------|
| End point type       | Primary |
| End point timeframe: |         |
| 5.5 years            |         |

Notes:

[4] - 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: The full analysis set was used for all data summaries. Summaries over time were produced for safety and efficacy parameters.

| End point values                                  | Chronocort      | Participants Experiencing Any AE | Participant Experiencing Any AE Causally Related to Chronocort | Participants Experiencing Any AE Leading to Sick Day Rules |
|---|-----------------|----------------------------------|--|--|
| Subject group type                                | Reporting group | Subject analysis set             | Subject analysis set   | Subject analysis set                                       |
| Number of subjects analysed                       | 91              | 91                               | 91   | 91   |
| Units: Subjects                                   |                 |                                  |  |  |
| Number of participants experiencing at least 1 AE | 90              | 90                               | 37   | 80   |
| Overall number of AE occurrences                  | 1533            | 1533                             | 83   | 700  |

| End point values                                  | Participant Experiencing AE Leading-Sick Day Rule-Chronocort | Participants Experiencing Any AE Leading to Adrenal Crisis | Participants Experiencing AE-Unexpected Therapeutic Benefit | AE of Unexpected Therapeutic Benefit-Related to Chronocort |
|---|--|--|---|--|
| Subject group type                                | Subject analysis set   | Subject analysis set                                       | Subject analysis set  | Subject analysis set                                       |
| Number of subjects analysed                       | 91   | 91   | 91  | 91   |
| Units: Subjects                                   |  |  |   |  |
| Number of participants experiencing at least 1 AE | 1  | 7  | 21  | 20   |
| Overall number of AE occurrences                  | 1  | 18   | 33  | 32   |

| End point values                                  | Participants Experiencing Any AE Leading to Death | Participants Experiencing Any AE Leading to Discontinuation | Any AE Leading to Discontinuation-Related to Chronocort | Participants Experiencing any Serious Adverse Events |
|---|---|---|---|--|
| Subject group type                                | Subject analysis set                              | Subject analysis set  | Subject analysis set                                    | Subject analysis set                                 |
| Number of subjects analysed                       | 91  | 91  | 91  | 91   |
| Units: Subjects                                   |   |   |   |  |
| Number of participants experiencing at least 1 AE | 1   | 6   | 3   | 28   |
| Overall number of AE occurrences                  | 1   | 7   | 4   | 78   |

| End point values | Participants with Any SAE Causally | Participants Experiencing Any Severe | Participants Experiencing Any AE | AE Associated with Dose Increase- |
|------------------|------------------------------------|--------------------------------------|----------------------------------|-----------------------------------|
|------------------|------------------------------------|--------------------------------------|----------------------------------|-----------------------------------|

|   | related to Chronocort | Adverse Events       | Associated with Dose Increase | Related to Chronocort |
|---|-----------------------|----------------------|-------------------------------|-----------------------|
| Subject group type                                | Subject analysis set  | Subject analysis set | Subject analysis set          | Subject analysis set  |
| Number of subjects analysed                       | 91                    | 91                   | 91                            | 91                    |
| Units: Subjects                                   |                       |                      |                               |                       |
| Number of participants experiencing at least 1 AE | 2                     | 24                   | 6                             | 2                     |
| Overall number of AE occurrences                  | 2                     | 63                   | 12                            | 2                     |

| End point values                                  | Participants Experiencing Any AE Associated with Dose Decrease | AE Associated with Dose Decrease-Related to Chronocort | Participants Experiencing Any AE - Dose Interruption |  |
|---|--|--|--|--|
| Subject group type                                | Subject analysis set   | Subject analysis set                                   | Subject analysis set                                 |  |
| Number of subjects analysed                       | 91   | 91   | 91   |  |
| Units: Subjects                                   |  |  |  |  |
| Number of participants experiencing at least 1 AE | 7  | 5  | 9  |  |
| Overall number of AE occurrences                  | 17   | 11   | 21   |  |

### Statistical analyses

No statistical analyses for this end point

### Primary: Safety and Tolerability of Chronocort Assessed by Pre-Chronocort Baseline-Laboratory Assessments -Minimum and Maximum Treatment Values-Biochemistry

|                 |  |
|-----------------|--|
| End point title | Safety and Tolerability of Chronocort Assessed by Pre-Chronocort Baseline-Laboratory Assessments -Minimum and Maximum Treatment Values-Biochemistry <sup>[5]</sup> |
|-----------------|--|

End point description:

Safety and tolerability of Chronocort, as assessed by change from pre-Chronocort baseline in safe laboratory assessments throughout the study. Number of participants with parameter value that shifted from baseline to minimum and maximum value on treatment

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

End point timeframe:

5.5 years

Notes:

[5] - 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: The full analysis set was used for all data summaries. Summaries over time were produced for safety and efficacy parameters.

| End point values                          | Change from Pre-Chronocort Baseline - Sodium | Change from Pre-Chronocort Baseline - Potassium | Change from Pre-Chronocort Baseline - Chloride | Change from Pre-Chronocort Baseline-Total carbon dioxide |
|---|--|---|--|--|
| Subject group type                        | Subject analysis set                         | Subject analysis set                            | Subject analysis set                           | Subject analysis set                                     |
| Number of subjects analysed               | 91   | 91  | 91   | 91   |
| Units: Subjects                           |  |   |  |  |
| No of Participants- Normal Value-Baseline | 87   | 85  | 76   | 80   |

|  |    |    |    |    |
|--|----|----|----|----|
| No Pts-pre-Chronocort Baseline val+treatment value | 87 | 87 | 87 | 87 |
| Shift from pre-Chronocort baseline - Minimum value | 6  | 4  | 1  | 34 |
| Shift from pre-Chronocort baseline - Maximum value | 1  | 0  | 7  | 1  |

| <b>End point values</b>                            | Change from Pre-Chronocort Baseline-Total Calcium | Change from Pre-Chronocort Baseline- Total Magnesium | Change from Pre-Chronocort Baseline- Inorganic phosphorus | Change from pre-Chronocort baseline- Creatinine |
|--|---|--|---|---|
| Subject group type                                 | Subject analysis set                              | Subject analysis set                                 | Subject analysis set                                      | Subject analysis set                            |
| Number of subjects analysed                        | 91  | 91   | 91  | 91  |
| Units: Subjects                                    |   |  |   |   |
| No of Participants- Normal Value- Baseline         | 84  | 87   | 70  | 77  |
| No Pts-pre-Chronocort Baseline val+treatment value | 87  | 87   | 87  | 87  |
| Shift from pre-Chronocort baseline - Minimum value | 4   | 0  | 7   | 12  |
| Shift from pre-Chronocort baseline - Maximum value | 1   | 2  | 5   | 2   |

| <b>End point values</b>                            | Change from Pre-Chronocort Baseline-Blood urea nitrogen | Change from Pre-Chronocort Baseline- Fasting glucose | Change from Pre-Chronocort Baseline-Uric Acid | Change from pre-Chronocort baseline -Total protein |
|--|---|--|---|--|
| Subject group type                                 | Subject analysis set                                    | Subject analysis set                                 | Subject analysis set                          | Subject analysis set                               |
| Number of subjects analysed                        | 91  | 91   | 91  | 91   |
| Units: Subjects                                    |   |  |   |  |
| No of Participants- Normal Value- Baseline         | 85  | 72   | 87  | 61   |
| No Pts-pre-Chronocort Baseline val+treatment value | 87  | 87   | 87  | 87   |
| Shift from pre-Chronocort baseline - Minimum value | 3   | 4  | 4   | 4  |
| Shift from pre-Chronocort baseline - Maximum value | 1   | 23   | 2   | 1  |

| <b>End point values</b>                            | Change from pre-Chronocort baseline- Albumin | Change from pre-Chronocort baseline -ALP | Change from pre-Chronocort baseline- ALT/GPT | Change from pre-Chronocort baseline- AST/GOT |
|--|--|--|--|--|
| Subject group type                                 | Subject analysis set                         | Subject analysis set                     | Subject analysis set                         | Subject analysis set                         |
| Number of subjects analysed                        | 91   | 91                                       | 91   | 91   |
| Units: Subjects                                    |  |  |  |  |
| No of Participants- Normal Value- Baseline         | 87   | 87                                       | 87   | 87   |
| No Pts-pre-Chronocort Baseline val+treatment value | 87   | 87                                       | 87   | 87   |

|  |   |   |   |   |
|--|---|---|---|---|
| Shift from pre-Chronocort baseline - Minimum value | 0 | 2 | 0 | 0 |
| Shift from pre-Chronocort baseline - Maximum value | 2 | 2 | 3 | 1 |

| End point values                                   | Change from pre-Chronocort baseline-Total creatine kinase | Change from pre-Chronocort baseline-Lactate dehydrogenase | Change from pre-Chronocort baseline-Total bilirubin | Change from pre-Chronocort baseline-Direct bilirubin |
|--|---|---|---|--|
| Subject group type                                 | Subject analysis set                                      | Subject analysis set                                      | Subject analysis set                                | Subject analysis set                                 |
| Number of subjects analysed                        | 91  | 91  | 91  | 91   |
| Units: Subjects                                    |   |   |   |  |
| No of Participants- Normal Value-Baseline          | 85  | 87  | 87  | 87   |
| No Pts-pre-Chronocort Baseline val+treatment value | 87  | 87  | 87  | 87   |
| Shift from pre-Chronocort baseline - Minimum value | 0   | 0   | 0   | 0  |
| Shift from pre-Chronocort baseline - Maximum value | 14  | 0   | 7   | 1  |

| End point values                                   | Change from pre-Chronocort baseline-Total cholesterol | Change from pre-Chronocort baseline-HDL cholesterol | Change from pre-Chronocort baseline-LDL cholesterol | Change from pre-Chronocort baseline-Triglycerides |
|--|---|---|---|---|
| Subject group type                                 | Subject analysis set                                  | Subject analysis set                                | Subject analysis set                                | Subject analysis set                              |
| Number of subjects analysed                        | 91  | 91  | 91  | 91  |
| Units: Subjects                                    |   |   |   |   |
| No of Participants- Normal Value-Baseline          | 67  | 85  | 34  | 84  |
| No Pts-pre-Chronocort Baseline val+treatment value | 87  | 87  | 88  | 87  |
| Shift from pre-Chronocort baseline - Minimum value | 3   | 4   | 4   | 0   |
| Shift from pre-Chronocort baseline - Maximum value | 36  | 0   | 24  | 12  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Safety and Tolerability of Chronocort Over Time Assessed by Change from Pre-Chronocort Baseline in Vital Signs

|                 |   |
|-----------------|---|
| End point title | Safety and Tolerability of Chronocort Over Time Assessed by Change from Pre-Chronocort Baseline in Vital Signs <sup>[6]</sup> |
|-----------------|---|

End point description:

Long term safety and tolerability of Chronocort assessed by change from pre-Chronocort baseline. Mean changes from pre Chronocort baseline to Month 30 in Vital Signs are provided.

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

End point timeframe:

5.5 years

Notes:

[6] - 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: The full analysis set was used for all data summaries. Summaries over time were produced for safety and efficacy parameters.

| End point values                     | Mean Change-Pre-Chronocort Baseline-Systolic Blood Pressure | Mean Change-Pre-Chronocort Baseline-Diastolic Blood Pressure | Mean Change-Pre-Chronocort Baseline-Pulse rate | Mean Change-Pre-Chronocort Baseline-Respiratory rate |
|--------------------------------------|---|--|--|--|
| Subject group type                   | Subject analysis set  | Subject analysis set   | Subject analysis set                           | Subject analysis set                                 |
| Number of subjects analysed          | 70  | 70   | 70   | 70   |
| Units: N/A                           |   |  |  |  |
| arithmetic mean (standard deviation) |   |  |  |  |
| Baseline                             | 120.4 (± 13.92)   | 70.6 (± 10.79)   | 71.1 (± 12.16)                                 | 16.3 (± 2.85)  |
| Change from baseline to Month 30     | -0.1 (± 12.81)  | 2.7 (± 11.34)  | 0.2 (± 12.38)                                  | -0.2 (± 3.41)  |

| End point values                     | Mean Change-Pre-Chronocort Baseline-Temperature | Mean Change-Pre-Chronocort Baseline-Weight | Mean Change-Pre-Chronocort Baseline-Body Mass Index | Mean Change-Pre-Chronocort Baseline-Waist Circumference |
|--------------------------------------|---|--|---|---|
| Subject group type                   | Subject analysis set                            | Subject analysis set                       | Subject analysis set                                | Subject analysis set                                    |
| Number of subjects analysed          | 70  | 70   | 70  | 70  |
| Units: N/A                           |   |  |   |   |
| arithmetic mean (standard deviation) |   |  |   |   |
| Baseline                             | 36.44 (± 0.427)                                 | 75.58 (± 16.091)                           | 28.802 (± 5.6692)                                   | 91.54 (± 14.810)  |
| Change from baseline to Month 30     | 0.03 (± 0.464)                                  | 0.14 (± 6.115)                             | 0.086 (± 2.4248)                                    | 1.95 (± 7.1028)   |

## Statistical analyses

No statistical analyses for this end point

## Primary: Safety and Tolerability of Chronocort Assessed by Pre-Chronocort Baseline-Laboratory Assessments -Minimum and Maximum Treatment Values-Haematology

|                 |   |
|-----------------|---|
| End point title | Safety and Tolerability of Chronocort Assessed by Pre-Chronocort Baseline-Laboratory Assessments -Minimum and Maximum Treatment Values-Haematology <sup>[7]</sup> |
|-----------------|---|

End point description:

Safety and tolerability of Chronocort, as assessed by change from pre-Chronocort baseline in safe laboratory assessments throughout the study. Shifts in haematology variables from within the reference range (normal) at pre Chronocort baseline to maximum or minimum values on treatment

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

End point timeframe:

5.5 years

Notes:

[7] - 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: The full analysis set was used for all data summaries. Summaries over time were produced for safety and efficacy parameters.

| End point values                                   | Change from Pre-Chronocort Baseline-RBC Count | Change from pre-Chronocort baseline-Haemoglobin | Change from pre-Chronocort baseline-Haematocrit | Change from pre-Chronocort baseline-RDW |
|--|---|---|---|---|
| Subject group type                                 | Subject analysis set                          | Subject analysis set                            | Subject analysis set                            | Subject analysis set                    |
| Number of subjects analysed                        | 91  | 91  | 91  | 91                                      |
| Units: Subjects                                    |   |   |   |   |
| No of Participants- Normal Value-Baseline          | 77  | 71  | 75  | 70                                      |
| No Pts-pre-Chronocort Baseline val+treatment value | 87  | 87  | 87  | 87                                      |
| Shift from pre-Chronocort baseline - Minimum value | 5   | 13  | 12  | 1                                       |
| Shift from pre-Chronocort baseline - Maximum value | 6   | 5   | 5   | 17                                      |

| End point values                                   | Change from pre-Chronocort baseline-MCV | Change from pre-Chronocort baseline-MCH | Change from pre-Chronocort baseline-MCH concentration | Change from pre-Chronocort baseline-Platelet count |
|--|---|---|---|--|
| Subject group type                                 | Subject analysis set                    | Subject analysis set                    | Subject analysis set                                  | Subject analysis set                               |
| Number of subjects analysed                        | 91                                      | 91                                      | 91  | 91   |
| Units: Subjects                                    |   |   |   |  |
| No of Participants- Normal Value-Baseline          | 85                                      | 82                                      | 82  | 81   |
| No Pts-pre-Chronocort Baseline val+treatment value | 87                                      | 87                                      | 87  | 86   |
| Shift from pre-Chronocort baseline - Minimum value | 3                                       | 5                                       | 13  | 1  |
| Shift from pre-Chronocort baseline - Maximum value | 3                                       | 6                                       | 1   | 3  |

| End point values                                   | Change from pre-Chronocort baseline-Total WBC Count | Change from pre-Chronocort baseline-Lymphocyte count abs | Change from pre-Chronocort baseline-Lymphocyte count % | Change from pre-Chronocort baseline-Monocyte count abs |
|--|---|--|--|--|
| Subject group type                                 | Subject analysis set                                | Subject analysis set                                     | Subject analysis set                                   | Subject analysis set                                   |
| Number of subjects analysed                        | 91  | 91   | 91   | 91   |
| Units: Subjects                                    |   |  |  |  |
| No of Participants- Normal Value-Baseline          | 82  | 79   | 64   | 78   |
| No Pts-pre-Chronocort Baseline val+treatment value | 87  | 83   | 83   | 83   |
| Shift from pre-Chronocort baseline - Minimum value | 8   | 0  | 8  | 10   |
| Shift from pre-Chronocort baseline - Maximum value | 10  | 1  | 9  | 0  |

| <b>End point values</b>                            | Change from pre-Chronocort baseline- Monocyte count % | Change from pre-Chronocort baseline- Neutrophil count abs | Change from pre-Chronocort baseline- Neutrophil count % | Change from pre-Chronocort baseline- Basophil count abs |
|--|---|---|---|---|
| Subject group type                                 | Subject analysis set                                  | Subject analysis set                                      | Subject analysis set                                    | Subject analysis set                                    |
| Number of subjects analysed                        | 91  | 91  | 91  | 91  |
| Units: Subjects                                    |   |   |   |   |
| No of Participants- Normal Value- Baseline         | 83  | 78  | 72  | 83  |
| No Pts-pre-Chronocort Baseline val+treatment value | 83  | 83  | 83  | 83  |
| Shift from pre-Chronocort baseline - Minimum value | 0   | 10  | 10  | 0   |
| Shift from pre-Chronocort baseline - Maximum value | 4   | 8   | 15  | 0   |

| <b>End point values</b>                            | Change from pre-Chronocort baseline- Basophil count % | Change from pre-Chronocort baseline- Eosinophil count abs | Change from pre-Chronocort baseline- Eosinophil count % |  |
|--|---|---|---|--|
| Subject group type                                 | Subject analysis set                                  | Subject analysis set                                      | Subject analysis set                                    |  |
| Number of subjects analysed                        | 91  | 91  | 91  |  |
| Units: Subjects                                    |   |   |   |  |
| No of Participants- Normal Value- Baseline         | 82  | 76  | 81  |  |
| No Pts-pre-Chronocort Baseline val+treatment value | 83  | 83  | 83  |  |
| Shift from pre-Chronocort baseline - Minimum value | 0   | 13  | 0   |  |
| Shift from pre-Chronocort baseline - Maximum value | 0   | 7   | 12  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

AEs collected for all subjects from the time of consent up to 30 days after the last visit or the early withdrawal visit. Any AEs experienced after this 30-day period were reported only if the Investigator suspected a causal relationship to Chronocort.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 23.0 |
|--------------------|------|

### Reporting groups

|                       |            |
|-----------------------|------------|
| Reporting group title | Chronocort |
|-----------------------|------------|

Reporting group description: -

| Serious adverse events  | Chronocort       |  |  |
|---|------------------|--|--|
| Total subjects affected by serious adverse events                   |                  |  |  |
| subjects affected / exposed   | 28 / 91 (30.77%) |  |  |
| number of deaths (all causes)                                       | 1                |  |  |
| number of deaths resulting from adverse events                      | 1                |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                  |  |  |
| Breast cancer   |                  |  |  |
| subjects affected / exposed   | 1 / 91 (1.10%)   |  |  |
| occurrences causally related to treatment / all                     | 0 / 1            |  |  |
| deaths causally related to treatment / all                          | 0 / 0            |  |  |
| Haemangiopericytoma   |                  |  |  |
| subjects affected / exposed   | 1 / 91 (1.10%)   |  |  |
| occurrences causally related to treatment / all                     | 0 / 2            |  |  |
| deaths causally related to treatment / all                          | 0 / 0            |  |  |
| Malignant haemangiopericytoma metastatic                            |                  |  |  |
| subjects affected / exposed   | 1 / 91 (1.10%)   |  |  |
| occurrences causally related to treatment / all                     | 0 / 1            |  |  |
| deaths causally related to treatment / all                          | 0 / 0            |  |  |
| Vascular disorders  |                  |  |  |
| Brachiocephalic vein thrombosis                                     |                  |  |  |



|  |                |  |  |
|--|----------------|--|--|
| subjects affected / exposed                          | 1 / 91 (1.10%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Haematoma  |                |  |  |
| subjects affected / exposed                          | 1 / 91 (1.10%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Surgical and medical procedures                      |                |  |  |
| Knee arthroplasty                                    |                |  |  |
| subjects affected / exposed                          | 1 / 91 (1.10%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Pregnancy, puerperium and perinatal conditions       |                |  |  |
| Abortion spontaneous                                 |                |  |  |
| subjects affected / exposed                          | 1 / 91 (1.10%) |  |  |
| occurrences causally related to treatment / all      | 0 / 2          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Neonatal disorder                                    |                |  |  |
| subjects affected / exposed                          | 1 / 91 (1.10%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| General disorders and administration site conditions |                |  |  |
| Asthenia   |                |  |  |
| subjects affected / exposed                          | 1 / 91 (1.10%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Fatigue  |                |  |  |
| subjects affected / exposed                          | 1 / 91 (1.10%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Pyrexia  |                |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 2 / 91 (2.20%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Reproductive system and breast disorders        |                |  |  |
| Vulvovaginal inflammation                       |                |  |  |
| subjects affected / exposed                     | 1 / 91 (1.10%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Respiratory, thoracic and mediastinal disorders |                |  |  |
| Asthma  |                |  |  |
| subjects affected / exposed                     | 1 / 91 (1.10%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Dyspnoea  |                |  |  |
| subjects affected / exposed                     | 1 / 91 (1.10%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pulmonary embolism                              |                |  |  |
| subjects affected / exposed                     | 1 / 91 (1.10%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Psychiatric disorders                           |                |  |  |
| Anxiety   |                |  |  |
| subjects affected / exposed                     | 1 / 91 (1.10%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Suicide attempt                                 |                |  |  |
| subjects affected / exposed                     | 1 / 91 (1.10%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Investigations                                  |                |  |  |
| Blood potassium decreased                       |                |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 2 / 91 (2.20%) |  |  |
| occurrences causally related to treatment / all | 2 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Red blood cell microcytes                       |                |  |  |
| subjects affected / exposed                     | 1 / 91 (1.10%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Injury, poisoning and procedural complications  |                |  |  |
| Contusion                                       |                |  |  |
| subjects affected / exposed                     | 1 / 91 (1.10%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Fall  |                |  |  |
| subjects affected / exposed                     | 1 / 91 (1.10%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Hip fracture                                    |                |  |  |
| subjects affected / exposed                     | 1 / 91 (1.10%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Joint dislocation                               |                |  |  |
| subjects affected / exposed                     | 1 / 91 (1.10%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Subcutaneous haematoma                          |                |  |  |
| subjects affected / exposed                     | 1 / 91 (1.10%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Cardiac disorders                               |                |  |  |
| Myocardial infarction                           |                |  |  |
| subjects affected / exposed                     | 1 / 91 (1.10%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 1          |  |  |

|   |                |  |  |
|---|----------------|--|--|
| Nervous system disorders                        |                |  |  |
| Depressed level of consciousness                |                |  |  |
| subjects affected / exposed                     | 1 / 91 (1.10%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Dizziness                                       |                |  |  |
| subjects affected / exposed                     | 1 / 91 (1.10%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Loss of consciousness                           |                |  |  |
| subjects affected / exposed                     | 1 / 91 (1.10%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Syncope   |                |  |  |
| subjects affected / exposed                     | 1 / 91 (1.10%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Gastrointestinal disorders                      |                |  |  |
| Abdominal discomfort                            |                |  |  |
| subjects affected / exposed                     | 1 / 91 (1.10%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Abdominal pain                                  |                |  |  |
| subjects affected / exposed                     | 2 / 91 (2.20%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Diarrhoea                                       |                |  |  |
| subjects affected / exposed                     | 1 / 91 (1.10%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Diverticulum                                    |                |  |  |
| subjects affected / exposed                     | 3 / 91 (3.30%) |  |  |
| occurrences causally related to treatment / all | 0 / 4          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

|   |                |  |  |
|---|----------------|--|--|
| Melaena   |                |  |  |
| subjects affected / exposed                     | 1 / 91 (1.10%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Vomiting  |                |  |  |
| subjects affected / exposed                     | 1 / 91 (1.10%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Endocrine disorders                             |                |  |  |
| Adrenal insufficiency                           |                |  |  |
| subjects affected / exposed                     | 1 / 91 (1.10%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Adrenocortical insufficiency acute              |                |  |  |
| subjects affected / exposed                     | 3 / 91 (3.30%) |  |  |
| occurrences causally related to treatment / all | 0 / 9          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Musculoskeletal and connective tissue disorders |                |  |  |
| Arthralgia                                      |                |  |  |
| subjects affected / exposed                     | 1 / 91 (1.10%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Intervertebral disc protrusion                  |                |  |  |
| subjects affected / exposed                     | 2 / 91 (2.20%) |  |  |
| occurrences causally related to treatment / all | 0 / 5          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pain in extremity                               |                |  |  |
| subjects affected / exposed                     | 1 / 91 (1.10%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Infections and infestations                     |                |  |  |
| Appendicitis perforated                         |                |  |  |

|   |                |  |  |  |
|---|----------------|--|--|--|
| subjects affected / exposed                     | 1 / 91 (1.10%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| COVID-19  |                |  |  |  |
| subjects affected / exposed                     | 1 / 91 (1.10%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Gastroenteritis                                 |                |  |  |  |
| subjects affected / exposed                     | 3 / 91 (3.30%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 3          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Gastroenteritis norovirus                       |                |  |  |  |
| subjects affected / exposed                     | 1 / 91 (1.10%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Gastroenteritis viral                           |                |  |  |  |
| subjects affected / exposed                     | 2 / 91 (2.20%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 4          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Influenza                                       |                |  |  |  |
| subjects affected / exposed                     | 1 / 91 (1.10%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Kidney infection                                |                |  |  |  |
| subjects affected / exposed                     | 1 / 91 (1.10%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Lower respiratory tract infection               |                |  |  |  |
| subjects affected / exposed                     | 2 / 91 (2.20%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 3          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Pharyngitis                                     |                |  |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 1 / 91 (1.10%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pneumonia                                       |                |  |  |
| subjects affected / exposed                     | 1 / 91 (1.10%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Urinary tract infection                         |                |  |  |
| subjects affected / exposed                     | 1 / 91 (1.10%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

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

| <b>Non-serious adverse events</b>                                   | Chronocort        |  |  |
|---|-------------------|--|--|
| Total subjects affected by non-serious adverse events               |                   |  |  |
| subjects affected / exposed   | 91 / 91 (100.00%) |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |  |  |
| Adrenal rest tumour of the testis                                   |                   |  |  |
| subjects affected / exposed   | 1 / 91 (1.10%)    |  |  |
| occurrences (all)   | 1                 |  |  |
| Carcinoid tumour of the small bowel                                 |                   |  |  |
| subjects affected / exposed   | 1 / 91 (1.10%)    |  |  |
| occurrences (all)   | 1                 |  |  |
| Melanocytic naevus  |                   |  |  |
| subjects affected / exposed   | 1 / 91 (1.10%)    |  |  |
| occurrences (all)   | 1                 |  |  |
| Vascular disorders  |                   |  |  |
| Haematoma   |                   |  |  |
| subjects affected / exposed   | 2 / 91 (2.20%)    |  |  |
| occurrences (all)   | 2                 |  |  |
| Hypertension  |                   |  |  |
| subjects affected / exposed   | 5 / 91 (5.49%)    |  |  |
| occurrences (all)   | 6                 |  |  |
| Peripheral venous disease   |                   |  |  |

|   |                         |  |  |
|---|-------------------------|--|--|
| subjects affected / exposed<br>occurrences (all)  | 1 / 91 (1.10%)<br>1     |  |  |
| Surgical and medical procedures<br>COVID-19 immunisation<br>subjects affected / exposed<br>occurrences (all)            | 17 / 91 (18.68%)<br>24  |  |  |
| Gingival graft<br>subjects affected / exposed<br>occurrences (all)  | 1 / 91 (1.10%)<br>2     |  |  |
| Tooth extraction<br>subjects affected / exposed<br>occurrences (all)  | 3 / 91 (3.30%)<br>3     |  |  |
| General disorders and administration<br>site conditions<br>Asthenia<br>subjects affected / exposed<br>occurrences (all) | 14 / 91 (15.38%)<br>21  |  |  |
| Chills<br>subjects affected / exposed<br>occurrences (all)  | 1 / 91 (1.10%)<br>1     |  |  |
| Facial pain<br>subjects affected / exposed<br>occurrences (all)   | 1 / 91 (1.10%)<br>1     |  |  |
| Fatigue<br>subjects affected / exposed<br>occurrences (all)   | 43 / 91 (47.25%)<br>106 |  |  |
| Feeling abnormal<br>subjects affected / exposed<br>occurrences (all)  | 1 / 91 (1.10%)<br>1     |  |  |
| Gait disturbance<br>subjects affected / exposed<br>occurrences (all)  | 1 / 91 (1.10%)<br>1     |  |  |
| Injection site dermatitis<br>subjects affected / exposed<br>occurrences (all)   | 1 / 91 (1.10%)<br>1     |  |  |
| Malaise   |                         |  |  |



|                                 |                  |  |  |
|---------------------------------|------------------|--|--|
| subjects affected / exposed     | 11 / 91 (12.09%) |  |  |
| occurrences (all)               | 16               |  |  |
| Oedema mucosal                  |                  |  |  |
| subjects affected / exposed     | 1 / 91 (1.10%)   |  |  |
| occurrences (all)               | 3                |  |  |
| Oedema peripheral               |                  |  |  |
| subjects affected / exposed     | 5 / 91 (5.49%)   |  |  |
| occurrences (all)               | 8                |  |  |
| Pain                            |                  |  |  |
| subjects affected / exposed     | 2 / 91 (2.20%)   |  |  |
| occurrences (all)               | 2                |  |  |
| Performance status decreased    |                  |  |  |
| subjects affected / exposed     | 1 / 91 (1.10%)   |  |  |
| occurrences (all)               | 1                |  |  |
| Peripheral swelling             |                  |  |  |
| subjects affected / exposed     | 2 / 91 (2.20%)   |  |  |
| occurrences (all)               | 2                |  |  |
| Pyrexia                         |                  |  |  |
| subjects affected / exposed     | 37 / 91 (40.66%) |  |  |
| occurrences (all)               | 66               |  |  |
| Swelling                        |                  |  |  |
| subjects affected / exposed     | 1 / 91 (1.10%)   |  |  |
| occurrences (all)               | 1                |  |  |
| Swelling face                   |                  |  |  |
| subjects affected / exposed     | 2 / 91 (2.20%)   |  |  |
| occurrences (all)               | 2                |  |  |
| Therapeutic response unexpected |                  |  |  |
| subjects affected / exposed     | 27 / 91 (29.67%) |  |  |
| occurrences (all)               | 46               |  |  |
| Vaccination site pain           |                  |  |  |
| subjects affected / exposed     | 1 / 91 (1.10%)   |  |  |
| occurrences (all)               | 1                |  |  |
| Vaccination site swelling       |                  |  |  |
| subjects affected / exposed     | 1 / 91 (1.10%)   |  |  |
| occurrences (all)               | 1                |  |  |
| Immune system disorders         |                  |  |  |

|   |                     |  |  |
|---|---------------------|--|--|
| Allergy to arthropod bite<br>subjects affected / exposed<br>occurrences (all) | 1 / 91 (1.10%)<br>2 |  |  |
| Allergy to chemicals<br>subjects affected / exposed<br>occurrences (all)      | 1 / 91 (1.10%)<br>1 |  |  |
| Seasonal allergy<br>subjects affected / exposed<br>occurrences (all)          | 2 / 91 (2.20%)<br>2 |  |  |
| Appendicitis<br>subjects affected / exposed<br>occurrences (all)              | 1 / 91 (1.10%)<br>1 |  |  |
| Social circumstances  |                     |  |  |
| Educational problem<br>subjects affected / exposed<br>occurrences (all)       | 2 / 91 (2.20%)<br>2 |  |  |
| Family stress<br>subjects affected / exposed<br>occurrences (all)             | 1 / 91 (1.10%)<br>1 |  |  |
| Impaired work ability<br>subjects affected / exposed<br>occurrences (all)     | 1 / 91 (1.10%)<br>1 |  |  |
| Physical assault<br>subjects affected / exposed<br>occurrences (all)          | 1 / 91 (1.10%)<br>1 |  |  |
| Stress at work<br>subjects affected / exposed<br>occurrences (all)            | 2 / 91 (2.20%)<br>3 |  |  |
| Psychiatric disorders   |                     |  |  |
| Adjustment disorder<br>subjects affected / exposed<br>occurrences (all)       | 1 / 91 (1.10%)<br>1 |  |  |
| Anticipatory anxiety<br>subjects affected / exposed<br>occurrences (all)      | 1 / 91 (1.10%)<br>1 |  |  |
| Anxiety   |                     |  |  |

|  |                  |  |  |
|--|------------------|--|--|
| subjects affected / exposed            | 7 / 91 (7.69%)   |  |  |
| occurrences (all)                      | 11               |  |  |
| Bipolar I disorder                     |                  |  |  |
| subjects affected / exposed            | 1 / 91 (1.10%)   |  |  |
| occurrences (all)                      | 11               |  |  |
| Depressed mood                         |                  |  |  |
| subjects affected / exposed            | 1 / 91 (1.10%)   |  |  |
| occurrences (all)                      | 1                |  |  |
| Depression                             |                  |  |  |
| subjects affected / exposed            | 10 / 91 (10.99%) |  |  |
| occurrences (all)                      | 11               |  |  |
| Insomnia                               |                  |  |  |
| subjects affected / exposed            | 20 / 91 (21.98%) |  |  |
| occurrences (all)                      | 23               |  |  |
| Libido decreased                       |                  |  |  |
| subjects affected / exposed            | 2 / 91 (2.20%)   |  |  |
| occurrences (all)                      | 2                |  |  |
| Panic attack                           |                  |  |  |
| subjects affected / exposed            | 1 / 91 (1.10%)   |  |  |
| occurrences (all)                      | 1                |  |  |
| Sleep disorder                         |                  |  |  |
| subjects affected / exposed            | 2 / 91 (2.20%)   |  |  |
| occurrences (all)                      | 3                |  |  |
| Stress                                 |                  |  |  |
| subjects affected / exposed            | 9 / 91 (9.89%)   |  |  |
| occurrences (all)                      | 16               |  |  |
| Investigations                         |                  |  |  |
| Blood androstenedione increased        |                  |  |  |
| subjects affected / exposed            | 1 / 91 (1.10%)   |  |  |
| occurrences (all)                      | 1                |  |  |
| Blood cholesterol increased            |                  |  |  |
| subjects affected / exposed            | 1 / 91 (1.10%)   |  |  |
| occurrences (all)                      | 1                |  |  |
| Blood creatine phosphokinase increased |                  |  |  |

|                              |                |  |  |
|------------------------------|----------------|--|--|
| subjects affected / exposed  | 3 / 91 (3.30%) |  |  |
| occurrences (all)            | 3              |  |  |
| Blood glucose increased      |                |  |  |
| subjects affected / exposed  | 1 / 91 (1.10%) |  |  |
| occurrences (all)            | 1              |  |  |
| Blood potassium decreased    |                |  |  |
| subjects affected / exposed  | 1 / 91 (1.10%) |  |  |
| occurrences (all)            | 1              |  |  |
| Blood potassium increased    |                |  |  |
| subjects affected / exposed  | 1 / 91 (1.10%) |  |  |
| occurrences (all)            | 1              |  |  |
| Blood sodium decreased       |                |  |  |
| subjects affected / exposed  | 1 / 91 (1.10%) |  |  |
| occurrences (all)            | 1              |  |  |
| Blood testosterone decreased |                |  |  |
| subjects affected / exposed  | 2 / 91 (2.20%) |  |  |
| occurrences (all)            | 2              |  |  |
| Blood testosterone increased |                |  |  |
| subjects affected / exposed  | 3 / 91 (3.30%) |  |  |
| occurrences (all)            | 3              |  |  |
| Bone density decreased       |                |  |  |
| subjects affected / exposed  | 3 / 91 (3.30%) |  |  |
| occurrences (all)            | 3              |  |  |
| Bone density increased       |                |  |  |
| subjects affected / exposed  | 1 / 91 (1.10%) |  |  |
| occurrences (all)            | 1              |  |  |
| C-reactive protein decreased |                |  |  |
| subjects affected / exposed  | 1 / 91 (1.10%) |  |  |
| occurrences (all)            | 1              |  |  |
| C-reactive protein increased |                |  |  |
| subjects affected / exposed  | 1 / 91 (1.10%) |  |  |
| occurrences (all)            | 1              |  |  |
| Eosinophil count decreased   |                |  |  |
| subjects affected / exposed  | 1 / 91 (1.10%) |  |  |
| occurrences (all)            | 1              |  |  |
| Haematocrit decreased        |                |  |  |

|                                   |                |  |  |
|-----------------------------------|----------------|--|--|
| subjects affected / exposed       | 3 / 91 (3.30%) |  |  |
| occurrences (all)                 | 3              |  |  |
| Haemoglobin decreased             |                |  |  |
| subjects affected / exposed       | 4 / 91 (4.40%) |  |  |
| occurrences (all)                 | 4              |  |  |
| Heart rate decreased              |                |  |  |
| subjects affected / exposed       | 1 / 91 (1.10%) |  |  |
| occurrences (all)                 | 1              |  |  |
| Liver function test abnormal      |                |  |  |
| subjects affected / exposed       | 1 / 91 (1.10%) |  |  |
| occurrences (all)                 | 1              |  |  |
| Low density lipoprotein increased |                |  |  |
| subjects affected / exposed       | 4 / 91 (4.40%) |  |  |
| occurrences (all)                 | 5              |  |  |
| Occult blood                      |                |  |  |
| subjects affected / exposed       | 1 / 91 (1.10%) |  |  |
| occurrences (all)                 | 1              |  |  |
| Red blood cell count decreased    |                |  |  |
| subjects affected / exposed       | 2 / 91 (2.20%) |  |  |
| occurrences (all)                 | 2              |  |  |
| Red blood cell microcytes         |                |  |  |
| subjects affected / exposed       | 1 / 91 (1.10%) |  |  |
| occurrences (all)                 | 1              |  |  |
| Renin decreased                   |                |  |  |
| subjects affected / exposed       | 2 / 91 (2.20%) |  |  |
| occurrences (all)                 | 2              |  |  |
| Renin increased                   |                |  |  |
| subjects affected / exposed       | 4 / 91 (4.40%) |  |  |
| occurrences (all)                 | 4              |  |  |
| Weight increased                  |                |  |  |
| subjects affected / exposed       | 3 / 91 (3.30%) |  |  |
| occurrences (all)                 | 3              |  |  |
| White blood cell count increased  |                |  |  |
| subjects affected / exposed       | 1 / 91 (1.10%) |  |  |
| occurrences (all)                 | 1              |  |  |
| Injury, poisoning and procedural  |                |  |  |

|                             |                |  |  |
|-----------------------------|----------------|--|--|
| complications               |                |  |  |
| Arthropod bite              |                |  |  |
| subjects affected / exposed | 1 / 91 (1.10%) |  |  |
| occurrences (all)           | 1              |  |  |
| Bone contusion              |                |  |  |
| subjects affected / exposed | 1 / 91 (1.10%) |  |  |
| occurrences (all)           | 1              |  |  |
| Contusion                   |                |  |  |
| subjects affected / exposed | 1 / 91 (1.10%) |  |  |
| occurrences (all)           | 3              |  |  |
| Corneal abrasion            |                |  |  |
| subjects affected / exposed | 1 / 91 (1.10%) |  |  |
| occurrences (all)           | 1              |  |  |
| Eye injury                  |                |  |  |
| subjects affected / exposed | 1 / 91 (1.10%) |  |  |
| occurrences (all)           | 1              |  |  |
| Fall                        |                |  |  |
| subjects affected / exposed | 3 / 91 (3.30%) |  |  |
| occurrences (all)           | 3              |  |  |
| Fibula fracture             |                |  |  |
| subjects affected / exposed | 1 / 91 (1.10%) |  |  |
| occurrences (all)           | 1              |  |  |
| Foot fracture               |                |  |  |
| subjects affected / exposed | 1 / 91 (1.10%) |  |  |
| occurrences (all)           | 1              |  |  |
| Hand fracture               |                |  |  |
| subjects affected / exposed | 3 / 91 (3.30%) |  |  |
| occurrences (all)           | 3              |  |  |
| Heat stroke                 |                |  |  |
| subjects affected / exposed | 2 / 91 (2.20%) |  |  |
| occurrences (all)           | 2              |  |  |
| Hypobarism                  |                |  |  |
| subjects affected / exposed | 1 / 91 (1.10%) |  |  |
| occurrences (all)           | 1              |  |  |
| Joint dislocation           |                |  |  |

|                                    |                |  |  |
|------------------------------------|----------------|--|--|
| subjects affected / exposed        | 2 / 91 (2.20%) |  |  |
| occurrences (all)                  | 2              |  |  |
| Ligament rupture                   |                |  |  |
| subjects affected / exposed        | 1 / 91 (1.10%) |  |  |
| occurrences (all)                  | 1              |  |  |
| Ligament sprain                    |                |  |  |
| subjects affected / exposed        | 4 / 91 (4.40%) |  |  |
| occurrences (all)                  | 4              |  |  |
| Limb injury                        |                |  |  |
| subjects affected / exposed        | 1 / 91 (1.10%) |  |  |
| occurrences (all)                  | 1              |  |  |
| Maternal exposure during pregnancy |                |  |  |
| subjects affected / exposed        | 5 / 91 (5.49%) |  |  |
| occurrences (all)                  | 6              |  |  |
| Meniscus injury                    |                |  |  |
| subjects affected / exposed        | 2 / 91 (2.20%) |  |  |
| occurrences (all)                  | 2              |  |  |
| Mouth injury                       |                |  |  |
| subjects affected / exposed        | 1 / 91 (1.10%) |  |  |
| occurrences (all)                  | 1              |  |  |
| Muscle strain                      |                |  |  |
| subjects affected / exposed        | 1 / 91 (1.10%) |  |  |
| occurrences (all)                  | 1              |  |  |
| Patella fracture                   |                |  |  |
| subjects affected / exposed        | 1 / 91 (1.10%) |  |  |
| occurrences (all)                  | 1              |  |  |
| Paternal exposure before pregnancy |                |  |  |
| subjects affected / exposed        | 3 / 91 (3.30%) |  |  |
| occurrences (all)                  | 5              |  |  |
| Post-traumatic neck syndrome       |                |  |  |
| subjects affected / exposed        | 1 / 91 (1.10%) |  |  |
| occurrences (all)                  | 1              |  |  |
| Procedural nausea                  |                |  |  |
| subjects affected / exposed        | 1 / 91 (1.10%) |  |  |
| occurrences (all)                  | 1              |  |  |
| Procedural pain                    |                |  |  |

|  |                |  |  |
|--|----------------|--|--|
| subjects affected / exposed                | 2 / 91 (2.20%) |  |  |
| occurrences (all)                          | 2              |  |  |
| Procedural vomiting                        |                |  |  |
| subjects affected / exposed                | 1 / 91 (1.10%) |  |  |
| occurrences (all)                          | 1              |  |  |
| Radius fracture                            |                |  |  |
| subjects affected / exposed                | 1 / 91 (1.10%) |  |  |
| occurrences (all)                          | 1              |  |  |
| Rib fracture                               |                |  |  |
| subjects affected / exposed                | 2 / 91 (2.20%) |  |  |
| occurrences (all)                          | 2              |  |  |
| Skin abrasion                              |                |  |  |
| subjects affected / exposed                | 1 / 91 (1.10%) |  |  |
| occurrences (all)                          | 1              |  |  |
| Skin laceration                            |                |  |  |
| subjects affected / exposed                | 4 / 91 (4.40%) |  |  |
| occurrences (all)                          | 4              |  |  |
| Spinal fracture                            |                |  |  |
| subjects affected / exposed                | 1 / 91 (1.10%) |  |  |
| occurrences (all)                          | 1              |  |  |
| Thermal burn                               |                |  |  |
| subjects affected / exposed                | 1 / 91 (1.10%) |  |  |
| occurrences (all)                          | 1              |  |  |
| Tooth fracture                             |                |  |  |
| subjects affected / exposed                | 1 / 91 (1.10%) |  |  |
| occurrences (all)                          | 1              |  |  |
| Upper limb fracture                        |                |  |  |
| subjects affected / exposed                | 1 / 91 (1.10%) |  |  |
| occurrences (all)                          | 1              |  |  |
| Vaccination complication                   |                |  |  |
| subjects affected / exposed                | 2 / 91 (2.20%) |  |  |
| occurrences (all)                          | 2              |  |  |
| Congenital, familial and genetic disorders |                |  |  |
| BRCA1 gene mutation                        |                |  |  |



|  |                     |  |  |
|--|---------------------|--|--|
| subjects affected / exposed<br>occurrences (all) | 1 / 91 (1.10%)<br>1 |  |  |
| Cardiac disorders                                |                     |  |  |
| Palpitations                                     |                     |  |  |
| subjects affected / exposed                      | 3 / 91 (3.30%)      |  |  |
| occurrences (all)                                | 3                   |  |  |
| Rebound tachycardia                              |                     |  |  |
| subjects affected / exposed                      | 1 / 91 (1.10%)      |  |  |
| occurrences (all)                                | 1                   |  |  |
| Nervous system disorders                         |                     |  |  |
| Ageusia  |                     |  |  |
| subjects affected / exposed                      | 2 / 91 (2.20%)      |  |  |
| occurrences (all)                                | 2                   |  |  |
| Anosmia  |                     |  |  |
| subjects affected / exposed                      | 2 / 91 (2.20%)      |  |  |
| occurrences (all)                                | 2                   |  |  |
| Carpal tunnel syndrome                           |                     |  |  |
| subjects affected / exposed                      | 10 / 91 (10.99%)    |  |  |
| occurrences (all)                                | 12                  |  |  |
| Circadian rhythm sleep disorder                  |                     |  |  |
| subjects affected / exposed                      | 1 / 91 (1.10%)      |  |  |
| occurrences (all)                                | 1                   |  |  |
| Clumsiness                                       |                     |  |  |
| subjects affected / exposed                      | 1 / 91 (1.10%)      |  |  |
| occurrences (all)                                | 1                   |  |  |
| Disturbance in attention                         |                     |  |  |
| subjects affected / exposed                      | 1 / 91 (1.10%)      |  |  |
| occurrences (all)                                | 1                   |  |  |
| Dizziness  |                     |  |  |
| subjects affected / exposed                      | 15 / 91 (16.48%)    |  |  |
| occurrences (all)                                | 25                  |  |  |
| Dizziness postural                               |                     |  |  |
| subjects affected / exposed                      | 1 / 91 (1.10%)      |  |  |
| occurrences (all)                                | 1                   |  |  |
| Headache   |                     |  |  |

|                             |                  |  |  |
|-----------------------------|------------------|--|--|
| subjects affected / exposed | 37 / 91 (40.66%) |  |  |
| occurrences (all)           | 66               |  |  |
| Hypoaesthesia               |                  |  |  |
| subjects affected / exposed | 3 / 91 (3.30%)   |  |  |
| occurrences (all)           | 3                |  |  |
| Lethargy                    |                  |  |  |
| subjects affected / exposed | 1 / 91 (1.10%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Memory impairment           |                  |  |  |
| subjects affected / exposed | 1 / 91 (1.10%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Migraine                    |                  |  |  |
| subjects affected / exposed | 5 / 91 (5.49%)   |  |  |
| occurrences (all)           | 21               |  |  |
| Paraesthesia                |                  |  |  |
| subjects affected / exposed | 9 / 91 (9.89%)   |  |  |
| occurrences (all)           | 9                |  |  |
| Paresthesia                 |                  |  |  |
| subjects affected / exposed | 1 / 91 (1.10%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Poor quality sleep          |                  |  |  |
| subjects affected / exposed | 2 / 91 (2.20%)   |  |  |
| occurrences (all)           | 3                |  |  |
| Presyncope                  |                  |  |  |
| subjects affected / exposed | 1 / 91 (1.10%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Seizure                     |                  |  |  |
| subjects affected / exposed | 1 / 91 (1.10%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Sensory loss                |                  |  |  |
| subjects affected / exposed | 1 / 91 (1.10%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Somnolence                  |                  |  |  |
| subjects affected / exposed | 2 / 91 (2.20%)   |  |  |
| occurrences (all)           | 4                |  |  |
| Syncope                     |                  |  |  |

|                                      |                |  |  |
|--------------------------------------|----------------|--|--|
| subjects affected / exposed          | 1 / 91 (1.10%) |  |  |
| occurrences (all)                    | 1              |  |  |
| Taste disorder                       |                |  |  |
| subjects affected / exposed          | 1 / 91 (1.10%) |  |  |
| occurrences (all)                    | 1              |  |  |
| Tension headache                     |                |  |  |
| subjects affected / exposed          | 1 / 91 (1.10%) |  |  |
| occurrences (all)                    | 1              |  |  |
| Tremor                               |                |  |  |
| subjects affected / exposed          | 2 / 91 (2.20%) |  |  |
| occurrences (all)                    | 2              |  |  |
| Blood and lymphatic system disorders |                |  |  |
| Anaemia                              |                |  |  |
| subjects affected / exposed          | 4 / 91 (4.40%) |  |  |
| occurrences (all)                    | 5              |  |  |
| Iron deficiency anaemia              |                |  |  |
| subjects affected / exposed          | 1 / 91 (1.10%) |  |  |
| occurrences (all)                    | 1              |  |  |
| Lymphadenopathy                      |                |  |  |
| subjects affected / exposed          | 1 / 91 (1.10%) |  |  |
| occurrences (all)                    | 1              |  |  |
| Ear and labyrinth disorders          |                |  |  |
| Ear deformity acquired               |                |  |  |
| subjects affected / exposed          | 1 / 91 (1.10%) |  |  |
| occurrences (all)                    | 2              |  |  |
| Ear pain                             |                |  |  |
| subjects affected / exposed          | 1 / 91 (1.10%) |  |  |
| occurrences (all)                    | 1              |  |  |
| Excessive cerumen production         |                |  |  |
| subjects affected / exposed          | 1 / 91 (1.10%) |  |  |
| occurrences (all)                    | 1              |  |  |
| Tinnitus                             |                |  |  |
| subjects affected / exposed          | 1 / 91 (1.10%) |  |  |
| occurrences (all)                    | 3              |  |  |
| Tympanic membrane perforation        |                |  |  |

|                                |                |  |  |
|--------------------------------|----------------|--|--|
| subjects affected / exposed    | 1 / 91 (1.10%) |  |  |
| occurrences (all)              | 1              |  |  |
| Vertigo                        |                |  |  |
| subjects affected / exposed    | 1 / 91 (1.10%) |  |  |
| occurrences (all)              | 1              |  |  |
| Eye disorders                  |                |  |  |
| Cataract                       |                |  |  |
| subjects affected / exposed    | 1 / 91 (1.10%) |  |  |
| occurrences (all)              | 2              |  |  |
| Dry eye                        |                |  |  |
| subjects affected / exposed    | 1 / 91 (1.10%) |  |  |
| occurrences (all)              | 1              |  |  |
| Episcleritis                   |                |  |  |
| subjects affected / exposed    | 1 / 91 (1.10%) |  |  |
| occurrences (all)              | 1              |  |  |
| Foreign body sensation in eyes |                |  |  |
| subjects affected / exposed    | 1 / 91 (1.10%) |  |  |
| occurrences (all)              | 1              |  |  |
| Lacrimation increased          |                |  |  |
| subjects affected / exposed    | 1 / 91 (1.10%) |  |  |
| occurrences (all)              | 1              |  |  |
| Ocular hyperaemia              |                |  |  |
| subjects affected / exposed    | 2 / 91 (2.20%) |  |  |
| occurrences (all)              | 2              |  |  |
| Optic ischaemic neuropathy     |                |  |  |
| subjects affected / exposed    | 1 / 91 (1.10%) |  |  |
| occurrences (all)              | 1              |  |  |
| Vision blurred                 |                |  |  |
| subjects affected / exposed    | 4 / 91 (4.40%) |  |  |
| occurrences (all)              | 5              |  |  |
| Vitreous floaters              |                |  |  |
| subjects affected / exposed    | 1 / 91 (1.10%) |  |  |
| occurrences (all)              | 1              |  |  |
| Gastrointestinal disorders     |                |  |  |
| Abdominal distension           |                |  |  |

|                             |                  |  |  |
|-----------------------------|------------------|--|--|
| subjects affected / exposed | 1 / 91 (1.10%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Abdominal pain              |                  |  |  |
| subjects affected / exposed | 5 / 91 (5.49%)   |  |  |
| occurrences (all)           | 8                |  |  |
| Abdominal pain upper        |                  |  |  |
| subjects affected / exposed | 10 / 91 (10.99%) |  |  |
| occurrences (all)           | 15               |  |  |
| Anal pruritus               |                  |  |  |
| subjects affected / exposed | 1 / 91 (1.10%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Colitis ulcerative          |                  |  |  |
| subjects affected / exposed | 1 / 91 (1.10%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Constipation                |                  |  |  |
| subjects affected / exposed | 4 / 91 (4.40%)   |  |  |
| occurrences (all)           | 6                |  |  |
| Diarrhoea                   |                  |  |  |
| subjects affected / exposed | 27 / 91 (29.67%) |  |  |
| occurrences (all)           | 63               |  |  |
| Diverticulum                |                  |  |  |
| subjects affected / exposed | 3 / 91 (3.30%)   |  |  |
| occurrences (all)           | 7                |  |  |
| Dyspepsia                   |                  |  |  |
| subjects affected / exposed | 3 / 91 (3.30%)   |  |  |
| occurrences (all)           | 3                |  |  |
| Dysphagia                   |                  |  |  |
| subjects affected / exposed | 1 / 91 (1.10%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Flatulence                  |                  |  |  |
| subjects affected / exposed | 1 / 91 (1.10%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Food poisoning              |                  |  |  |
| subjects affected / exposed | 2 / 91 (2.20%)   |  |  |
| occurrences (all)           | 2                |  |  |
| Gastritis                   |                  |  |  |

|                                  |                  |  |  |
|----------------------------------|------------------|--|--|
| subjects affected / exposed      | 2 / 91 (2.20%)   |  |  |
| occurrences (all)                | 2                |  |  |
| Gastrooesophageal reflux disease |                  |  |  |
| subjects affected / exposed      | 3 / 91 (3.30%)   |  |  |
| occurrences (all)                | 3                |  |  |
| Haemorrhoidal haemorrhage        |                  |  |  |
| subjects affected / exposed      | 1 / 91 (1.10%)   |  |  |
| occurrences (all)                | 1                |  |  |
| Hiatus hernia                    |                  |  |  |
| subjects affected / exposed      | 1 / 91 (1.10%)   |  |  |
| occurrences (all)                | 1                |  |  |
| Inguinal hernia                  |                  |  |  |
| subjects affected / exposed      | 1 / 91 (1.10%)   |  |  |
| occurrences (all)                | 1                |  |  |
| Mouth ulceration                 |                  |  |  |
| subjects affected / exposed      | 2 / 91 (2.20%)   |  |  |
| occurrences (all)                | 2                |  |  |
| Nausea                           |                  |  |  |
| subjects affected / exposed      | 20 / 91 (21.98%) |  |  |
| occurrences (all)                | 26               |  |  |
| Oesophagitis                     |                  |  |  |
| subjects affected / exposed      | 2 / 91 (2.20%)   |  |  |
| occurrences (all)                | 2                |  |  |
| Oral disorder                    |                  |  |  |
| subjects affected / exposed      | 1 / 91 (1.10%)   |  |  |
| occurrences (all)                | 1                |  |  |
| Oral pain                        |                  |  |  |
| subjects affected / exposed      | 1 / 91 (1.10%)   |  |  |
| occurrences (all)                | 1                |  |  |
| Proctalgia                       |                  |  |  |
| subjects affected / exposed      | 1 / 91 (1.10%)   |  |  |
| occurrences (all)                | 1                |  |  |
| Teeth brittle                    |                  |  |  |
| subjects affected / exposed      | 1 / 91 (1.10%)   |  |  |
| occurrences (all)                | 1                |  |  |
| Toothache                        |                  |  |  |

|  |                  |  |  |
|--|------------------|--|--|
| subjects affected / exposed            | 4 / 91 (4.40%)   |  |  |
| occurrences (all)                      | 4                |  |  |
| Vomiting                               |                  |  |  |
| subjects affected / exposed            | 31 / 91 (34.07%) |  |  |
| occurrences (all)                      | 48               |  |  |
| Skin and subcutaneous tissue disorders |                  |  |  |
| Acne                                   |                  |  |  |
| subjects affected / exposed            | 1 / 91 (1.10%)   |  |  |
| occurrences (all)                      | 1                |  |  |
| Alopecia areata                        |                  |  |  |
| subjects affected / exposed            | 1 / 91 (1.10%)   |  |  |
| occurrences (all)                      | 1                |  |  |
| Blister                                |                  |  |  |
| subjects affected / exposed            | 1 / 91 (1.10%)   |  |  |
| occurrences (all)                      | 1                |  |  |
| Cold sweat                             |                  |  |  |
| subjects affected / exposed            | 1 / 91 (1.10%)   |  |  |
| occurrences (all)                      | 1                |  |  |
| Dermatosis                             |                  |  |  |
| subjects affected / exposed            | 1 / 91 (1.10%)   |  |  |
| occurrences (all)                      | 1                |  |  |
| Dry skin                               |                  |  |  |
| subjects affected / exposed            | 1 / 91 (1.10%)   |  |  |
| occurrences (all)                      | 2                |  |  |
| Eczema                                 |                  |  |  |
| subjects affected / exposed            | 2 / 91 (2.20%)   |  |  |
| occurrences (all)                      | 2                |  |  |
| Hyperhidrosis                          |                  |  |  |
| subjects affected / exposed            | 5 / 91 (5.49%)   |  |  |
| occurrences (all)                      | 5                |  |  |
| Hyperkeratosis                         |                  |  |  |
| subjects affected / exposed            | 1 / 91 (1.10%)   |  |  |
| occurrences (all)                      | 1                |  |  |
| Lichen planus                          |                  |  |  |
| subjects affected / exposed            | 1 / 91 (1.10%)   |  |  |
| occurrences (all)                      | 1                |  |  |

|   |                |  |  |
|---|----------------|--|--|
| Lichen sclerosus                                |                |  |  |
| subjects affected / exposed                     | 1 / 91 (1.10%) |  |  |
| occurrences (all)                               | 1              |  |  |
| Night sweats                                    |                |  |  |
| subjects affected / exposed                     | 4 / 91 (4.40%) |  |  |
| occurrences (all)                               | 4              |  |  |
| Pruritus  |                |  |  |
| subjects affected / exposed                     | 3 / 91 (3.30%) |  |  |
| occurrences (all)                               | 3              |  |  |
| Psoriasis                                       |                |  |  |
| subjects affected / exposed                     | 2 / 91 (2.20%) |  |  |
| occurrences (all)                               | 5              |  |  |
| Rash  |                |  |  |
| subjects affected / exposed                     | 8 / 91 (8.79%) |  |  |
| occurrences (all)                               | 9              |  |  |
| Skin laxity                                     |                |  |  |
| subjects affected / exposed                     | 1 / 91 (1.10%) |  |  |
| occurrences (all)                               | 1              |  |  |
| Skin lesion                                     |                |  |  |
| subjects affected / exposed                     | 1 / 91 (1.10%) |  |  |
| occurrences (all)                               | 1              |  |  |
| Skin striae                                     |                |  |  |
| subjects affected / exposed                     | 1 / 91 (1.10%) |  |  |
| occurrences (all)                               | 1              |  |  |
| Urticaria                                       |                |  |  |
| subjects affected / exposed                     | 2 / 91 (2.20%) |  |  |
| occurrences (all)                               | 2              |  |  |
| Endocrine disorders                             |                |  |  |
| Thyroid mass                                    |                |  |  |
| subjects affected / exposed                     | 1 / 91 (1.10%) |  |  |
| occurrences (all)                               | 1              |  |  |
| Thyroiditis subacute                            |                |  |  |
| subjects affected / exposed                     | 1 / 91 (1.10%) |  |  |
| occurrences (all)                               | 1              |  |  |
| Musculoskeletal and connective tissue disorders |                |  |  |



|                                |                  |  |  |
|--------------------------------|------------------|--|--|
| Arthralgia                     |                  |  |  |
| subjects affected / exposed    | 14 / 91 (15.38%) |  |  |
| occurrences (all)              | 16               |  |  |
| Axillary mass                  |                  |  |  |
| subjects affected / exposed    | 1 / 91 (1.10%)   |  |  |
| occurrences (all)              | 1                |  |  |
| Back pain                      |                  |  |  |
| subjects affected / exposed    | 16 / 91 (17.58%) |  |  |
| occurrences (all)              | 22               |  |  |
| Bursitis                       |                  |  |  |
| subjects affected / exposed    | 1 / 91 (1.10%)   |  |  |
| occurrences (all)              | 1                |  |  |
| Flank pain                     |                  |  |  |
| subjects affected / exposed    | 1 / 91 (1.10%)   |  |  |
| occurrences (all)              | 1                |  |  |
| Intervertebral disc protrusion |                  |  |  |
| subjects affected / exposed    | 4 / 91 (4.40%)   |  |  |
| occurrences (all)              | 4                |  |  |
| Joint effusion                 |                  |  |  |
| subjects affected / exposed    | 1 / 91 (1.10%)   |  |  |
| occurrences (all)              | 1                |  |  |
| Joint stiffness                |                  |  |  |
| subjects affected / exposed    | 2 / 91 (2.20%)   |  |  |
| occurrences (all)              | 2                |  |  |
| Joint swelling                 |                  |  |  |
| subjects affected / exposed    | 4 / 91 (4.40%)   |  |  |
| occurrences (all)              | 4                |  |  |
| Limb mass                      |                  |  |  |
| subjects affected / exposed    | 1 / 91 (1.10%)   |  |  |
| occurrences (all)              | 1                |  |  |
| Muscle spasms                  |                  |  |  |
| subjects affected / exposed    | 1 / 91 (1.10%)   |  |  |
| occurrences (all)              | 1                |  |  |
| Muscular weakness              |                  |  |  |
| subjects affected / exposed    | 1 / 91 (1.10%)   |  |  |
| occurrences (all)              | 2                |  |  |

|  |                        |  |  |
|--|------------------------|--|--|
| Musculoskeletal chest pain<br>subjects affected / exposed<br>occurrences (all) | 1 / 91 (1.10%)<br>1    |  |  |
| Musculoskeletal pain<br>subjects affected / exposed<br>occurrences (all)       | 3 / 91 (3.30%)<br>3    |  |  |
| Musculoskeletal stiffness<br>subjects affected / exposed<br>occurrences (all)  | 3 / 91 (3.30%)<br>3    |  |  |
| Myalgia<br>subjects affected / exposed<br>occurrences (all)                    | 1 / 91 (1.10%)<br>1    |  |  |
| Myositis<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 91 (1.10%)<br>1    |  |  |
| Neck pain<br>subjects affected / exposed<br>occurrences (all)                  | 2 / 91 (2.20%)<br>2    |  |  |
| Osteoarthritis<br>subjects affected / exposed<br>occurrences (all)             | 4 / 91 (4.40%)<br>5    |  |  |
| Osteopenia<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 91 (1.10%)<br>1    |  |  |
| Osteoporosis<br>subjects affected / exposed<br>occurrences (all)               | 1 / 91 (1.10%)<br>1    |  |  |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)          | 13 / 91 (14.29%)<br>15 |  |  |
| Plantar fasciitis<br>subjects affected / exposed<br>occurrences (all)          | 1 / 91 (1.10%)<br>1    |  |  |
| Rotator cuff syndrome<br>subjects affected / exposed<br>occurrences (all)      | 1 / 91 (1.10%)<br>1    |  |  |

|                             |                  |  |  |
|-----------------------------|------------------|--|--|
| Synovial cyst               |                  |  |  |
| subjects affected / exposed | 2 / 91 (2.20%)   |  |  |
| occurrences (all)           | 2                |  |  |
| Tendonitis                  |                  |  |  |
| subjects affected / exposed | 4 / 91 (4.40%)   |  |  |
| occurrences (all)           | 4                |  |  |
| Trigger finger              |                  |  |  |
| subjects affected / exposed | 1 / 91 (1.10%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Infections and infestations |                  |  |  |
| Acute sinusitis             |                  |  |  |
| subjects affected / exposed | 1 / 91 (1.10%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Bacterial vaginosis         |                  |  |  |
| subjects affected / exposed | 2 / 91 (2.20%)   |  |  |
| occurrences (all)           | 4                |  |  |
| Balanitis candida           |                  |  |  |
| subjects affected / exposed | 1 / 91 (1.10%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Bronchitis                  |                  |  |  |
| subjects affected / exposed | 10 / 91 (10.99%) |  |  |
| occurrences (all)           | 23               |  |  |
| Candida infection           |                  |  |  |
| subjects affected / exposed | 1 / 91 (1.10%)   |  |  |
| occurrences (all)           | 1                |  |  |
| COVID-19                    |                  |  |  |
| subjects affected / exposed | 17 / 91 (18.68%) |  |  |
| occurrences (all)           | 18               |  |  |
| Cystitis                    |                  |  |  |
| subjects affected / exposed | 4 / 91 (4.40%)   |  |  |
| occurrences (all)           | 8                |  |  |
| Device related infection    |                  |  |  |
| subjects affected / exposed | 1 / 91 (1.10%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Ear infection               |                  |  |  |

|                                   |                  |  |  |
|-----------------------------------|------------------|--|--|
| subjects affected / exposed       | 4 / 91 (4.40%)   |  |  |
| occurrences (all)                 | 4                |  |  |
| Fungal infection                  |                  |  |  |
| subjects affected / exposed       | 1 / 91 (1.10%)   |  |  |
| occurrences (all)                 | 1                |  |  |
| Fungal skin infection             |                  |  |  |
| subjects affected / exposed       | 1 / 91 (1.10%)   |  |  |
| occurrences (all)                 | 1                |  |  |
| Gastroenteritis                   |                  |  |  |
| subjects affected / exposed       | 23 / 91 (25.27%) |  |  |
| occurrences (all)                 | 27               |  |  |
| Gastroenteritis norovirus         |                  |  |  |
| subjects affected / exposed       | 1 / 91 (1.10%)   |  |  |
| occurrences (all)                 | 1                |  |  |
| Gastroenteritis viral             |                  |  |  |
| subjects affected / exposed       | 6 / 91 (6.59%)   |  |  |
| occurrences (all)                 | 6                |  |  |
| Gingivitis                        |                  |  |  |
| subjects affected / exposed       | 2 / 91 (2.20%)   |  |  |
| occurrences (all)                 | 2                |  |  |
| Helicobacter infection            |                  |  |  |
| subjects affected / exposed       | 2 / 91 (2.20%)   |  |  |
| occurrences (all)                 | 2                |  |  |
| Herpes zoster                     |                  |  |  |
| subjects affected / exposed       | 1 / 91 (1.10%)   |  |  |
| occurrences (all)                 | 1                |  |  |
| Influenza                         |                  |  |  |
| subjects affected / exposed       | 30 / 91 (32.97%) |  |  |
| occurrences (all)                 | 54               |  |  |
| Localised infection               |                  |  |  |
| subjects affected / exposed       | 1 / 91 (1.10%)   |  |  |
| occurrences (all)                 | 1                |  |  |
| Lower respiratory tract infection |                  |  |  |
| subjects affected / exposed       | 8 / 91 (8.79%)   |  |  |
| occurrences (all)                 | 12               |  |  |
| Nasopharyngitis                   |                  |  |  |

|                             |                  |  |  |
|-----------------------------|------------------|--|--|
| subjects affected / exposed | 34 / 91 (37.36%) |  |  |
| occurrences (all)           | 105              |  |  |
| Oral candidiasis            |                  |  |  |
| subjects affected / exposed | 1 / 91 (1.10%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Oral herpes                 |                  |  |  |
| subjects affected / exposed | 1 / 91 (1.10%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Otitis externa              |                  |  |  |
| subjects affected / exposed | 4 / 91 (4.40%)   |  |  |
| occurrences (all)           | 4                |  |  |
| Otitis media                |                  |  |  |
| subjects affected / exposed | 1 / 91 (1.10%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Pharyngitis                 |                  |  |  |
| subjects affected / exposed | 7 / 91 (7.69%)   |  |  |
| occurrences (all)           | 7                |  |  |
| Pharyngitis streptococcal   |                  |  |  |
| subjects affected / exposed | 1 / 91 (1.10%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Pneumonia                   |                  |  |  |
| subjects affected / exposed | 1 / 91 (1.10%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Pulpitis dental             |                  |  |  |
| subjects affected / exposed | 1 / 91 (1.10%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Rhinitis                    |                  |  |  |
| subjects affected / exposed | 1 / 91 (1.10%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Sinusitis                   |                  |  |  |
| subjects affected / exposed | 9 / 91 (9.89%)   |  |  |
| occurrences (all)           | 16               |  |  |
| Staphylococcal infection    |                  |  |  |
| subjects affected / exposed | 1 / 91 (1.10%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Tonsillitis                 |                  |  |  |

|                                    |                  |  |  |
|------------------------------------|------------------|--|--|
| subjects affected / exposed        | 2 / 91 (2.20%)   |  |  |
| occurrences (all)                  | 2                |  |  |
| Tooth abscess                      |                  |  |  |
| subjects affected / exposed        | 1 / 91 (1.10%)   |  |  |
| occurrences (all)                  | 1                |  |  |
| Tooth infection                    |                  |  |  |
| subjects affected / exposed        | 3 / 91 (3.30%)   |  |  |
| occurrences (all)                  | 3                |  |  |
| Upper respiratory tract infection  |                  |  |  |
| subjects affected / exposed        | 11 / 91 (12.09%) |  |  |
| occurrences (all)                  | 16               |  |  |
| Urinary tract infection            |                  |  |  |
| subjects affected / exposed        | 12 / 91 (13.19%) |  |  |
| occurrences (all)                  | 13               |  |  |
| Viral infection                    |                  |  |  |
| subjects affected / exposed        | 3 / 91 (3.30%)   |  |  |
| occurrences (all)                  | 4                |  |  |
| Vulval abscess                     |                  |  |  |
| subjects affected / exposed        | 1 / 91 (1.10%)   |  |  |
| occurrences (all)                  | 1                |  |  |
| Vulvovaginal candidiasis           |                  |  |  |
| subjects affected / exposed        | 1 / 91 (1.10%)   |  |  |
| occurrences (all)                  | 1                |  |  |
| Vulvovaginal mycotic infection     |                  |  |  |
| subjects affected / exposed        | 1 / 91 (1.10%)   |  |  |
| occurrences (all)                  | 1                |  |  |
| Vulvovaginitis                     |                  |  |  |
| subjects affected / exposed        | 1 / 91 (1.10%)   |  |  |
| occurrences (all)                  | 1                |  |  |
| Metabolism and nutrition disorders |                  |  |  |
| Abnormal weight gain               |                  |  |  |
| subjects affected / exposed        | 7 / 91 (7.69%)   |  |  |
| occurrences (all)                  | 7                |  |  |
| Alcohol intolerance                |                  |  |  |
| subjects affected / exposed        | 1 / 91 (1.10%)   |  |  |
| occurrences (all)                  | 1                |  |  |

|  |                     |  |  |
|--|---------------------|--|--|
| Decreased appetite<br>subjects affected / exposed<br>occurrences (all)       | 3 / 91 (3.30%)<br>3 |  |  |
| Dehydration<br>subjects affected / exposed<br>occurrences (all)              | 1 / 91 (1.10%)<br>1 |  |  |
| Gluten sensitivity<br>subjects affected / exposed<br>occurrences (all)       | 1 / 91 (1.10%)<br>1 |  |  |
| Hypercholesterolaemia<br>subjects affected / exposed<br>occurrences (all)    | 4 / 91 (4.40%)<br>5 |  |  |
| Hyperinsulinaemia<br>subjects affected / exposed<br>occurrences (all)        | 1 / 91 (1.10%)<br>1 |  |  |
| Impaired fasting glucose<br>subjects affected / exposed<br>occurrences (all) | 1 / 91 (1.10%)<br>1 |  |  |
| Increased appetite<br>subjects affected / exposed<br>occurrences (all)       | 4 / 91 (4.40%)<br>4 |  |  |
| Iron deficiency<br>subjects affected / exposed<br>occurrences (all)          | 1 / 91 (1.10%)<br>1 |  |  |
| Type 2 diabetes mellitus<br>subjects affected / exposed<br>occurrences (all) | 1 / 91 (1.10%)<br>1 |  |  |
| Vitamin B12 deficiency<br>subjects affected / exposed<br>occurrences (all)   | 1 / 91 (1.10%)<br>1 |  |  |
| Vitamin D deficiency<br>subjects affected / exposed<br>occurrences (all)     | 1 / 91 (1.10%)<br>1 |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date         | Amendment  |
|--------------|--|
| 20 June 2016 | <p>Protocol Version 2.0 dated 20 Jun 2016</p> <ol style="list-style-type: none"><li>1) The Sponsor signatory was changed.</li><li>2) In response to comments from the Medicines and Healthcare products Regulatory Agency (MHRA), it was clarified that the assessments at Week 18 and then 3 monthly thereafter were not formal study visits and just comprised telephone calls to check on the welfare of the participant.</li><li>3) The protocol originally stated that participants would continue in the study until a decision was reached concerning a marketing authorisation for Chronocort in the relevant territory. This open-ended study design was not considered acceptable to the MHRA so the protocol was revised to state that the length of the study would be 2.5 years from the date of the first participant entering the study, so participants were to be treated for a maximum of 2.5 years. If after this timepoint a decision was not reached concerning a marketing authorisation for Chronocort, a further extension of the study through a protocol amendment could be considered.</li></ol>  |
| 26 July 2016 | <p>Protocol Version 3.0 dated 26 Jul 2016</p> <ol style="list-style-type: none"><li>1) Conversion factors for dexamethasone to hydrocortisone - protocol was amended to state that the conversion rate of x80 was to be used as per protocol up to a maximum starting dose of Chronocort 30 mg</li><li>2) Conduction of genotyping to participants. protocol was amended to either obtain a blood sample for genotyping at screening, if necessary, or if previous genotyping had been performed the participant was to be asked for their permission for this information to be taken from their medical records.</li><li>3) Participants who routinely worked night shifts and so did not sleep during the usual night-time hours were added to the exclusion criteria.</li><li>4) The text revised to say 'No dose adjustments outside of the protocol-defined dose adjustments should be conducted, unless clinical signs and symptoms indicate an immediate need.</li><li>5) The protocol stated that a DEXA scan had to be conducted at the final visit. This was an error since DEXA scans were required annually and not automatically at the final visit.</li><li>6) A follow-up telephone call 30 days after the final visit was added to collect information on any AEs that occurred within the 30-day post-treatment period.</li><li>7) The maximum planned blood volume drawn at each visit was increased from 20 mL to 40 mL following a recalculation of the volume of blood needed at each visit.</li><li>8) The AE reporting period after the last dose of study medication was extended from 7 days to 30 days.</li><li>9) The text was revised 'If the Chronocort dose is changed at any point after the Week 24 visit, the participant should have an interim visit which includes the assessments noted for Week 4, after which they will then continue with visits every 6 months'.</li><li>10) The term 'safety analysis set' was renamed 'full analysis set' to match the SAP.</li><li>11) The telephone number of Emas Pharma was added, and the international dialling code was added to the fax number</li></ol> |



|                  |  |
|------------------|--|
| 04 November 2016 | <p>Protocol Version 5.0 dated 04 Nov 2016</p> <p>The following changes were made to the protocol:</p> <ol style="list-style-type: none"> <li>1) It was stated that participants who became pregnant during the study could continue to receive Chronocort outside of the study after discussion with the Sponsor and if the Investigator considered this to be in the best interest of the participant. However, in Sweden use of Chronocort is not allowed for pregnant women once they are withdrawn from the study, therefore, it was added that all participants who became pregnant in Sweden had to be switched to standard care.</li> <li>2) It was stated that data would be collected on participants continuing Chronocort through the pregnancy, although not all of the assessments required in this study were to be performed (e.g. DEXA scans were not to be performed). This text was removed and replaced with a link to another section that described in more detail the collection of data during pregnancy.</li> <li>3) Protocol Version 3.0 (dated 26 Jul 2016) extended the AE reporting period at the end of the study from 7 days to 30 days. As such the definition of the end of the study was revised to state that the end of the study would be the final telephone call (30 days after the last visit) of the last participant. The AE section was also revised to state that AEs would be collected for all participants from the time of consent up to 30 days after the last visit, rather than as previously stated up to 30 days after the end of the study.</li> <li>4) It was stated that all essential documents would be archived for a minimum of 5 years after completion of the study. However, according to Swedish legislation the minimum reporting period is 10 years, therefore, this was added.</li> <li>5) The responsible statistician was changed.</li> </ol>  |
| 21 June 2017     | <p>Protocol Version 7.0 dated 21 Jun 2017</p> <ol style="list-style-type: none"> <li>1) Due to delays in the supply of study medication for this study, some participants who entered from Study DIUR 005 had to be treated with standard GC therapy for a short period and needed to have safety blood test and adrenal hormone level assessed for DIUR-006 at baseline visit.</li> <li>2) Maximum number of participants eligible to enter this extension study was increased from 126 to 136 participants due to sample size in DIUR-005 increases from 110 to 120.</li> <li>3) The wording in the main protocol was revised to match the synopsis to state 'Subjects with CAH who have successfully completed the DIUR 003 or DIUR 005 clinical trials with the current formulation of Chronocort.' (Note: this change was implemented in France in protocol version 6.0).</li> <li>4) It was clarified that female participants who presented with oligomenorrhoea or amenorrhoea who were aged <math>\leq 55</math> years of age were to be considered potentially fertile and, therefore, were still to undergo pregnancy testing like all other female participants.</li> <li>5) AE section was updated to present an improvement in the participant's condition e.g. restoration of menses.</li> <li>6) The visit windows from Week 18 onwards were extended to <math>\pm 2</math> weeks to allow flexibility in scheduling the visits so they could occur at 6-monthly intervals.</li> <li>7) Change added to allow Chronocort capsules to be supplied in only in blister packs.</li> <li>8) The definition of pre-Chronocort baseline was revised to match the SAP</li> <li>9) Synopsis corrected to make consistency with protocol or SAP.</li> <li>10) Corrected to bring inline with SAP to state that shift tables from baseline to the maximum and minimum on-treatment values would be presented.</li> <li>11) Statement added to state the Interim data analyses were expected to be required for regulatory review as part of any Marketing Authorisation Application (MAA), but no changes to the overall study conduct and no changes to the planned formal statistical analyses were anticipated.</li> </ol> |

|                  |   |
|------------------|---|
| 08 November 2017 | <p>Protocol Version 9.0 dated 08 Nov 2017</p> <ol style="list-style-type: none"> <li>1) Correction made state the amount of blood drawn at any visit as 40 mL in consistent with the laboratory manual.</li> <li>2) Frequency of supply of study medication was revised to allow for participants to be issued with 6 months' supply of Chronocort at each visit after Week 18 rather than participants having to return to the study centre to collect new supplies every 3 months.</li> <li>3) The description of the analysis sets was updated to include an interim analysis set, which could be used for any interim analyses carried out in this study.</li> <li>4) It was clarified that any use of medication from the safety pack was to be recorded for drug accountability purposes and any such use was also to be recorded on the sick day medication page of the eCRF.</li> <li>5) The schedule of study assessments was amended - addition of 'X' - Screening Visit for collection of AEs and SAEs for consistency with footnote 12. Footnote 8 revised -clarifying that dose adjustments also took into account clinical symptoms assessed using the Adrenal Insufficiency Checklist</li> <li>6) clarified that any prior genotyping information collected from DIUR 003 participants would be recorded in the eCRF.</li> <li>7) Clarified that the last GC dose taken prior to the baseline visit was to be recorded.</li> <li>8) Prednisone conversion to Chronocort of x5 also applied to prednisolone</li> <li>9) Clarified that all communications between the Sponsor, designated study representative, and Investigators were to be documented in the TMF</li> <li>10) Clarified Investigator was required to maintain all study documentation for 2 years following the approval date of the MAA, as well as for a New Drug Application</li> <li>11) The dates of the protocol amendments in Appendix 9 of the protocol were incorrect so these were corrected.</li> </ol>  |
| 21 August 2018   | <p>Protocol Version 10.0 dated 21 Aug 2018</p> <ol style="list-style-type: none"> <li>1) The project Manager was changed.</li> <li>2) Since a decision concerning a marketing authorisation for Chronocort had not yet been reached, the estimated end of the study was extended by 1 year. The total length of the study was to be 3.5 years from the date of the first participant entering the study (August 2016 until February 2020)</li> <li>3) An end date for enrolment was added to ensure all participants were enrolled promptly and sufficient data were obtained before the end of the study. So it was specified that all participants must be enrolled by 31 Oct 2018.</li> <li>4) The description of Study DIUR 007 was updated to reflect the final design of this study.</li> <li>5) The Chronocort formulation was revised to state that the Chronocort capsules could be printed with either 'CHRONOCORT 5 mg/10 mg/20 mg' or 'CHC 5 mg/10 mg/20 mg' on the capsule body.</li> <li>6) Some centres do not allow the pharmacist to write the participant numbers on the safety packs (printed labels have to be used) so the sentence 'The subject number will be written on the study pack by the pharmacist' was deleted.</li> <li>7) The wording of the first bullet point in the Other Study Medications (Non Investigational Medicinal Products) section has been revised to make the statement more general, thus just stating that a supply of oral hydrocortisone will be provided that would allow dosage of up to 20 mg three times daily.</li> <li>8) It was originally stated that participants who became pregnant during the study could continue to receive Chronocort outside of the study after discussion with the Sponsor and if the Investigator considered this to be in the best interest of the participant. Previously it was added that in Sweden, the use of Chronocort is not allowed for pregnant women once they are withdrawn from the study, so participants who became pregnant in Sweden were to be switched to standard care. The criterion has now been added for the USA as well.</li> </ol> |

|                   |  |
|-------------------|--|
| 04 September 2019 | <p>Protocol Version 12.0 dated 04 Sept 2019</p> <p>The following changes were made to the protocol:</p> <ol style="list-style-type: none"> <li>1) The statistician was changed.</li> <li>2) The name of the CRO being used changed its name from CCA to ARG so this was changed throughout.</li> <li>3) Since Study DIUR-005 had finished, the actual number of participants enrolled in this study could be added (a total of 122 participants). As such, the maximum number of participants potentially eligible to enter this extension study was increased from 136 to 138 participants.</li> <li>4) Since a decision concerning a marketing authorisation for Chronocort had not been reached, the estimated end of the study was extended until February 2022. Thus the total length of the study was to be approximately 5.5 years from the date of the first participant entering the study i.e. from August 2016 until February 2022.</li> <li>5) If the Chronocort dose was changed at any point after the Week 24 visit, the participant was previously required to have an interim dose titration visit where the assessments noted for Week 4 were required to be repeated. However, this was been replaced with an option to perform either an interim dose titration visit or a telephone call to check on the well-being of the participant (i.e. formal assessments were not needed). The same assessments as noted for the Week 4 visit were to be performed at the interim dose titration visit. If an interim dose titration telephone call was used instead, blood sampling for 17-OHP and A4 and the urine pregnancy test were not performed but all other Week 4 assessments were performed.</li> <li>6) During the interim analyses for this study, two additional exploratory analyses were added to the SAP to further explore the pattern of Chronocort dosing (based on the proportion of the dose given at night and the dose by BSA). These new analyses were therefore added to the protocol for consistency with the SAP.</li> <li>7) Summary of the results from Study DIUR-005 added.</li> </ol> |
| 04 September 2019 | <p>Continuation from the above ...</p> <ol style="list-style-type: none"> <li>8) The Chronocort capsules could now be supplied in either blister packs or bottles so the treatment sections were updated. In addition, the label text in Appendix 8 was updated to the latest label text.</li> <li>9) A new category of "related to study medication from previous Chronocort study" was been added for any AEs that might have occurred in participants who had recently joined the DIUR-006 study from one of the feeder studies.</li> <li>10) The definition of "unexpected" was updated to reference the Reference Safety Information (RSI) in the Investigator's Brochure.</li> <li>11) Clarification added on the different definitions for the 'Interim Analysis 1' data set and subsequent interim analysis data sets.</li> <li>12) It was clarified that testosterone was to be analysed for males and females separately.</li> <li>13) Study monitoring was moved to a risk-based monitoring approach, with full details of this methodology included in the Monitoring Plan.</li> <li>14) The reference to the Summary of Product Characteristics of hydrocortisone in Appendix 2 for expected AEs was removed since this was no longer used in the RSI.</li> <li>15) Some minor administrative and consistency changes were made throughout the protocol.</li> </ol>   |

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|----------------|--|
| 17 April 2020  | <p>Protocol Version 14.0 dated 17 Apr 2020</p> <p>The following changes were made to the protocol:</p> <ol style="list-style-type: none"> <li>1) Footnote added to the schedule of assessments to clarify that the DEXA scans were only needed once a year.</li> <li>2) Footnote added to the schedule of assessments to show that the Baseline and Week 4 visits were repeated for participants who re-entered the study post pregnancy.</li> <li>3) Added that participants who became pregnant still had to be withdrawn from the study, but they were allowed to re-enter the study 6 weeks after the pregnancy was complete (i.e. 6 weeks post-partum regardless of outcome or 6 weeks after abortion or termination) or 6 weeks after they had finished lactating and were no longer breast feeding. Details of re entry into the study and of the post-pregnancy visits were included.</li> <li>4) Emas Pharma details updated to Bionical-Emas and updated email address from Drug.Safety@emaspharma.com to Drug.Safety@bionical-emas.com.</li> <li>5) Contact details for medical monitor updated.</li> <li>6) Expiry date and bottle number added to the example bottle labels to reflect the bottle labels being used.</li> </ol>                                     |
| 17 August 2020 | <p>Protocol Version 15.0 dated 17 Aug 2020</p> <p>The following changes were made to the protocol:</p> <ol style="list-style-type: none"> <li>1) It was clarified that the time period before pregnant participants could re enter the study was at least 6 weeks.</li> <li>2) It was clarified that the end of the study would be the final telephone call (30 days after the last visit) of the last participant, i.e. March 2022.</li> <li>3) Added that participants would be provided with an ad hoc diary in which they were asked to record any use of sick day medications and to record any AEs that occurred between study visits.</li> <li>4) New section added to describe the interim measures put in place to enable the study to continue during the COVID-19 restrictions.</li> <li>5) Statistical Considerations section updated in line with changes made to the SAP (Version 4.0 dated 13 Jul 2020).</li> <li>6) The window around the blood sampling times for analysis of 17-OHP and A4 at 09:00 and 13:00 was increased from half an hour to 1 hour.</li> <li>7) The option to conduct remote monitoring was added, with SDV conducted using the participant's electronic medical records or using scanned documents, if either were permitted.</li> </ol> |
| 28 June 2021   | <p>Protocol Version 16.0 dated 28 Jun 2021</p> <p>The following changes were made to the protocol:</p> <ol style="list-style-type: none"> <li>1) Address for Worldwide Clinical Trials Inc. updated.</li> <li>2) Clarification added for what should happen if a participant received a COVID-19 vaccine to bring the protocol in line with the latest MHRA guidance on COVID-19 vaccinations and clinical trials.</li> <li>3) Added that if the EOS visit was within 3 months after a scheduled 6 monthly visit then only minimal safety assessments (AE and SAE collection only) were performed.</li> <li>4) Added that if a participant had received the COVID-19 vaccine then the next visit had to be scheduled at least 5 days post vaccine.</li> <li>5) Added that the first dose of Chronocort after re-entry following pregnancy was to be taken in the evening of the first dosing day.</li> <li>6) It was clarified that the specified COVID-19 measures could only be implemented after Sponsor approval had been obtained.</li> <li>7) Bottle labels were updated to reflect current labels in use.</li> </ol>  |

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.

None

Notes: