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 x 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:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	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.

Number of subjects in period 1	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 (overall period)	Total	
Number of subjects	91	91	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 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 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 months-None	86	86	
Number of adrenal crisis in 12 months-One	5	5	

Body Mass Index (BMI) Units: kg/m2 arithmetic mean standard deviation	 28.802 ± 5.669	 -	
Body Surface Area (BSA) Units: m2 arithmetic mean standard deviation	 1.798 ± 0.2099	 -	
Waist circumference Units: cm arithmetic mean standard deviation	 91.54 ± 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:

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:

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:

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:

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:

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:

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:

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:

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:

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:

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:

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 bilirubin
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-Direct bilirubin
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 cholesterol
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-HDL cholesterol
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-LDL cholesterol
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-Triglycerides
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	Mean Change-Pre-Chronocort Baseline- Systolic Blood Pressure
Subject analysis set type	Per protocol

Subject analysis set description:

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:

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:

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:

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:

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:

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:

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:

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:

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:

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:

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:

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:

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:

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:

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.

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

End point title	Safety and Tolerability of Chronocort Over Time, as Assessed by Signs and symptoms of Adrenal Insufficiency.[1]

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	

Statistical analyses

No statistical analyses for this end point

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

End point title	Safety and Tolerability of Chronocort as Assessed by Incidence of Use of Sick Day Rules.[2]

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[3]

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[4]

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[5]

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

End point values	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

End point values	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

End point values	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[6]

End point description:

Long term safety and tolerability of Chronocort assesed 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[7]

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

End point values	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

End point values	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 %

Non-serious adverse events	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	1 / 91 (1.10%)		
occurrences (all)	1		
Surgical and medical procedures			
COVID-19 immunisation			
subjects affected / exposed	17 / 91 (18.68%)		
occurrences (all)	24		
Gingival graft			
subjects affected / exposed	1 / 91 (1.10%)		
occurrences (all)	2		
Tooth extraction			
subjects affected / exposed	3 / 91 (3.30%)		
occurrences (all)	3		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	14 / 91 (15.38%)		
occurrences (all)	21		
Chills			
subjects affected / exposed	1 / 91 (1.10%)		
occurrences (all)	1		
Facial pain			
subjects affected / exposed	1 / 91 (1.10%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	43 / 91 (47.25%)		
occurrences (all)	106		
Feeling abnormal			
subjects affected / exposed	1 / 91 (1.10%)		
occurrences (all)	1		
Gait disturbance			
subjects affected / exposed	1 / 91 (1.10%)		
occurrences (all)	1		
Injection site dermatitis			
subjects affected / exposed	1 / 91 (1.10%)		
occurrences (all)	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 subjects affected / exposed occurrences (all)	1 / 91 (1.10%) 2		
Allergy to chemicals subjects affected / exposed occurrences (all)	1 / 91 (1.10%) 1		
Seasonal allergy subjects affected / exposed occurrences (all)	2 / 91 (2.20%) 2		
Appendicitis subjects affected / exposed occurrences (all)	1 / 91 (1.10%) 1		
Social circumstances Educational problem subjects affected / exposed occurrences (all)	2 / 91 (2.20%) 2		
Family stress subjects affected / exposed occurrences (all)	1 / 91 (1.10%) 1		
Impaired work ability subjects affected / exposed occurrences (all)	1 / 91 (1.10%) 1		
Physical assault subjects affected / exposed occurrences (all)	1 / 91 (1.10%) 1		
Stress at work subjects affected / exposed occurrences (all)	2 / 91 (2.20%) 3		
Psychiatric disorders Adjustment disorder subjects affected / exposed occurrences (all)	1 / 91 (1.10%) 1		
Anticipatory anxiety subjects affected / exposed occurrences (all)	1 / 91 (1.10%) 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	1 / 91 (1.10%)		
occurrences (all)	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 occurrences (all)	1 / 91 (1.10%) 1		
Night sweats subjects affected / exposed occurrences (all)	4 / 91 (4.40%) 4		
Pruritus subjects affected / exposed occurrences (all)	3 / 91 (3.30%) 3		
Psoriasis subjects affected / exposed occurrences (all)	2 / 91 (2.20%) 5		
Rash subjects affected / exposed occurrences (all)	8 / 91 (8.79%) 9		
Skin laxity subjects affected / exposed occurrences (all)	1 / 91 (1.10%) 1		
Skin lesion subjects affected / exposed occurrences (all)	1 / 91 (1.10%) 1		
Skin striae subjects affected / exposed occurrences (all)	1 / 91 (1.10%) 1		
Urticaria subjects affected / exposed occurrences (all)	2 / 91 (2.20%) 2		
Endocrine disorders Thyroid mass subjects affected / exposed occurrences (all)	1 / 91 (1.10%) 1		
Thyroiditis subacute subjects affected / exposed occurrences (all)	1 / 91 (1.10%) 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				
subjects affected / exposed	1 / 91 (1.10%)			
occurrences (all)	1			
Musculoskeletal pain				
subjects affected / exposed	3 / 91 (3.30%)			
occurrences (all)	3			
Musculoskeletal stiffness				
subjects affected / exposed	3 / 91 (3.30%)			
occurrences (all)	3			
Myalgia				
subjects affected / exposed	1 / 91 (1.10%)			
occurrences (all)	1			
Myositis				
subjects affected / exposed	1 / 91 (1.10%)			
occurrences (all)	1			
Neck pain				
subjects affected / exposed	2 / 91 (2.20%)			
occurrences (all)	2			
Osteoarthritis				
subjects affected / exposed	4 / 91 (4.40%)			
occurrences (all)	5			
Osteopenia				
subjects affected / exposed	1 / 91 (1.10%)			
occurrences (all)	1			
Osteoporosis				
subjects affected / exposed	1 / 91 (1.10%)			
occurrences (all)	1			
Pain in extremity				
subjects affected / exposed	13 / 91 (14.29%)			
occurrences (all)	15			
Plantar fasciitis				
subjects affected / exposed	1 / 91 (1.10%)			
occurrences (all)	1			
Rotator cuff syndrome				
subjects affected / exposed	1 / 91 (1.10%)			
occurrences (all)	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			
subjects affected / exposed	3 / 91 (3.30%)		
occurrences (all)	3		
Dehydration			
subjects affected / exposed	1 / 91 (1.10%)		
occurrences (all)	1		
Gluten sensitivity			
subjects affected / exposed	1 / 91 (1.10%)		
occurrences (all)	1		
Hypercholesterolaemia			
subjects affected / exposed	4 / 91 (4.40%)		
occurrences (all)	5		
Hyperinsulinaemia			
subjects affected / exposed	1 / 91 (1.10%)		
occurrences (all)	1		
Impaired fasting glucose			
subjects affected / exposed	1 / 91 (1.10%)		
occurrences (all)	1		
Increased appetite			
subjects affected / exposed	4 / 91 (4.40%)		
occurrences (all)	4		
Iron deficiency			
subjects affected / exposed	1 / 91 (1.10%)		
occurrences (all)	1		
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 91 (1.10%)		
occurrences (all)	1		
Vitamin B12 deficiency			
subjects affected / exposed	1 / 91 (1.10%)		
occurrences (all)	1		
Vitamin D deficiency			
subjects affected / exposed	1 / 91 (1.10%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 June 2016	Protocol Version 2.0 dated 20 Jun 2016 1) The Sponsor signatory was changed. 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. 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.
26 July 2016	Protocol Version 3.0 dated 26 Jul 2016 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 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. 3) Participants who routinely worked night shifts and so did not sleep during the usual night-time hours were added to the exclusion criteria. 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. 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. 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. 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. 8) The AE reporting period after the last dose of study medication was extended from 7 days to 30 days. 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'. 10) The term 'safety analysis set' was renamed 'full analysis set' to match the SAP. 11) The telephone number of Emas Pharma was added, and the international dialling code was added to the fax number

04 November 2016	Protocol Version 5.0 dated 04 Nov 2016 The following changes were made to the protocol: 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. 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. 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. 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. 5) The responsible statistician was changed.
21 June 2017	Protocol Version 7.0 dated 21 Jun 2017 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. 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. 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). 4) It was clarified that female participants who presented with oligomenorrhoea or amenorrhoea who were aged ≤55 years of age were to be considered potentially fertile and, therefore, were still to undergo pregnancy testing like all other female participants. 5) AE section was updated to present an improvement in the participant's condition e.g. restoration of menses. 6) The visit windows from Week 18 onwards were extended to ±2 weeks to allow flexibility in scheduling the visits so they could occur at 6-monthly intervals. 7) Change added to allow Chronocort capsules to be supplied in only in blister packs. 8) The definition of pre-Chronocort baseline was revised to match the SAP 9) Synopsis corrected to make consistency with protocol or SAP. 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. 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.

08 November 2017	Protocol Version 9.0 dated 08 Nov 2017 1) Correction made state the amount of blood drawn at any visit as 40 mL in consistent with the laboratory manual. 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. 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. 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. 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 6) clarified that any prior genotyping information collected from DIUR 003 participants would be recorded in the eCRF. 7) Clarified that the last GC dose taken prior to the baseline visit was to be recorded. 8) Prednisone conversion to Chronocort of x5 also applied to prednisolone 9) Clarified that all communications between the Sponsor, designated study representative, and Investigators were to be documented in the TMF 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 11) The dates of the protocol amendments in Appendix 9 of the protocol were incorrect so these were corrected.
21 August 2018	Protocol Version 10.0 dated 21 Aug 2018 1) The project Manager was changed. 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) 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. 4) The description of Study DIUR 007 was updated to reflect the final design of this study. 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. 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. 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. 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.

04 September 2019	Protocol Version 12.0 dated 04 Sept 2019 The following changes were made to the protocol: 1) The statistician was changed. 2) The name of the CRO being used changed its name from CCA to ARG so this was changed throughout. 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. 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. 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. 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. 7) Summary of the results from Study DIUR-005 added.
04 September 2019	Continuation from the above ... 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. 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. 10) The definition of “unexpected” was updated to reference the Reference Safety Information (RSI) in the Investigator's Brochure. 11) Clarification added on the different definitions for the 'Interim Analysis 1' data set and subsequent interim analysis data sets. 12) It was clarified that testosterone was to be analysed for males and females separately. 13) Study monitoring was moved to a risk-based monitoring approach, with full details of this methodology included in the Monitoring Plan. 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. 15) Some minor administrative and consistency changes were made throughout the protocol.

17 April 2020	Protocol Version 14.0 dated 17 Apr 2020 The following changes were made to the protocol: 1) Footnote added to the schedule of assessments to clarify that the DEXA scans were only needed once a year. 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. 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. 4) Emas Pharma details updated to Bionical-Emas and updated email address from Drug.Safety@emaspharma.com to Drug.Safety@bionical-emas.com. 5) Contact details for medical monitor updated. 6) Expiry date and bottle number added to the example bottle labels to reflect the bottle labels being used.
17 August 2020	Protocol Version 15.0 dated 17 Aug 2020 The following changes were made to the protocol: 1) It was clarified that the time period before pregnant participants could re enter the study was at least 6 weeks. 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. 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. 4) New section added to describe the interim measures put in place to enable the study to continue during the COVID-19 restrictions. 5) Statistical Considerations section updated in line with changes made to the SAP (Version 4.0 dated 13 Jul 2020). 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. 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.
28 June 2021	Protocol Version 16.0 dated 28 Jun 2021 The following changes were made to the protocol: 1) Address for Worldwide Clinical Trials Inc. updated. 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. 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. 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. 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. 6) It was clarified that the specified COVID-19 measures could only be implemented after Sponsor approval had been obtained. 7) Bottle labels were updated to reflect current labels in use.

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: