



Clinical trial results:

A Phase 3 Open-label Extension Study to Evaluate the Long-term Safety and Tolerability of Chronocort in the Treatment of Participants Aged 16 Years and Over with Congenital Adrenal Hyperplasia

Summary

EudraCT number	2021-004467-26
Trial protocol	FR
Global end of trial date	15 December 2025

Results information

Result version number	v1 (current)
This version publication date	01 July 2026
First version publication date	01 July 2026

Trial information

Trial identification

Sponsor protocol code	DIUR-015
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05299554
WHO universal trial number (UTN)	-
Other trial identifiers	IND Number: 76485

Notes:

Sponsors

Sponsor organisation name	Immedica Pharma AB
Sponsor organisation address	Solnavägen 3H, Stockholm, Sweden, 113 63
Public contact	Global Integrated Evidence Generation, Immedica Pharma AB, clinical@immedica.com
Scientific contact	Global Integrated Evidence Generation, Immedica Pharma AB, clinical@immedica.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	03 February 2026
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 December 2025
Global end of trial reached?	Yes
Global end of trial date	15 December 2025
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the long-term safety and tolerability of Chronocort in the treatment of participants with Congenital Adrenal Hyperplasia (CAH).

Protection of trial subjects:

The study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki, with ICH Good Clinical Practice (GCP) requirements, and with the USA Code of Federal Regulations (CFR) on Protection of Human Rights (21 CFR 50) (USA only). The principles of informed consent in the Declaration of Helsinki, in the current requirements of GCP and local regulation, whichever afforded the greater participant protection, were implemented before any procedures or interventions were carried out. A signed and dated informed consent form (ICF) was obtained from each adult participant prior to entering the study. Minors were assented and parental consent sought in keeping with local laws and local IEC/IRB requirements. Minors were re-consented on reaching the age of majority if still participating at that time. The Investigator was responsible for obtaining written informed consent 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 GCP compliance. All ICFs were provided in local language. Acquisition of informed consent was documented in the participant's medical record and the ICF was signed and dated by the participant or their legally acceptable representative, as well as by the person who conducted the discussion. The original signed ICF was retained with the medical records at site, with a copy in the 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 were filed in the Trial Master File.

Background therapy:

Fludrocortisone dose adjustments were made if medically indicated and were based on blood pressure measurements and laboratory data.

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	01 April 2022
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 42
Country: Number of subjects enrolled	Japan: 8
Country: Number of subjects enrolled	United States: 26

Worldwide total number of subjects	76
EEA total number of subjects	42

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)	4
Adults (18-64 years)	71
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

All eligible participants from France, USA and Japan who completed Study DIUR-006 (up to 30 participants) or DIUR-014 (up to 46 participants) could have entered this study, giving a maximum of 76 participants. The study centres in this study were the same centres that recruited the participants into the feeder studies.

Pre-assignment

Screening details:

Participants attended a screening visit prior to baseline assessments to allow DIUR-015 to be fully explained and to give informed consent/assent. Participants who had a gap between completing the feeder study and starting DIUR-015 had safety blood tests as part of screening.

Period 1

Period 1 title	Overall 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 this open-label extension study where all participants received Chronocort

Arms

Arm title	Chronocort
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Arm description:

Open-label treatment with Chronocort

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

Dosage and administration details:

Participants from DIUR-006 continued on the same total daily dose of Chronocort received in the feeder study, unless the Investigator thought a dose titration was needed, in which case details of the titration were recorded in the eCRF. As study DIUR-014 was blinded, the treatment and dose were not known to the Investigator so each participant's total hydrocortisone daily dose recorded in the IRT from DIUR-014 was provided to the Investigator. Participants then received their initial dose of Chronocort in DIUR-015 matched to this 1:1. To ensure all participants entering from DIUR-014 were receiving the correct dose, they had a titration visit at Week 6, with an optional 2nd dose titration at Week 12 of DIUR 015. All participants were instructed to take Chronocort 2 times daily: on waking and just prior to bed. The daily Chronocort dose was split approximately $\frac{1}{4}$ in the morning and $\frac{3}{4}$ in the evening (exceptions to this dosing split could be made by the Investigator if warranted).

Number of subjects in period 1	Chronocort
Started	76
Completed	70
Not completed	6
Consent withdrawn by subject	2
Participant Request	4

Baseline characteristics

Reporting groups

Reporting group title	Overall Treatment Period
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Reporting group description: -

Reporting group values	Overall Treatment Period	Total	
Number of subjects	76	76	
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)	4	4	
Adults (18-64 years)	71	71	
From 65-84 years	1	1	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	36.4		
standard deviation	± 12.74	-	
Gender categorical			
Units: Subjects			
Female	45	45	
Male	31	31	
Race			
Units: Subjects			
White	47	47	
Black or African American	3	3	
Asian	8	8	
Not Reportable	18	18	
Unknown	0	0	
Other	0	0	
American Indian or Alaska Native	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Ethnicity			
Units: Subjects			
Hispanic or Latino	3	3	
Not Hispanic or Latino	66	66	
Not Reported	7	7	
Unknown	0	0	
Fertility Status			
Note: WoCBP = Women of Child Bearing Potential			
Units: Subjects			

Not applicable - Male	31	31	
Female - Post Menopausal	8	8	
Female - Surgically Sterile	0	0	
Female - WoCBP taking hormonal contraceptives	12	12	
Female - WoCBP not taking hormonal contraceptives	25	25	
Basis of CAH Diagnosis			
Units: Subjects			
Genetic Only	2	2	
Clinical Only	17	17	
Both Genetic and Clinical	57	57	
Clinical Diagnosis Based On			
Units: Subjects			
Signs and Symptoms	37	37	
Salt Wasting	8	8	
Both Signs and Symptoms and Salt Wasting	29	29	
Not collected	2	2	
Number of Adrenal Crises in the Last Year			
Units: Subjects			
Zero	75	75	
One	1	1	
Two	0	0	
Three	0	0	
Has the Subject Been Hospitalized due to CAH in the Last Year			
Units: Subjects			
Yes	1	1	
No	75	75	
Height			
Units: cm			
arithmetic mean	162.39		
standard deviation	± 9.774	-	
Weight			
Units: kg			
arithmetic mean	75.11		
standard deviation	± 15.573	-	
Waist Circumference			
Units: cm			
arithmetic mean	91.28		
standard deviation	± 16.294	-	
Body Mass Index (BMI)			
Units: kg/m ²			
arithmetic mean	28.53		
standard deviation	± 5.727	-	
Time since CAH Diagnosis			
Units: Years			
arithmetic mean	35.16		
standard deviation	± 13.073	-	
Number of Adrenal Crises in the Last Year			

Units: Occurences			
arithmetic mean	0.0		
standard deviation	± 0.11	-	

End points

End points reporting groups

Reporting group title	Chronocort
Reporting group description:	
Open-label treatment with Chronocort	

Primary: Safety and Tolerability: Signs and symptoms of adrenal insufficiency or over-treatment – Baseline

End point title	Safety and Tolerability: Signs and symptoms of adrenal insufficiency or over-treatment – Baseline ^[1]
End point description:	
Adrenal insufficiency checklist results as reported at DIUR-015 study visits	
End point type	Primary
End point timeframe:	
DIUR-015 Baseline	

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	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	76			
Units: Participants				
Under Replacement	7			
Over Replacement	1			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Signs and symptoms of adrenal insufficiency or over-treatment – Week 6

End point title	Safety and Tolerability: Signs and symptoms of adrenal insufficiency or over-treatment – Week 6 ^[2]
End point description:	
Adrenal insufficiency checklist results as reported at DIUR-015 study visits	
End point type	Primary
End point timeframe:	
DIUR-015 Week 6	

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	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	47			
Units: Participants				
Under Replacement	3			
Over Replacement	4			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Signs and symptoms of adrenal insufficiency or over-treatment – Week 12

End point title	Safety and Tolerability: Signs and symptoms of adrenal insufficiency or over-treatment – Week 12 ^[3]
End point description:	Adrenal insufficiency checklist results as reported at DIUR-015 study visits
End point type	Primary
End point timeframe:	DIUR-015 week 12

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.

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: Participants				
Under Replacement	3			
Over Replacement	2			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Signs and symptoms of adrenal insufficiency or over-treatment – week 24

End point title	Safety and Tolerability: Signs and symptoms of adrenal insufficiency or over-treatment – week 24 ^[4]
End point description:	Adrenal insufficiency checklist results as reported at DIUR-015 study visits
End point type	Primary
End point timeframe:	DIUR-015 Week 24

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			
Subject group type	Reporting group			
Number of subjects analysed	76			
Units: Participants				
Under Replacement	4			
Over Replacement	3			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Signs and symptoms of adrenal insufficiency or over-treatment – 1 Year

End point title	Safety and Tolerability: Signs and symptoms of adrenal insufficiency or over-treatment – 1 Year ^[5]
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End point description:

Adrenal insufficiency checklist results as reported at DIUR-015 study visits

End point type	Primary
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End point timeframe:

DIUR-015 1 year

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	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	71			
Units: Participants				
Under Replacement	1			
Over Replacement	5			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Signs and symptoms of adrenal insufficiency or over-treatment – 2 years

End point title	Safety and Tolerability: Signs and symptoms of adrenal insufficiency or over-treatment – 2 years ^[6]
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End point description:

Adrenal insufficiency checklist results as reported at DIUR-015 study visits

End point type	Primary
End point timeframe:	
DIUR-015 2 year visit	
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	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: Participants				
Under Replacement	0			
Over Replacement	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Signs and symptoms of adrenal insufficiency or over-treatment – 2.5 Years

End point title	Safety and Tolerability: Signs and symptoms of adrenal insufficiency or over-treatment – 2.5 Years ^[7]
End point description:	
Adrenal insufficiency checklist results as reported at DIUR-015 study visits	
End point type	Primary
End point timeframe:	
DIUR-015 2.5 Year visit	
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	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: Participants				
Under Replacement	0			
Over Replacement	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Signs and symptoms of adrenal insufficiency or over-treatment – 3 Years

End point title	Safety and Tolerability: Signs and symptoms of adrenal insufficiency or over-treatment – 3 Years ^[8]
End point description: Adrenal insufficiency checklist results as reported at DIUR-015 study visits	
End point type	Primary
End point timeframe: DIUR-015 3 Year visit	

Notes:

[8] - 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			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: Participants				
Under Replacement	1			
Over Replacement	1			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Use of Sick Day Medications

End point title	Safety and Tolerability: Use of Sick Day Medications ^[9]
End point description: Safety and tolerability of Chronocort as assessed by number of participants using of sick day medications throughout the study.	
End point type	Primary
End point timeframe: 3 Years (assessed at each DIUR-015 visit)	

Notes:

[9] - 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			
Subject group type	Reporting group			
Number of subjects analysed	76			
Units: Participants				
Use of sick-day medication from rescue pack	48			
Use of sick-day medication not from rescue pack	56			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Occurrence of adrenal crises throughout the study

End point title	Safety and Tolerability: Occurrence of adrenal crises throughout the study ^[10]
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End point description:

Participants experiencing adrenal crisis during the study

End point type	Primary
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End point timeframe:

3 Years (assessed at each study visit)

Notes:

[10] - 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			
Subject group type	Reporting group			
Number of subjects analysed	76			
Units: Participants	4			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Participants experiencing adverse events throughout the study

End point title	Safety and Tolerability: Participants experiencing adverse events throughout the study ^[11]
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End point description:

Summary of participants experiencing adverse events throughout the study

End point type	Primary
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End point timeframe:

3 Years (assessed at each study visit)

Notes:

[11] - 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			
Subject group type	Reporting group			
Number of subjects analysed	76			
Units: Participants				
Treatment Emergent Adverse Events (TEAEs)	68			
Treatment Related TEAEs	14			
Serious TEAEs	8			
TEAEs leading to Withdrawal of Drug	0			
TEAEs leading to Study Drug Dose Increase	6			

TEAEs leading to Study Drug Dose Decrease	1			
TEAEs leading to Study Drug Dose Interruption	2			
TEAEs leading to use of Rescue Medication	45			
Severe TEAEs	9			
TEAEs of Special Interest	4			
TEAEs leading to Stress Dosing	51			
TEAEs leading to Adrenal Crisis	3			
TEAEs leading to Death	0			
Non-Treatment Emergent >30 days after last dose	1			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline - Eosinophils

End point title	Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline - Eosinophils ^[12]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the minimum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the minimum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category.

No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[12] - 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			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: Participants				
Pre-Chronocort BL Low – Min. on Treatment Low	5			
Pre-Chronocort BL Low – Min. on Treatment Normal	1			
Pre-Chronocort BL Low - Min. on Treatment High	0			
Pre-Chronocort BL Normal - Min. on Treatment Low	8			
Pre-Chronocort BL Normal- Min. on Treatment Normal	53			

Pre-Chronocort BL Normal - Min. on Treatment High	0			
Pre-Chronocort BL High - Min. on Treatment Low	1			
Pre-Chronocort BL High - Min. on Treatment Normal	4			
Pre-Chronocort BL High - Min. on Treatment High	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline - Eosinophils

End point title	Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline - Eosinophils ^[13]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the maximum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the maximum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[13] - 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			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: Participants				
Pre-Chronocort BL Low – Max. on Treatment Low	0			
Pre-Chronocort BL Low – Max. on Treatment Normal	6			
Pre-Chronocort BL Low - Max. on Treatment High	0			
Pre-Chronocort BL Normal - Max. on Treatment Low	0			
Pre-Chronocort BL Normal- Max. on Treatment Normal	57			
Pre-Chronocort BL Normal - Max. on Treatment High	4			
Pre-Chronocort BL High - Max. on Treatment Low	0			
Pre-Chronocort BL High - Max. on Treatment Normal	2			

Pre-Chronocort BL High - Max. on Treatment High	3			
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Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline - Haemoglobin

End point title	Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline - Haemoglobin ^[14]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the minimum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the minimum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[14] - 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			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: Participants				
Pre-Chronocort BL Low – Min. on Treatment Low	5			
Pre-Chronocort BL Low – Min. on Treatment Normal	2			
Pre-Chronocort BL Low - Min. on Treatment High	0			
Pre-Chronocort BL Normal - Min. on Treatment Low	12			
Pre-Chronocort BL Normal- Min. on Treatment Normal	50			
Pre-Chronocort BL Normal - Min. on Treatment High	0			
Pre-Chronocort BL High - Min. on Treatment Low	0			
Pre-Chronocort BL High - Min. on Treatment Normal	3			
Pre-Chronocort BL High - Min. on Treatment High	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline - Haemoglobin

End point title	Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline - Haemoglobin ^[15]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the maximum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the maximum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[15] - 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			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: Participants				
Pre-Chronocort BL Low – Max. on Treatment Low	3			
Pre-Chronocort BL Low – Max. on Treatment Normal	4			
Pre-Chronocort BL Low – Max. on Treatment High	0			
Pre-Chronocort BL Normal – Max. on Treatment Low	0			
Pre-Chronocort BL Normal – Max. on Treatment Normal	59			
Pre-Chronocort BL Normal – Max. on Treatment High	3			
Pre-Chronocort BL High – Max. on Treatment Low	0			
Pre-Chronocort BL High – Max. on Treatment Normal	1			
Pre-Chronocort BL High – Max. on Treatment High	2			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline - Basophils

End point title	Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline - Basophils ^[16]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the minimum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the minimum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[16] - 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			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: Participants				
Pre-Chronocort BL Low – Min. on Treatment Low	0			
Pre-Chronocort BL Low – Min. on Treatment Normal	0			
Pre-Chronocort BL Low – Min. on Treatment High	0			
Pre-Chronocort BL Normal – Min. on Treatment Low	0			
Pre-Chronocort BL Normal – Min. on Treatment Normal	72			
Pre-Chronocort BL Normal – Min. on Treatment High	0			
Pre-Chronocort BL High – Min. on Treatment Low	0			
Pre-Chronocort BL High – Min. on Treatment Normal	0			
Pre-Chronocort BL High – Min. on Treatment High	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline - Basophils

End point title	Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline - Basophils ^[17]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the maximum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the maximum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[17] - 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			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: Participants				
Pre-Chronocort BL Low – Max. on Treatment Low	0			
Pre-Chronocort BL Low – Max. on Treatment Normal	0			
Pre-Chronocort BL Low – Max. on Treatment High	0			
Pre-Chronocort BL Normal – Max. on Treatment Low	0			
Pre-Chronocort BL Normal – Max. on Treatment Normal	72			
Pre-Chronocort BL Normal – Max. on Treatment High	0			
Pre-Chronocort BL High – Max. on Treatment Low	0			
Pre-Chronocort BL High – Max. on Treatment Normal	0			
Pre-Chronocort BL High – Max. on Treatment High	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Basophils/Leukocytes (%)

End point title	Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Basophils/Leukocytes (%) ^[18]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the minimum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the minimum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[18] - 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			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: Participants				
Pre-Chronocort BL Low – Min. on Treatment Low	0			
Pre-Chronocort BL Low – Min. on Treatment Normal	0			
Pre-Chronocort BL Low – Min. on Treatment High	0			
Pre-Chronocort BL Normal – Min. on Treatment Low	0			
Pre-Chronocort BL Normal – Min. on Treatment Normal	72			
Pre-Chronocort BL Normal – Min. on Treatment High	0			
Pre-Chronocort BL High – Min. on Treatment Low	0			
Pre-Chronocort BL High – Min. on Treatment Normal	0			
Pre-Chronocort BL High – Min. on Treatment High	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline - Basophils/Leukocytes (%)

End point title	Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline - Basophils/Leukocytes (%) ^[19]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the maximum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the maximum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[19] - 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			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: Participants				
Pre-Chronocort BL Low – Max. on Treatment Low	0			
Pre-Chronocort BL Low – Max. on Treatment Normal	0			
Pre-Chronocort BL Low – Max. on Treatment High	0			
Pre-Chronocort BL Normal – Max. on Treatment Low	0			
Pre-Chronocort BL Normal – Max. on Treatment Normal	72			
Pre-Chronocort BL Normal – Max. on Treatment High	0			
Pre-Chronocort BL High – Max. on Treatment Low	0			
Pre-Chronocort BL High – Max. on Treatment Normal	0			
Pre-Chronocort BL High – Max. on Treatment High	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Eosinophils/Leukocytes (%)

End point title	Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Eosinophils/Leukocytes (%) ^[20]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the minimum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the minimum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[20] - 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			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: Participants				
Pre-Chronocort BL Low – Min. on Treatment Low	0			
Pre-Chronocort BL Low – Min. on Treatment Normal	0			
Pre-Chronocort BL Low – Min. on Treatment High	0			
Pre-Chronocort BL Normal – Min. on Treatment Low	0			
Pre-Chronocort BL Normal – Min. on Treatment Normal	67			
Pre-Chronocort BL Normal – Min. on Treatment High	0			
Pre-Chronocort BL High – Min. on Treatment Low	0			
Pre-Chronocort BL High – Min. on Treatment Normal	5			
Pre-Chronocort BL High – Min. on Treatment High	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline - Eosinophils/Leukocytes (%)

End point title	Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline - Eosinophils/Leukocytes (%) ^[21]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the maximum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the maximum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[21] - 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			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: Participants				
Pre-Chronocort BL Low – Max. on Treatment Low	0			
Pre-Chronocort BL Low – Max. on Treatment Normal	0			
Pre-Chronocort BL Low – Max. on Treatment High	0			
Pre-Chronocort BL Normal – Max. on Treatment Low	0			
Pre-Chronocort BL Normal – Max. on Treatment Normal	60			
Pre-Chronocort BL Normal – Max. on Treatment High	7			
Pre-Chronocort BL High – Max. on Treatment Low	0			
Pre-Chronocort BL High – Max. on Treatment Normal	1			
Pre-Chronocort BL High – Max. on Treatment High	4			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – MCHC (g/l)

End point title	Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – MCHC (g/l) ^[22]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the minimum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the minimum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[22] - 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			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: Participants				
Pre-Chronocort BL Low – Min. on Treatment Low	7			
Pre-Chronocort BL Low – Min. on Treatment Normal	2			
Pre-Chronocort BL Low – Min. on Treatment High	0			
Pre-Chronocort BL Normal – Min. on Treatment Low	8			
Pre-Chronocort BL Normal – Min. on Treatment Normal	55			
Pre-Chronocort BL Normal – Min. on Treatment High	0			
Pre-Chronocort BL High – Min. on Treatment Low	0			
Pre-Chronocort BL High – Min. on Treatment Normal	0			
Pre-Chronocort BL High – Min. on Treatment High	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline - MCHC (g/l)

End point title	Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline - MCHC (g/l) ^[23]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the maximum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the maximum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[23] - 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			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: Participants				
Pre-Chronocort BL Low – Max. on Treatment Low	3			
Pre-Chronocort BL Low – Max. on Treatment Normal	6			
Pre-Chronocort BL Low – Max. on Treatment High	0			
Pre-Chronocort BL Normal – Max. on Treatment Low	0			
Pre-Chronocort BL Normal – Max. on Treatment Normal	63			
Pre-Chronocort BL Normal – Max. on Treatment High	0			
Pre-Chronocort BL High – Max. on Treatment Low	0			
Pre-Chronocort BL High – Max. on Treatment Normal	0			
Pre-Chronocort BL High – Max. on Treatment High	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – MCH (pg)

End point title	Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – MCH (pg) ^[24]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the minimum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the minimum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[24] - 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			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: Participants				
Pre-Chronocort BL Low – Min. on Treatment Low	4			
Pre-Chronocort BL Low – Min. on Treatment Normal	0			
Pre-Chronocort BL Low – Min. on Treatment High	0			
Pre-Chronocort BL Normal – Min. on Treatment Low	3			
Pre-Chronocort BL Normal – Min. on Treatment Normal	61			
Pre-Chronocort BL Normal – Min. on Treatment High	0			
Pre-Chronocort BL High – Min. on Treatment Low	0			
Pre-Chronocort BL High – Min. on Treatment Normal	2			
Pre-Chronocort BL High – Min. on Treatment High	2			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – MCH (pg)

End point title	Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – MCH (pg) ^[25]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the maximum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the maximum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[25] - 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			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: Participants				
Pre-Chronocort BL Low – Max. on Treatment Low	4			
Pre-Chronocort BL Low – Max. on Treatment Normal	0			
Pre-Chronocort BL Low – Max. on Treatment High	0			
Pre-Chronocort BL Normal – Max. on Treatment Low	0			
Pre-Chronocort BL Normal – Max. on Treatment Normal	62			
Pre-Chronocort BL Normal – Max. on Treatment High	2			
Pre-Chronocort BL High – Max. on Treatment Low	0			
Pre-Chronocort BL High – Max. on Treatment Normal	2			
Pre-Chronocort BL High – Max. on Treatment High	2			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – MCV (fL)

End point title	Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – MCV (fL) ^[26]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the minimum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the minimum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[26] - 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			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: Participants				
Pre-Chronocort BL Low – Min. on Treatment Low	3			
Pre-Chronocort BL Low – Min. on Treatment Normal	0			
Pre-Chronocort BL Low – Min. on Treatment High	0			
Pre-Chronocort BL Normal – Min. on Treatment Low	1			
Pre-Chronocort BL Normal – Min. on Treatment Normal	64			
Pre-Chronocort BL Normal – Min. on Treatment High	0			
Pre-Chronocort BL High – Min. on Treatment Low	0			
Pre-Chronocort BL High – Min. on Treatment Normal	3			
Pre-Chronocort BL High – Min. on Treatment High	1			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – MCV (fL)

End point title	Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – MCV (fL) ^[27]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the maximum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the maximum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[27] - 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			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: Participants				
Pre-Chronocort BL Low – Max. on Treatment Low	2			
Pre-Chronocort BL Low – Max. on Treatment Normal	1			
Pre-Chronocort BL Low – Max. on Treatment High	0			
Pre-Chronocort BL Normal – Max. on Treatment Low	0			
Pre-Chronocort BL Normal – Max. on Treatment Normal	63			
Pre-Chronocort BL Normal – Max. on Treatment High	2			
Pre-Chronocort BL High – Max. on Treatment Low	0			
Pre-Chronocort BL High – Max. on Treatment Normal	1			
Pre-Chronocort BL High – Max. on Treatment High	3			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Erythrocytes ($10^{12}/L$)

End point title	Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Erythrocytes ($10^{12}/L$) ^[28]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the minimum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the minimum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[28] - 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			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: Participants				
Pre-Chronocort BL Low – Min. on Treatment Low	0			
Pre-Chronocort BL Low – Min. on Treatment Normal	3			
Pre-Chronocort BL Low – Min. on Treatment High	0			
Pre-Chronocort BL Normal – Min. on Treatment Low	3			
Pre-Chronocort BL Normal – Min. on Treatment Normal	61			
Pre-Chronocort BL Normal – Min. on Treatment High	0			
Pre-Chronocort BL High – Min. on Treatment Low	0			
Pre-Chronocort BL High – Min. on Treatment Normal	5			
Pre-Chronocort BL High – Min. on Treatment High	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – Erythrocytes ($10^{12}/L$)

End point title	Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – Erythrocytes ($10^{12}/L$) ^[29]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the maximum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the maximum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[29] - 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			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: Participants				
Pre-Chronocort BL Low – Max. on Treatment Low	0			
Pre-Chronocort BL Low – Max. on Treatment Normal	3			
Pre-Chronocort BL Low – Max. on Treatment High	0			
Pre-Chronocort BL Normal – Max. on Treatment Low	0			
Pre-Chronocort BL Normal – Max. on Treatment Normal	61			
Pre-Chronocort BL Normal – Max. on Treatment High	3			
Pre-Chronocort BL High – Max. on Treatment Low	0			
Pre-Chronocort BL High – Max. on Treatment Normal	2			
Pre-Chronocort BL High – Max. on Treatment High	3			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – RDW

End point title	Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – RDW ^[30]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the minimum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the minimum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[30] - 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			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: Participants				
Pre-Chronocort BL Low – Min. on Treatment Low	0			
Pre-Chronocort BL Low – Min. on Treatment Normal	0			
Pre-Chronocort BL Low - Min. on Treatment High	0			
Pre-Chronocort BL Normal - Min. on Treatment Low	0			
Pre-Chronocort BL Normal- Min. on Treatment Normal	60			
Pre-Chronocort BL Normal - Min. on Treatment High	0			
Pre-Chronocort BL High - Min. on Treatment Low	0			
Pre-Chronocort BL High - Min. on Treatment Normal	8			
Pre-Chronocort BL High - Min. on Treatment High	4			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – RDW

End point title	Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – RDW ^[31]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the maximum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the maximum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[31] - 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			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: Participants				
Pre-Chronocort BL Low – Max. on Treatment Low	0			
Pre-Chronocort BL Low – Max. on Treatment Normal	0			
Pre-Chronocort BL Low - Max. on Treatment High	0			
Pre-Chronocort BL Normal - Max. on Treatment Low	0			
Pre-Chronocort BL Normal- Max. on Treatment Normal	53			
Pre-Chronocort BL Normal - Max. on Treatment High	7			
Pre-Chronocort BL High - Max. on Treatment Low	0			
Pre-Chronocort BL High - Max. on Treatment Normal	2			
Pre-Chronocort BL High - Max. on Treatment High	10			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Haematocrit

End point title	Safety and Tolerability: Categorical distribution of values at
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the minimum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the minimum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type Primary

End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[32] - 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			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: Participants				
Pre-Chronocort BL Low – Min. on Treatment Low	4			
Pre-Chronocort BL Low – Min. on Treatment Normal	1			
Pre-Chronocort BL Low - Min. on Treatment High	0			
Pre-Chronocort BL Normal - Min. on Treatment Low	10			
Pre-Chronocort BL Normal- Min. on Treatment Normal	52			
Pre-Chronocort BL Normal - Min. on Treatment High	0			
Pre-Chronocort BL High - Min. on Treatment Low	0			
Pre-Chronocort BL High - Min. on Treatment Normal	3			
Pre-Chronocort BL High - Min. on Treatment High	2			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – Haematocrit

End point title Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – Haematocrit^[33]

End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the maximum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the maximum value observed during the on-treatment period was identified and categorised accordingly. Results are

presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
End point timeframe:	
Throughout DIUR-015 treatment period of up to 3 years	

Notes:

[33] - 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			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: Participants				
Pre-Chronocort BL Low – Max. on Treatment Low	2			
Pre-Chronocort BL Low – Max. on Treatment Normal	3			
Pre-Chronocort BL Low - Max. on Treatment High	0			
Pre-Chronocort BL Normal - Max. on Treatment Low	1			
Pre-Chronocort BL Normal- Max. on Treatment Normal	56			
Pre-Chronocort BL Normal - Max. on Treatment High	5			
Pre-Chronocort BL High - Max. on Treatment Low	0			
Pre-Chronocort BL High - Max. on Treatment Normal	0			
Pre-Chronocort BL High - Max. on Treatment High	5			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Leukocytes

End point title	Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Leukocytes ^[34]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the minimum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the minimum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
End point timeframe:	
Throughout DIUR-015 treatment period of up to 3 years	

Notes:

[34] - 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			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: Participants				
Pre-Chronocort BL Low – Min. on Treatment Low	0			
Pre-Chronocort BL Low – Min. on Treatment Normal	0			
Pre-Chronocort BL Low - Min. on Treatment High	0			
Pre-Chronocort BL Normal - Min. on Treatment Low	7			
Pre-Chronocort BL Normal- Min. on Treatment Normal	59			
Pre-Chronocort BL Normal - Min. on Treatment High	0			
Pre-Chronocort BL High - Min. on Treatment Low	0			
Pre-Chronocort BL High - Min. on Treatment Normal	6			
Pre-Chronocort BL High - Min. on Treatment High	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – Leukocytes

End point title	Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – Leukocytes ^[35]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the maximum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the maximum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[35] - 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			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: Participants				
Pre-Chronocort BL Low – Max. on Treatment Low	0			
Pre-Chronocort BL Low – Max. on Treatment Normal	0			
Pre-Chronocort BL Low – Max. on Treatment High	0			
Pre-Chronocort BL Normal – Max. on Treatment Low	0			
Pre-Chronocort BL Normal – Max. on Treatment Normal	64			
Pre-Chronocort BL Normal – Max. on Treatment High	2			
Pre-Chronocort BL High – Max. on Treatment Low	0			
Pre-Chronocort BL High – Max. on Treatment Normal	4			
Pre-Chronocort BL High – Max. on Treatment High	2			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Lymphocytes

End point title	Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Lymphocytes ^[36]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the minimum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the minimum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[36] - 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			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: Participants				
Pre-Chronocort BL Low – Min. on Treatment Low	1			
Pre-Chronocort BL Low – Min. on Treatment Normal	0			
Pre-Chronocort BL Low - Min. on Treatment High	0			
Pre-Chronocort BL Normal - Min. on Treatment Low	1			
Pre-Chronocort BL Normal- Min. on Treatment Normal	69			
Pre-Chronocort BL Normal - Min. on Treatment High	0			
Pre-Chronocort BL High - Min. on Treatment Low	0			
Pre-Chronocort BL High - Min. on Treatment Normal	1			
Pre-Chronocort BL High - Min. on Treatment High	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – Lymphocytes

End point title	Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – Lymphocytes ^[37]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the maximum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the maximum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[37] - 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			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: Participants				
Pre-Chronocort BL Low – Max. on Treatment Low	0			
Pre-Chronocort BL Low – Max. on Treatment Normal	1			
Pre-Chronocort BL Low – Max. on Treatment High	0			
Pre-Chronocort BL Normal – Max. on Treatment Low	0			
Pre-Chronocort BL Normal – Max. on Treatment Normal	68			
Pre-Chronocort BL Normal – Max. on Treatment High	2			
Pre-Chronocort BL High – Max. on Treatment Low	0			
Pre-Chronocort BL High – Max. on Treatment Normal	1			
Pre-Chronocort BL High – Max. on Treatment High	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Lymphocytes/Leukocytes

End point title	Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Lymphocytes/Leukocytes ^[38]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the minimum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the minimum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[38] - 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			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: Participants				
Pre-Chronocort BL Low – Min. on Treatment Low	1			
Pre-Chronocort BL Low – Min. on Treatment Normal	1			
Pre-Chronocort BL Low - Min. on Treatment High	0			
Pre-Chronocort BL Normal - Min. on Treatment Low	9			
Pre-Chronocort BL Normal- Min. on Treatment Normal	49			
Pre-Chronocort BL Normal - Min. on Treatment High	0			
Pre-Chronocort BL High - Min. on Treatment Low	0			
Pre-Chronocort BL High - Min. on Treatment Normal	12			
Pre-Chronocort BL High - Min. on Treatment High	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – Lymphocytes/Leukocytes

End point title	Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – Lymphocytes/Leukocytes ^[39]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the maximum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the maximum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[39] - 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			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: Participants				
Pre-Chronocort BL Low – Max. on Treatment Low	0			
Pre-Chronocort BL Low – Max. on Treatment Normal	2			
Pre-Chronocort BL Low – Max. on Treatment High	0			
Pre-Chronocort BL Normal – Max. on Treatment Low	0			
Pre-Chronocort BL Normal – Max. on Treatment Normal	51			
Pre-Chronocort BL Normal – Max. on Treatment High	7			
Pre-Chronocort BL High – Max. on Treatment Low	0			
Pre-Chronocort BL High – Max. on Treatment Normal	8			
Pre-Chronocort BL High – Max. on Treatment High	4			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Monocytes

End point title	Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Monocytes ^[40]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the minimum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the minimum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[40] - 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			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: Participants				
Pre-Chronocort BL Low – Min. on Treatment Low	5			
Pre-Chronocort BL Low – Min. on Treatment Normal	0			
Pre-Chronocort BL Low – Min. on Treatment High	0			
Pre-Chronocort BL Normal – Min. on Treatment Low	11			
Pre-Chronocort BL Normal – Min. on Treatment Normal	56			
Pre-Chronocort BL Normal – Min. on Treatment High	0			
Pre-Chronocort BL High – Min. on Treatment Low	0			
Pre-Chronocort BL High – Min. on Treatment Normal	0			
Pre-Chronocort BL High – Min. on Treatment High	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – Monocytes

End point title	Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – Monocytes ^[41]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the maximum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the maximum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[41] - 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			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: Participants				
Pre-Chronocort BL Low – Max. on Treatment Low	0			
Pre-Chronocort BL Low – Max. on Treatment Normal	5			
Pre-Chronocort BL Low – Max. on Treatment High	0			
Pre-Chronocort BL Normal – Max. on Treatment Low	1			
Pre-Chronocort BL Normal – Max. on Treatment Normal	66			
Pre-Chronocort BL Normal – Max. on Treatment High	0			
Pre-Chronocort BL High – Max. on Treatment Low	0			
Pre-Chronocort BL High – Max. on Treatment Normal	0			
Pre-Chronocort BL High – Max. on Treatment High	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Monocytes/Leukocytes

End point title	Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Monocytes/Leukocytes ^[42]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the minimum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the minimum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[42] - 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			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: Participants				
Pre-Chronocort BL Low – Min. on Treatment Low	0			
Pre-Chronocort BL Low – Min. on Treatment Normal	0			
Pre-Chronocort BL Low - Min. on Treatment High	0			
Pre-Chronocort BL Normal - Min. on Treatment Low	0			
Pre-Chronocort BL Normal- Min. on Treatment Normal	70			
Pre-Chronocort BL Normal - Min. on Treatment High	0			
Pre-Chronocort BL High - Min. on Treatment Low	0			
Pre-Chronocort BL High - Min. on Treatment Normal	2			
Pre-Chronocort BL High - Min. on Treatment High	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – Monocytes/Leukocytes

End point title	Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – Monocytes/Leukocytes ^[43]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the maximum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the maximum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[43] - 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			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: Participants				
Pre-Chronocort BL Low – Max. on Treatment Low	0			
Pre-Chronocort BL Low – Max. on Treatment Normal	0			
Pre-Chronocort BL Low – Max. on Treatment High	0			
Pre-Chronocort BL Normal – Max. on Treatment Low	0			
Pre-Chronocort BL Normal – Max. on Treatment Normal	65			
Pre-Chronocort BL Normal – Max. on Treatment High	5			
Pre-Chronocort BL High – Max. on Treatment Low	0			
Pre-Chronocort BL High – Max. on Treatment Normal	1			
Pre-Chronocort BL High – Max. on Treatment High	1			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Neutrophils

End point title	Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Neutrophils ^[44]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the minimum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the minimum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[44] - 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			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: Participants				
Pre-Chronocort BL Low – Min. on Treatment Low	2			
Pre-Chronocort BL Low – Min. on Treatment Normal v	0			
Pre-Chronocort BL Low - Min. on Treatment High	0			
Pre-Chronocort BL Normal - Min. on Treatment Low	5			
Pre-Chronocort BL Normal- Min. on Treatment Normal	61			
Pre-Chronocort BL Normal - Min. on Treatment High	0			
Pre-Chronocort BL High - Min. on Treatment Low	1			
Pre-Chronocort BL High - Min. on Treatment Normal	3			
Pre-Chronocort BL High - Min. on Treatment High	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – Neutrophils

End point title	Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – Neutrophils ^[45]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the maximum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the maximum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[45] - 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			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: Participants				
Pre-Chronocort BL Low – Max. on Treatment Low	0			
Pre-Chronocort BL Low – Max. on Treatment Normal	2			
Pre-Chronocort BL Low – Max. on Treatment High	0			
Pre-Chronocort BL Normal – Max. on Treatment Low	0			
Pre-Chronocort BL Normal – Max. on Treatment Normal	62			
Pre-Chronocort BL Normal – Max. on Treatment High	4			
Pre-Chronocort BL High – Max. on Treatment Low	0			
Pre-Chronocort BL High – Max. on Treatment Normal	4			
Pre-Chronocort BL High – Max. on Treatment High	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Neutrophils/Leukocytes

End point title	Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Neutrophils/Leukocytes ^[46]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the minimum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the minimum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[46] - 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			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: Participants				
Pre-Chronocort BL Low – Min. on Treatment Low	1			
Pre-Chronocort BL Low – Min. on Treatment Normal	6			
Pre-Chronocort BL Low - Min. on Treatment High	0			
Pre-Chronocort BL Normal - Min. on Treatment Low	9			
Pre-Chronocort BL Normal- Min. on Treatment Normal	49			
Pre-Chronocort BL Normal - Min. on Treatment High	0			
Pre-Chronocort BL High - Min. on Treatment Low	0			
Pre-Chronocort BL High - Min. on Treatment Normal	7			
Pre-Chronocort BL High - Min. on Treatment High	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – Neutrophils/Leukocytes

End point title	Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – Neutrophils/Leukocytes ^[47]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the maximum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the maximum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[47] - 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			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: Participants				
Pre-Chronocort BL Low – Max. on Treatment Low	0			
Pre-Chronocort BL Low – Max. on Treatment Normal	7			
Pre-Chronocort BL Low – Max. on Treatment High	0			
Pre-Chronocort BL Normal – Max. on Treatment Low	0			
Pre-Chronocort BL Normal– Max. on Treatment Normal	45			
Pre-Chronocort BL Normal – Max. on Treatment High	13			
Pre-Chronocort BL High – Max. on Treatment Low	0			
Pre-Chronocort BL High – Max. on Treatment Normal	5			
Pre-Chronocort BL High – Max. on Treatment High	2			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Platelets

End point title	Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Platelets ^[48]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the minimum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the minimum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[48] - 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			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: Participants				
Pre-Chronocort BL Low – Min. on Treatment Low	0			
Pre-Chronocort BL Low – Min. on Treatment Normal	0			
Pre-Chronocort BL Low - Min. on Treatment High	0			
Pre-Chronocort BL Normal - Min. on Treatment Low	1			
Pre-Chronocort BL Normal- Min. on Treatment Normal	68			
Pre-Chronocort BL Normal - Min. on Treatment High	1			
Pre-Chronocort BL High - Min. on Treatment Low	0			
Pre-Chronocort BL High - Min. on Treatment Normal	2			
Pre-Chronocort BL High - Min. on Treatment High	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – Platelets

End point title	Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – Platelets ^[49]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the maximum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the maximum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[49] - 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			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: Participants				
Pre-Chronocort BL Low – Max. on Treatment Low	0			
Pre-Chronocort BL Low – Max. on Treatment Normal	0			
Pre-Chronocort BL Low – Max. on Treatment High	0			
Pre-Chronocort BL Normal – Max. on Treatment Low	0			
Pre-Chronocort BL Normal – Max. on Treatment Normal	67			
Pre-Chronocort BL Normal – Max. on Treatment High	3			
Pre-Chronocort BL High – Max. on Treatment Low	0			
Pre-Chronocort BL High – Max. on Treatment Normal	0			
Pre-Chronocort BL High – Max. on Treatment High	2			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Alanine Aminotransferase

End point title	Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Alanine Aminotransferase ^[50]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the minimum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the minimum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[50] - 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			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: Participants				
Pre-Chronocort BL Low – Min. on Treatment Low	0			
Pre-Chronocort BL Low – Min. on Treatment Normal	0			
Pre-Chronocort BL Low - Min. on Treatment High	0			
Pre-Chronocort BL Normal - Min. on Treatment Low	0			
Pre-Chronocort BL Normal- Min. on Treatment Normal	66			
Pre-Chronocort BL Normal - Min. on Treatment High	0			
Pre-Chronocort BL High - Min. on Treatment Low	0			
Pre-Chronocort BL High - Min. on Treatment Normal	7			
Pre-Chronocort BL High - Min. on Treatment High	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – Alanine Aminotransferase

End point title	Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – Alanine Aminotransferase ^[51]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the maximum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the maximum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[51] - 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			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: Participants				
Pre-Chronocort BL Low – Max. on Treatment Low	0			
Pre-Chronocort BL Low – Max. on Treatment Normal	0			
Pre-Chronocort BL Low – Max. on Treatment High	0			
Pre-Chronocort BL Normal – Max. on Treatment Low	0			
Pre-Chronocort BL Normal – Max. on Treatment Normal	59			
Pre-Chronocort BL Normal – Max. on Treatment High	7			
Pre-Chronocort BL High – Max. on Treatment Low	0			
Pre-Chronocort BL High – Max. on Treatment Normal	4			
Pre-Chronocort BL High – Max. on Treatment High	3			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Albumin

End point title	Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Albumin ^[52]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the minimum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the minimum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[52] - 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			
Subject group type	Reporting group			
Number of subjects analysed	74			
Units: Participants				
Pre-Chronocort BL Low – Min. on Treatment Low	0			

Pre-Chronocort BL Low – Min. on Treatment Normal	1			
Pre-Chronocort BL Low – Min. on Treatment High	0			
Pre-Chronocort BL Normal – Min. on Treatment Low	4			
Pre-Chronocort BL Normal- Min. on Treatment Normal	69			
Pre-Chronocort BL Normal – Min. on Treatment High	0			
Pre-Chronocort BL High – Min. on Treatment Low	0			
Pre-Chronocort BL High – Min. on Treatment Normal	0			
Pre-Chronocort BL High – Min. on Treatment High	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – Albumin

End point title	Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – Albumin ^[53]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the maximum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the maximum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[53] - 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			
Subject group type	Reporting group			
Number of subjects analysed	74			
Units: Participants				
Pre-Chronocort BL Low – Max. on Treatment Low	0			
Pre-Chronocort BL Low – Max. on Treatment Normal	1			
Pre-Chronocort BL Low – Max. on Treatment High	0			
Pre-Chronocort BL Normal – Max. on Treatment Low	0			

Pre-Chronocort BL Normal- Max. on Treatment Normal	73			
Pre-Chronocort BL Normal - Max. on Treatment High	0			
Pre-Chronocort BL High - Max. on Treatment Low	0			
Pre-Chronocort BL High - Max. on Treatment Normal	0			
Pre-Chronocort BL High - Max. on Treatment High	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Alkaline Phosphatase

End point title	Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Alkaline Phosphatase ^[54]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the minimum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the minimum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[54] - 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			
Subject group type	Reporting group			
Number of subjects analysed	74			
Units: Participants				
Pre-Chronocort BL Low – Min. on Treatment Low	1			
Pre-Chronocort BL Low – Min. on Treatment Normal	0			
Pre-Chronocort BL Low - Min. on Treatment High	0			
Pre-Chronocort BL Normal - Min. on Treatment Low	1			
Pre-Chronocort BL Normal- Min. on Treatment Normal	71			
Pre-Chronocort BL Normal - Min. on Treatment High	0			
Pre-Chronocort BL High - Min. on Treatment Low	0			
Pre-Chronocort BL High - Min. on Treatment Normal	0			

Pre-Chronocort BL High - Min. on Treatment High	1			
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Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – Alkaline Phosphatase

End point title	Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – Alkaline Phosphatase ^[55]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the maximum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the maximum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[55] - 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			
Subject group type	Reporting group			
Number of subjects analysed	74			
Units: Participants				
Pre-Chronocort BL Low – Max. on Treatment Low	0			
Pre-Chronocort BL Low – Max. on Treatment Normal	1			
Pre-Chronocort BL Low - Max. on Treatment High	0			
Pre-Chronocort BL Normal - Max. on Treatment Low	0			
Pre-Chronocort BL Normal- Max. on Treatment Normal	68			
Pre-Chronocort BL Normal - Max. on Treatment High	4			
Pre-Chronocort BL High - Max. on Treatment Low	0			
Pre-Chronocort BL High - Max. on Treatment Normal	0			
Pre-Chronocort BL High - Max. on Treatment High	1			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Aspartate Aminotransferase

End point title	Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Aspartate Aminotransferase ^[56]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the minimum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the minimum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[56] - 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			
Subject group type	Reporting group			
Number of subjects analysed	71			
Units: Participants				
Pre-Chronocort BL Low – Min. on Treatment Low	0			
Pre-Chronocort BL Low – Min. on Treatment Normal	0			
Pre-Chronocort BL Low - Min. on Treatment High	0			
Pre-Chronocort BL Normal - Min. on Treatment Low	0			
Pre-Chronocort BL Normal- Min. on Treatment Normal	71			
Pre-Chronocort BL Normal - Min. on Treatment High	0			
Pre-Chronocort BL High - Min. on Treatment Low	0			
Pre-Chronocort BL High - Min. on Treatment Normal	0			
Pre-Chronocort BL High - Min. on Treatment High	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – Aspartate Aminotransferase

End point title	Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – Aspartate Aminotransferase ^[57]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the maximum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the maximum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[57] - 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			
Subject group type	Reporting group			
Number of subjects analysed	71			
Units: Participants				
Pre-Chronocort BL Low – Max. on Treatment Low	0			
Pre-Chronocort BL Low – Max. on Treatment Normal	0			
Pre-Chronocort BL Low - Max. on Treatment High	0			
Pre-Chronocort BL Normal - Max. on Treatment Low	0			
Pre-Chronocort BL Normal- Max. on Treatment Normal	69			
Pre-Chronocort BL Normal - Max. on Treatment High	2			
Pre-Chronocort BL High - Max. on Treatment Low	0			
Pre-Chronocort BL High - Max. on Treatment Normal	0			
Pre-Chronocort BL High - Max. on Treatment High	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Bicarbonate

End point title	Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Bicarbonate ^[58]
End point description: This endpoint summarises the categorical distribution of laboratory parameter values at the minimum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the minimum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort	
End point type	Primary
End point timeframe: Throughout DIUR-015 treatment period of up to 3 years	
Notes: [58] - 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			
Subject group type	Reporting group			
Number of subjects analysed	55			
Units: Participants				
Pre-Chronocort BL Low – Min. on Treatment Low	4			
Pre-Chronocort BL Low – Min. on Treatment Normal	2			
Pre-Chronocort BL Low - Min. on Treatment High	0			
Pre-Chronocort BL Normal - Min. on Treatment Low	12			
Pre-Chronocort BL Normal- Min. on Treatment Normal	37			
Pre-Chronocort BL Normal - Min. on Treatment High	0			
Pre-Chronocort BL High - Min. on Treatment Low	0			
Pre-Chronocort BL High - Min. on Treatment Normal	0			
Pre-Chronocort BL High - Min. on Treatment High	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – Bicarbonate

End point title	Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – Bicarbonate ^[59]
End point description: This endpoint summarises the categorical distribution of laboratory parameter values at the maximum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the maximum value observed during the on-treatment period was identified and categorised accordingly. Results are	

presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
End point timeframe:	
Throughout DIUR-015 treatment period of up to 3 years	

Notes:

[59] - 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			
Subject group type	Reporting group			
Number of subjects analysed	55			
Units: Participants				
Pre-Chronocort BL Low – Max. on Treatment Low	0			
Pre-Chronocort BL Low – Max. on Treatment Normal	6			
Pre-Chronocort BL Low - Max. on Treatment High	0			
Pre-Chronocort BL Normal - Max. on Treatment Low	0			
Pre-Chronocort BL Normal- Max. on Treatment Normal	49			
Pre-Chronocort BL Normal - Max. on Treatment High	0			
Pre-Chronocort BL High - Max. on Treatment Low	0			
Pre-Chronocort BL High - Max. on Treatment Normal	0			
Pre-Chronocort BL High - Max. on Treatment High	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Bilirubin

End point title	Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Bilirubin ^[60]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the minimum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the minimum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort

End point type	Primary
End point timeframe:	
Throughout DIUR-015 treatment period of up to 3 years	

Notes:

[60] - 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			
Subject group type	Reporting group			
Number of subjects analysed	74			
Units: Participants				
Pre-Chronocort BL Low – Min. on Treatment Low	0			
Pre-Chronocort BL Low – Min. on Treatment Normal	0			
Pre-Chronocort BL Low - Min. on Treatment High	0			
Pre-Chronocort BL Normal - Min. on Treatment Low	0			
Pre-Chronocort BL Normal- Min. on Treatment Normal	74			
Pre-Chronocort BL Normal - Min. on Treatment High	0			
Pre-Chronocort BL High - Min. on Treatment Low	0			
Pre-Chronocort BL High - Min. on Treatment Normal	0			
Pre-Chronocort BL High - Min. on Treatment High	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – Bilirubin

End point title	Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – Bilirubin ^[61]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the maximum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the maximum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[61] - 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			
Subject group type	Reporting group			
Number of subjects analysed	74			
Units: Participants				
Pre-Chronocort BL Low – Max. on Treatment Low	0			
Pre-Chronocort BL Low – Max. on Treatment Normal	0			
Pre-Chronocort BL Low – Max. on Treatment High	0			
Pre-Chronocort BL Normal – Max. on Treatment Low	0			
Pre-Chronocort BL Normal – Max. on Treatment Normal	69			
Pre-Chronocort BL Normal – Max. on Treatment High	5			
Pre-Chronocort BL High – Max. on Treatment Low	0			
Pre-Chronocort BL High – Max. on Treatment Normal	0			
Pre-Chronocort BL High – Max. on Treatment High	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Calcium

End point title	Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Calcium ^[62]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the minimum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the minimum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[62] - 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			
Subject group type	Reporting group			
Number of subjects analysed	74			
Units: Participants				
Pre-Chronocort BL Low – Min. on Treatment Low	4			
Pre-Chronocort BL Low – Min. on Treatment Normal	0			
Pre-Chronocort BL Low - Min. on Treatment High	0			
Pre-Chronocort BL Normal - Min. on Treatment Low	6			
Pre-Chronocort BL Normal- Min. on Treatment Normal	62			
Pre-Chronocort BL Normal - Min. on Treatment High	0			
Pre-Chronocort BL High - Min. on Treatment Low	0			
Pre-Chronocort BL High - Min. on Treatment Normal	2			
Pre-Chronocort BL High - Min. on Treatment High	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – Calcium

End point title	Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – Calcium ^[63]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the maximum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the maximum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[63] - 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			
Subject group type	Reporting group			
Number of subjects analysed	74			
Units: Participants				
Pre-Chronocort BL Low – Max. on Treatment Low	1			
Pre-Chronocort BL Low – Max. on Treatment Normal	3			
Pre-Chronocort BL Low – Max. on Treatment High	0			
Pre-Chronocort BL Normal – Max. on Treatment Low	0			
Pre-Chronocort BL Normal – Max. on Treatment Normal	61			
Pre-Chronocort BL Normal – Max. on Treatment High	7			
Pre-Chronocort BL High – Max. on Treatment Low	0			
Pre-Chronocort BL High – Max. on Treatment Normal	0			
Pre-Chronocort BL High – Max. on Treatment High	2			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Chloride

End point title	Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Chloride ^[64]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the minimum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the minimum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[64] - 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			
Subject group type	Reporting group			
Number of subjects analysed	74			
Units: Participants				
Pre-Chronocort BL Low – Min. on Treatment Low	0			
Pre-Chronocort BL Low – Min. on Treatment Normal	0			
Pre-Chronocort BL Low - Min. on Treatment High	0			
Pre-Chronocort BL Normal - Min. on Treatment Low	3			
Pre-Chronocort BL Normal- Min. on Treatment Normal	66			
Pre-Chronocort BL Normal - Min. on Treatment High	0			
Pre-Chronocort BL High - Min. on Treatment Low	0			
Pre-Chronocort BL High - Min. on Treatment Normal	5			
Pre-Chronocort BL High - Min. on Treatment High	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – Chloride

End point title	Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – Chloride ^[65]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the maximum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the maximum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[65] - 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			
Subject group type	Reporting group			
Number of subjects analysed	74			
Units: Participants				
Pre-Chronocort BL Low – Max. on Treatment Low	0			
Pre-Chronocort BL Low – Max. on Treatment Normal	0			
Pre-Chronocort BL Low – Max. on Treatment High	0			
Pre-Chronocort BL Normal – Max. on Treatment Low	0			
Pre-Chronocort BL Normal– Max. on Treatment Normal	64			
Pre-Chronocort BL Normal – Max. on Treatment High	5			
Pre-Chronocort BL High – Max. on Treatment Low	0			
Pre-Chronocort BL High – Max. on Treatment Normal	4			
Pre-Chronocort BL High – Max. on Treatment High	1			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Creatine Kinase

End point title	Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Creatine Kinase ^[66]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the minimum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the minimum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[66] - 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			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: Participants				
Pre-Chronocort BL Low – Min. on Treatment Low	1			
Pre-Chronocort BL Low – Min. on Treatment Normal	0			
Pre-Chronocort BL Low - Min. on Treatment High	0			
Pre-Chronocort BL Normal - Min. on Treatment Low	1			
Pre-Chronocort BL Normal- Min. on Treatment Normal	67			
Pre-Chronocort BL Normal - Min. on Treatment High	0			
Pre-Chronocort BL High - Min. on Treatment Low	0			
Pre-Chronocort BL High - Min. on Treatment Normal	4			
Pre-Chronocort BL High - Min. on Treatment High	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – Creatine Kinase

End point title	Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – Creatine Kinase ^[67]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the maximum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the maximum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[67] - 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			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: Participants				
Pre-Chronocort BL Low – Max. on Treatment Low	0			
Pre-Chronocort BL Low – Max. on Treatment Normal	1			
Pre-Chronocort BL Low – Max. on Treatment High	0			
Pre-Chronocort BL Normal – Max. on Treatment Low	1			
Pre-Chronocort BL Normal – Max. on Treatment Normal	56			
Pre-Chronocort BL Normal – Max. on Treatment High	11			
Pre-Chronocort BL High – Max. on Treatment Low	0			
Pre-Chronocort BL High – Max. on Treatment Normal	0			
Pre-Chronocort BL High – Max. on Treatment High	4			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Creatinine Enzymatic

End point title	Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Creatinine Enzymatic ^[68]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the minimum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the minimum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[68] - 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			
Subject group type	Reporting group			
Number of subjects analysed	55			
Units: Participants				
Pre-Chronocort BL Low – Min. on Treatment Low	1			
Pre-Chronocort BL Low – Min. on Treatment Normal	1			
Pre-Chronocort BL Low - Min. on Treatment High	0			
Pre-Chronocort BL Normal - Min. on Treatment Low	0			
Pre-Chronocort BL Normal- Min. on Treatment Normal	51			
Pre-Chronocort BL Normal - Min. on Treatment High	0			
Pre-Chronocort BL High - Min. on Treatment Low	0			
Pre-Chronocort BL High - Min. on Treatment Normal	1			
Pre-Chronocort BL High - Min. on Treatment High	1			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – Creatinine Enzymatic

End point title	Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – Creatinine Enzymatic ^[69]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the maximum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the maximum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[69] - 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			
Subject group type	Reporting group			
Number of subjects analysed	55			
Units: Participants				
Pre-Chronocort BL Low – Max. on Treatment Low	1			
Pre-Chronocort BL Low – Max. on Treatment Normal	1			
Pre-Chronocort BL Low – Max. on Treatment High	0			
Pre-Chronocort BL Normal – Max. on Treatment Low	0			
Pre-Chronocort BL Normal– Max. on Treatment Normal	40			
Pre-Chronocort BL Normal – Max. on Treatment High	11			
Pre-Chronocort BL High – Max. on Treatment Low	0			
Pre-Chronocort BL High – Max. on Treatment Normal	0			
Pre-Chronocort BL High – Max. on Treatment High	2			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Direct Bilirubin

End point title	Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Direct Bilirubin ^[70]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the minimum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the minimum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[70] - 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			
Subject group type	Reporting group			
Number of subjects analysed	69			
Units: Participants				
Pre-Chronocort BL Low – Min. on Treatment Low	0			
Pre-Chronocort BL Low – Min. on Treatment Normal	0			
Pre-Chronocort BL Low - Min. on Treatment High	0			
Pre-Chronocort BL Normal - Min. on Treatment Low	0			
Pre-Chronocort BL Normal- Min. on Treatment Normal	69			
Pre-Chronocort BL Normal - Min. on Treatment High	0			
Pre-Chronocort BL High - Min. on Treatment Low	0			
Pre-Chronocort BL High - Min. on Treatment Normal	0			
Pre-Chronocort BL High - Min. on Treatment High	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – Direct Bilirubin

End point title	Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – Direct Bilirubin ^[71]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the maximum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the maximum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[71] - 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			
Subject group type	Reporting group			
Number of subjects analysed	69			
Units: Participants				
Pre-Chronocort BL Low – Max. on Treatment Low	0			
Pre-Chronocort BL Low – Max. on Treatment Normal	0			
Pre-Chronocort BL Low – Max. on Treatment High	0			
Pre-Chronocort BL Normal – Max. on Treatment Low	0			
Pre-Chronocort BL Normal– Max. on Treatment Normal	64			
Pre-Chronocort BL Normal – Max. on Treatment High	5			
Pre-Chronocort BL High – Max. on Treatment Low	0			
Pre-Chronocort BL High – Max. on Treatment Normal	0			
Pre-Chronocort BL High – Max. on Treatment High	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Lactate Dehydrogenase

End point title	Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Lactate Dehydrogenase ^[72]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the minimum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the minimum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[72] - 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			
Subject group type	Reporting group			
Number of subjects analysed	68			
Units: Participants				
Pre-Chronocort BL Low – Min. on Treatment Low	0			
Pre-Chronocort BL Low – Min. on Treatment Normal	0			
Pre-Chronocort BL Low – Min. on Treatment High	0			
Pre-Chronocort BL Normal – Min. on Treatment Low	0			
Pre-Chronocort BL Normal – Min. on Treatment Normal	68			
Pre-Chronocort BL Normal – Min. on Treatment High	0			
Pre-Chronocort BL High – Min. on Treatment Low	0			
Pre-Chronocort BL High – Min. on Treatment Normal	0			
Pre-Chronocort BL High – Min. on Treatment High	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – Lactate Dehydrogenase

End point title	Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – Lactate Dehydrogenase ^[73]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the maximum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the maximum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[73] - 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			
Subject group type	Reporting group			
Number of subjects analysed	68			
Units: Participants				
Pre-Chronocort BL Low – Max. on Treatment Low	0			
Pre-Chronocort BL Low – Max. on Treatment Normal	0			
Pre-Chronocort BL Low – Max. on Treatment High	0			
Pre-Chronocort BL Normal – Max. on Treatment Low	0			
Pre-Chronocort BL Normal – Max. on Treatment Normal	68			
Pre-Chronocort BL Normal – Max. on Treatment High	0			
Pre-Chronocort BL High – Max. on Treatment Low	0			
Pre-Chronocort BL High – Max. on Treatment Normal	0			
Pre-Chronocort BL High – Max. on Treatment High	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Magnesium

End point title	Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Magnesium ^[74]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the minimum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the minimum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[74] - 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			
Subject group type	Reporting group			
Number of subjects analysed	74			
Units: Participants				
Pre-Chronocort BL Low – Min. on Treatment Low	0			
Pre-Chronocort BL Low – Min. on Treatment Normal	0			
Pre-Chronocort BL Low - Min. on Treatment High	0			
Pre-Chronocort BL Normal - Min. on Treatment Low	0			
Pre-Chronocort BL Normal- Min. on Treatment Normal	74			
Pre-Chronocort BL Normal - Min. on Treatment High	0			
Pre-Chronocort BL High - Min. on Treatment Low	0			
Pre-Chronocort BL High - Min. on Treatment Normal	0			
Pre-Chronocort BL High - Min. on Treatment High	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – Magnesium

End point title	Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – Magnesium ^[75]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the maximum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the maximum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[75] - 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			
Subject group type	Reporting group			
Number of subjects analysed	74			
Units: Participants				
Pre-Chronocort BL Low – Max. on Treatment Low	0			
Pre-Chronocort BL Low – Max. on Treatment Normal	0			
Pre-Chronocort BL Low – Max. on Treatment High	0			
Pre-Chronocort BL Normal – Max. on Treatment Low	0			
Pre-Chronocort BL Normal – Max. on Treatment Normal	73			
Pre-Chronocort BL Normal – Max. on Treatment High	1			
Pre-Chronocort BL High – Max. on Treatment Low	0			
Pre-Chronocort BL High – Max. on Treatment Normal	0			
Pre-Chronocort BL High – Max. on Treatment High	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Phosphate

End point title	Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Phosphate ^[76]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the minimum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the minimum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[76] - 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			
Subject group type	Reporting group			
Number of subjects analysed	74			
Units: Participants				
Pre-Chronocort BL Low – Min. on Treatment Low	0			
Pre-Chronocort BL Low – Min. on Treatment Normal	1			
Pre-Chronocort BL Low - Min. on Treatment High	0			
Pre-Chronocort BL Normal - Min. on Treatment Low	2			
Pre-Chronocort BL Normal- Min. on Treatment Normal	63			
Pre-Chronocort BL Normal - Min. on Treatment High	0			
Pre-Chronocort BL High - Min. on Treatment Low	0			
Pre-Chronocort BL High - Min. on Treatment Normal	8			
Pre-Chronocort BL High - Min. on Treatment High	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – Phosphate

End point title	Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – Phosphate ^[77]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the maximum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the maximum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[77] - 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			
Subject group type	Reporting group			
Number of subjects analysed	74			
Units: Participants				
Pre-Chronocort BL Low – Max. on Treatment Low	0			
Pre-Chronocort BL Low – Max. on Treatment Normal	1			
Pre-Chronocort BL Low – Max. on Treatment High	0			
Pre-Chronocort BL Normal – Max. on Treatment Low	0			
Pre-Chronocort BL Normal – Max. on Treatment Normal	55			
Pre-Chronocort BL Normal – Max. on Treatment High	10			
Pre-Chronocort BL High – Max. on Treatment Low	0			
Pre-Chronocort BL High – Max. on Treatment Normal	6			
Pre-Chronocort BL High – Max. on Treatment High	2			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Potassium

End point title	Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Potassium ^[78]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the minimum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the minimum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[78] - 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			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: Participants				
Pre-Chronocort BL Low – Min. on Treatment Low	0			
Pre-Chronocort BL Low – Min. on Treatment Normal	1			
Pre-Chronocort BL Low - Min. on Treatment High	0			
Pre-Chronocort BL Normal - Min. on Treatment Low	1			
Pre-Chronocort BL Normal- Min. on Treatment Normal	70			
Pre-Chronocort BL Normal - Min. on Treatment High	0			
Pre-Chronocort BL High - Min. on Treatment Low	0			
Pre-Chronocort BL High - Min. on Treatment Normal	1			
Pre-Chronocort BL High - Min. on Treatment High	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – Potassium

End point title	Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – Potassium ^[79]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the maximum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the maximum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[79] - 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			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: Participants				
Pre-Chronocort BL Low – Max. on Treatment Low	0			
Pre-Chronocort BL Low – Max. on Treatment Normal	1			
Pre-Chronocort BL Low – Max. on Treatment High	0			
Pre-Chronocort BL Normal – Max. on Treatment Low	0			
Pre-Chronocort BL Normal – Max. on Treatment Normal	67			
Pre-Chronocort BL Normal – Max. on Treatment High	4			
Pre-Chronocort BL High – Max. on Treatment Low	0			
Pre-Chronocort BL High – Max. on Treatment Normal	1			
Pre-Chronocort BL High – Max. on Treatment High	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Protein

End point title	Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Protein ^[80]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the minimum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the minimum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[80] - 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			
Subject group type	Reporting group			
Number of subjects analysed	74			
Units: Participants				
Pre-Chronocort BL Low – Min. on Treatment Low	2			
Pre-Chronocort BL Low – Min. on Treatment Normal	6			
Pre-Chronocort BL Low - Min. on Treatment High	0			
Pre-Chronocort BL Normal - Min. on Treatment Low	6			
Pre-Chronocort BL Normal- Min. on Treatment Normal	60			
Pre-Chronocort BL Normal - Min. on Treatment High	0			
Pre-Chronocort BL High - Min. on Treatment Low	0			
Pre-Chronocort BL High - Min. on Treatment Normal	0			
Pre-Chronocort BL High - Min. on Treatment High	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – Protein

End point title	Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – Protein ^[81]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the maximum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the maximum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[81] - 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			
Subject group type	Reporting group			
Number of subjects analysed	74			
Units: Participants				
Pre-Chronocort BL Low – Max. on Treatment Low	0			
Pre-Chronocort BL Low – Max. on Treatment Normal	8			
Pre-Chronocort BL Low – Max. on Treatment High	0			
Pre-Chronocort BL Normal – Max. on Treatment Low	0			
Pre-Chronocort BL Normal – Max. on Treatment Normal	64			
Pre-Chronocort BL Normal – Max. on Treatment High	2			
Pre-Chronocort BL High – Max. on Treatment Low	0			
Pre-Chronocort BL High – Max. on Treatment Normal	0			
Pre-Chronocort BL High – Max. on Treatment High	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Sodium

End point title	Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Sodium ^[82]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the minimum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the minimum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[82] - 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			
Subject group type	Reporting group			
Number of subjects analysed	74			
Units: Participants				
Pre-Chronocort BL Low – Min. on Treatment Low	2			
Pre-Chronocort BL Low – Min. on Treatment Normal	1			
Pre-Chronocort BL Low - Min. on Treatment High	0			
Pre-Chronocort BL Normal - Min. on Treatment Low	11			
Pre-Chronocort BL Normal- Min. on Treatment Normal	59			
Pre-Chronocort BL Normal - Min. on Treatment High	0			
Pre-Chronocort BL High - Min. on Treatment Low	0			
Pre-Chronocort BL High - Min. on Treatment Normal	1			
Pre-Chronocort BL High - Min. on Treatment High	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – Sodium

End point title	Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – Sodium ^[83]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the maximum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the maximum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[83] - 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			
Subject group type	Reporting group			
Number of subjects analysed	74			
Units: Participants				
Pre-Chronocort BL Low – Max. on Treatment Low	0			
Pre-Chronocort BL Low – Max. on Treatment Normal	3			
Pre-Chronocort BL Low – Max. on Treatment High	0			
Pre-Chronocort BL Normal – Max. on Treatment Low	0			
Pre-Chronocort BL Normal – Max. on Treatment Normal	70			
Pre-Chronocort BL Normal – Max. on Treatment High	0			
Pre-Chronocort BL High – Max. on Treatment Low	0			
Pre-Chronocort BL High – Max. on Treatment Normal	0			
Pre-Chronocort BL High – Max. on Treatment High	1			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Urate

End point title	Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Urate ^[84]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the minimum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the minimum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[84] - 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			
Subject group type	Reporting group			
Number of subjects analysed	74			
Units: Participants				
Pre-Chronocort BL Low – Min. on Treatment Low	0			

Pre-Chronocort BL Low – Min. on Treatment Normal	0			
Pre-Chronocort BL Low – Min. on Treatment High	0			
Pre-Chronocort BL Normal – Min. on Treatment Low	1			
Pre-Chronocort BL Normal– Min. on Treatment Normal	66			
Pre-Chronocort BL Normal – Min. on Treatment High	1			
Pre-Chronocort BL High – Min. on Treatment Low	0			
Pre-Chronocort BL High – Min. on Treatment Normal	3			
Pre-Chronocort BL High – Min. on Treatment High	3			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – Urate

End point title	Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – Urate ^[85]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the maximum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the maximum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[85] - 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			
Subject group type	Reporting group			
Number of subjects analysed	74			
Units: Participants				
Pre-Chronocort BL Low – Max. on Treatment Low	0			
Pre-Chronocort BL Low – Max. on Treatment Normal	0			
Pre-Chronocort BL Low – Max. on Treatment High	0			
Pre-Chronocort BL Normal – Max. on Treatment Low	0			

Pre-Chronocort BL Normal- Max. on Treatment Normal	58			
Pre-Chronocort BL Normal - Max. on Treatment High	10			
Pre-Chronocort BL High - Max. on Treatment Low	0			
Pre-Chronocort BL High - Max. on Treatment Normal	1			
Pre-Chronocort BL High - Max. on Treatment High	5			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Urea Nitrogen

End point title	Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Urea Nitrogen ^[86]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the minimum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the minimum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[86] - 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			
Subject group type	Reporting group			
Number of subjects analysed	74			
Units: Participants				
Pre-Chronocort BL Low – Min. on Treatment Low	0			
Pre-Chronocort BL Low – Min. on Treatment Normal	0			
Pre-Chronocort BL Low - Min. on Treatment High	0			
Pre-Chronocort BL Normal - Min. on Treatment Low	1			
Pre-Chronocort BL Normal- Min. on Treatment Normal	68			
Pre-Chronocort BL Normal - Min. on Treatment High	0			
Pre-Chronocort BL High - Min. on Treatment Low	0			

Pre-Chronocort BL High - Min. on Treatment Normal	5			
Pre-Chronocort BL High - Min. on Treatment High	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – Urea Nitrogen

End point title	Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – Urea Nitrogen ^[87]
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End point description:

This endpoint summarises the categorical distribution of laboratory parameter values at the maximum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined laboratory reference ranges. For each participant, the maximum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[87] - 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			
Subject group type	Reporting group			
Number of subjects analysed	74			
Units: Participants				
Pre-Chronocort BL Low – Max. on Treatment Low	0			
Pre-Chronocort BL Low – Max. on Treatment Normal	0			
Pre-Chronocort BL Low - Max. on Treatment High	0			
Pre-Chronocort BL Normal - Max. on Treatment Low	0			
Pre-Chronocort BL Normal- Max. on Treatment Normal	62			
Pre-Chronocort BL Normal - Max. on Treatment High	7			
Pre-Chronocort BL High - Max. on Treatment Low	0			
Pre-Chronocort BL High - Max. on Treatment Normal	1			
Pre-Chronocort BL High - Max. on Treatment High	4			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Diastolic Blood Pressure

End point title	Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Diastolic Blood Pressure ^[88]
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End point description:

This endpoint summarises the categorical distribution of vital signs values at the minimum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined reference ranges. For each participant, the minimum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[88] - 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			
Subject group type	Reporting group			
Number of subjects analysed	74			
Units: Participants				
Pre-Chronocort BL Low – Min. on Treatment Low	10			
Pre-Chronocort BL Low – Min. on Treatment Normal	4			
Pre-Chronocort BL Low - Min. on Treatment High	0			
Pre-Chronocort BL Normal - Min. on Treatment Low	19			
Pre-Chronocort BL Normal- Min. on Treatment Normal	39			
Pre-Chronocort BL Normal - Min. on Treatment High	0			
Pre-Chronocort BL High - Min. on Treatment Low	0			
Pre-Chronocort BL High - Min. on Treatment Normal	2			
Pre-Chronocort BL High - Min. on Treatment High	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – Diastolic Blood Pressure

End point title	Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – Diastolic Blood Pressure ^[89]
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End point description:

This endpoint summarises the categorical distribution of vital signs values at the maximum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined reference ranges. For each participant, the maximum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[89] - 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			
Subject group type	Reporting group			
Number of subjects analysed	74			
Units: Participants				
Pre-Chronocort BL Low – Max. on Treatment Low	0			
Pre-Chronocort BL Low – Max. on Treatment Normal	14			
Pre-Chronocort BL Low - Max. on Treatment High	0			
Pre-Chronocort BL Normal - Max. on Treatment Low	0			
Pre-Chronocort BL Normal- Max. on Treatment Normal	56			
Pre-Chronocort BL Normal - Max. on Treatment High	2			
Pre-Chronocort BL High - Max. on Treatment Low	0			
Pre-Chronocort BL High - Max. on Treatment Normal	1			
Pre-Chronocort BL High - Max. on Treatment High	1			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at minimum on-treatment versus pre-Chronocort baseline – Systolic Blood Pressure

End point title	Safety and Tolerability: Categorical distribution of values at
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End point description:

This endpoint summarises the categorical distribution of vital signs values at the minimum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined reference ranges. For each participant, the minimum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No formal statistical comparisons were performed; analyses are descriptive in nature.

End point type Primary

End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[90] - 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			
Subject group type	Reporting group			
Number of subjects analysed	74			
Units: Participants				
Pre-Chronocort BL Low – Min. on Treatment Low	0			
Pre-Chronocort BL Low – Min. on Treatment Normal	0			
Pre-Chronocort BL Low - Min. on Treatment High	0			
Pre-Chronocort BL Normal - Min. on Treatment Low	0			
Pre-Chronocort BL Normal- Min. on Treatment Normal	71			
Pre-Chronocort BL Normal - Min. on Treatment High	0			
Pre-Chronocort BL High - Min. on Treatment Low	0			
Pre-Chronocort BL High - Min. on Treatment Normal	3			
Pre-Chronocort BL High - Min. on Treatment High	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – Systolic Blood Pressure

End point title Safety and Tolerability: Categorical distribution of values at maximum on-treatment versus pre-Chronocort baseline – Systolic Blood Pressure^[91]

End point description:

This endpoint summarises the categorical distribution of vital signs values at the maximum on-treatment timepoint compared with pre-Chronocort baseline. Values were categorised as low, normal, or high according to predefined reference ranges. For each participant, the maximum value observed during the on-treatment period was identified and categorised accordingly. Results are presented as the number of participants in each category, stratified by their corresponding pre-Chronocort baseline category. No

formal statistical comparisons were performed; analyses are descriptive in nature.

End point type	Primary
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End point timeframe:

Throughout DIUR-015 treatment period of up to 3 years

Notes:

[91] - 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			
Subject group type	Reporting group			
Number of subjects analysed	74			
Units: Participants				
Pre-Chronocort BL Low – Max. on Treatment Low	0			
Pre-Chronocort BL Low – Max. on Treatment Normal	0			
Pre-Chronocort BL Low - Max. on Treatment High	0			
Pre-Chronocort BL Normal - Max. on Treatment Low	0			
Pre-Chronocort BL Normal- Max. on Treatment Normal	68			
Pre-Chronocort BL Normal - Max. on Treatment High	3			
Pre-Chronocort BL High - Max. on Treatment Low	0			
Pre-Chronocort BL High - Max. on Treatment Normal	2			
Pre-Chronocort BL High - Max. on Treatment High	1			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and Tolerability: Signs and symptoms of adrenal insufficiency or over-treatment – 1.5 years

End point title	Safety and Tolerability: Signs and symptoms of adrenal insufficiency or over-treatment – 1.5 years ^[92]
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End point description:

Adrenal insufficiency checklist results as reported at DIUR-015 study visits

End point type	Primary
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End point timeframe:

DIUR-015 1.5 year visit

Notes:

[92] - 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			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: Participants				
Under Replacement	2			
Over Replacement	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from pre-Chronocort baseline in mean total daily steroid dose at Week 24

End point title	Change from pre-Chronocort baseline in mean total daily steroid dose at Week 24
End point description: Change from pre-Chronocort baseline in total daily steroid dose in hydrocortisone equivalent dose. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.	
End point type	Secondary
End point timeframe: Pre-Chronocort Baseline, Week 24	

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	46			
Units: mg				
arithmetic mean (standard deviation)	-0.11 (± 5.399)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from pre-Chronocort baseline in mean total daily steroid dose at 1 Year

End point title	Change from pre-Chronocort baseline in mean total daily steroid dose at 1 Year
End point description: Change from pre-Chronocort baseline in total daily steroid dose in hydrocortisone equivalent dose. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.	
End point type	Secondary

End point timeframe:
Pre-Chronocort Baseline, 1-year

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	53			
Units: mg				
arithmetic mean (standard deviation)	0.49 ($\pm$ 6.937)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from pre-Chronocort baseline in mean total daily steroid dose at 1.5 years

End point title	Change from pre-Chronocort baseline in mean total daily steroid dose at 1.5 years
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End point description:

Change from pre-Chronocort baseline in total daily steroid dose in hydrocortisone equivalent dose. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.

End point type	Secondary
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End point timeframe:

Pre-Chronocort Baseline, 1.5 Years

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	36			
Units: mg				
arithmetic mean (standard deviation)	0.03 ($\pm$ 7.071)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from pre-Chronocort baseline in mean total daily steroid dose at 2 Years

End point title	Change from pre-Chronocort baseline in mean total daily steroid dose at 2 Years
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End point description:

Change from pre-Chronocort baseline in total daily steroid dose in hydrocortisone equivalent dose. Pre-

Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.

End point type	Secondary
End point timeframe:	
Pre-Chronocort Baseline, 2 Years	

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: mg				
arithmetic mean (standard deviation)	0.77 ($\pm$ 7.919)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from pre-Chronocort baseline in mean total daily steroid dose at 2.5 years

End point title	Change from pre-Chronocort baseline in mean total daily steroid dose at 2.5 years
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End point description:

Change from pre-Chronocort baseline in total daily steroid dose in hydrocortisone equivalent dose. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.

End point type	Secondary
End point timeframe:	
Pre-Chronocort Baseline, 2.5 years	

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: mg				
arithmetic mean (standard deviation)	2.05 ($\pm$ 10.297)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from pre-Chronocort baseline in mean total daily steroid dose at 3 years

End point title	Change from pre-Chronocort baseline in mean total daily steroid dose at 3 years
End point description: Change from pre-Chronocort baseline in total daily steroid dose in hydrocortisone equivalent dose. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.	
End point type	Secondary
End point timeframe: Pre-Chronocort Baseline, 3 Years	

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: mg				
arithmetic mean (standard deviation)	2.95 (± 10.771)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from pre-Chronocort baseline in mean total daily steroid dose at 4 Years

End point title	Change from pre-Chronocort baseline in mean total daily steroid dose at 4 Years
End point description: Change from pre-Chronocort baseline in total daily steroid dose in hydrocortisone equivalent dose. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.	
End point type	Secondary
End point timeframe: Pre-Chronocort Baseline, 4 Years	

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: mg				
arithmetic mean (standard deviation)	-1.88 (± 3.720)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from pre-Chronocort baseline in mean total daily steroid dose at 4.5 Years

End point title	Change from pre-Chronocort baseline in mean total daily steroid dose at 4.5 Years
End point description: Change from pre-Chronocort baseline in total daily steroid dose in hydrocortisone equivalent dose. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.	
End point type	Secondary
End point timeframe: Pre-Chronocort Baseline, 4.5 Years	

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: mg				
arithmetic mean (standard deviation)	-1.33 ($\pm$ 3.994)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from pre-Chronocort baseline in mean total daily steroid dose at 5 Years

End point title	Change from pre-Chronocort baseline in mean total daily steroid dose at 5 Years
End point description: Change from pre-Chronocort baseline in total daily steroid dose in hydrocortisone equivalent dose. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.	
End point type	Secondary
End point timeframe: Pre-Chronocort Baseline, 5 Years	

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: mg				
arithmetic mean (standard deviation)	-0.53 ($\pm$ 4.376)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from pre-Chronocort baseline in mean total daily steroid dose at 5.5 Years

End point title	Change from pre-Chronocort baseline in mean total daily steroid dose at 5.5 Years
End point description: Change from pre-Chronocort baseline in total daily steroid dose in hydrocortisone equivalent dose. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.	
End point type	Secondary
End point timeframe: Pre-Chronocort Baseline, 5.5 Years	

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: mg				
arithmetic mean (standard deviation)	-0.53 (± 4.376)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from pre-Chronocort baseline in mean total daily steroid dose at 6 Years

End point title	Change from pre-Chronocort baseline in mean total daily steroid dose at 6 Years
End point description: Change from pre-Chronocort baseline in total daily steroid dose in hydrocortisone equivalent dose. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.	
End point type	Secondary
End point timeframe: Pre-Chronocort Baseline, 6 Years	

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: mg				
arithmetic mean (standard deviation)	-1.18 (± 4.517)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from pre-Chronocort baseline in mean total daily steroid dose at 6.5 Years

End point title	Change from pre-Chronocort baseline in mean total daily steroid dose at 6.5 Years
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End point description:

Change from pre-Chronocort baseline in total daily steroid dose in hydrocortisone equivalent dose. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.

End point type	Secondary
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End point timeframe:

Pre-Chronocort Baseline, 6.5 Years

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: mg				
arithmetic mean (standard deviation)	-1.58 (± 4.730)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from pre-Chronocort baseline in mean total daily steroid dose at 7 Years

End point title	Change from pre-Chronocort baseline in mean total daily steroid dose at 7 Years
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End point description:

Change from pre-Chronocort baseline in total daily steroid dose in hydrocortisone equivalent dose. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous

Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.

End point type	Secondary
End point timeframe:	
Pre-Chronocort Baseline, 7 Years	

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: mg				
arithmetic mean (standard deviation)	-1.50 (± 4.743)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from pre-Chronocort baseline in mean total daily steroid dose at 7.5 Years

End point title	Change from pre-Chronocort baseline in mean total daily steroid dose at 7.5 Years
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End point description:

Change from pre-Chronocort baseline in total daily steroid dose in hydrocortisone equivalent dose. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.

End point type	Secondary
End point timeframe:	
Pre-Chronocort Baseline, 7.5 Years	

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: mg				
arithmetic mean (standard deviation)	0.00 (± 0.000)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Pre-Chronocort Baseline in 17-OHP Levels at Week 24

End point title	Change from Pre-Chronocort Baseline in 17-OHP Levels at Week 24
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End point description:

Change from pre-Chronocort baseline in mean 17-Hydroxyprogesterone (17-OHP) levels. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.

End point type	Secondary
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End point timeframe:

Pre-Chronocort Baseline, Week 24

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	47			
Units: ng/dL				
arithmetic mean (standard deviation)	-4511.0 (± 9134.14)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Pre-Chronocort Baseline in 17-OHP Levels at 1 Year

End point title	Change from Pre-Chronocort Baseline in 17-OHP Levels at 1 Year
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End point description:

Change from pre-Chronocort baseline in mean 17-Hydroxyprogesterone (17-OHP) levels. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.

End point type	Secondary
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End point timeframe:

Pre-Chronocort Baseline, 1 year

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	54			
Units: ng/dL				
arithmetic mean (standard deviation)	-4895.0 (± 9306.62)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Pre-Chronocort Baseline in 17-OHP Levels at 2 Years

End point title	Change from Pre-Chronocort Baseline in 17-OHP Levels at 2 Years
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End point description:

Change from pre-Chronocort baseline in mean 17-Hydroxyprogesterone (17-OHP) levels. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.

End point type	Secondary
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End point timeframe:

Pre-Chronocort Baseline, 2 years

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	36			
Units: ng/dL				
arithmetic mean (standard deviation)	-3812.9 ($\pm$ 7778.35)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Pre-Chronocort Baseline in 17-OHP Levels at 3 Years

End point title	Change from Pre-Chronocort Baseline in 17-OHP Levels at 3 Years
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End point description:

Change from pre-Chronocort baseline in mean 17-Hydroxyprogesterone (17-OHP) levels. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.

End point type	Secondary
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End point timeframe:

Pre-Chronocort Baseline, 3 years

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: ng/dL				
arithmetic mean (standard deviation)	522.8 ($\pm$ 3395.56)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Pre-Chronocort Baseline in 17-OHP Levels at 4 Years

End point title	Change from Pre-Chronocort Baseline in 17-OHP Levels at 4 Years
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End point description:

Change from pre-Chronocort baseline in mean 17-Hydroxyprogesterone (17-OHP) levels. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.

End point type	Secondary
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End point timeframe:

Pre-Chronocort Baseline, 4 years

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: ng/dL				
arithmetic mean (standard deviation)	-3555.7 ($\pm$ 4218.31)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Pre-Chronocort Baseline in 17-OHP Levels at 5 Years

End point title	Change from Pre-Chronocort Baseline in 17-OHP Levels at 5 Years
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End point description:

Change from pre-Chronocort baseline in mean 17-Hydroxyprogesterone (17-OHP) levels. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.

End point type	Secondary
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End point timeframe:

Pre-Chronocort Baseline, 5 years

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: ng/dL				
arithmetic mean (standard deviation)	-4101.7 ($\pm$ 4582.09)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Pre-Chronocort Baseline in 17-OHP Levels at 6 Years

End point title	Change from Pre-Chronocort Baseline in 17-OHP Levels at 6 Years
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End point description:

Change from pre-Chronocort baseline in mean 17-Hydroxyprogesterone (17-OHP) levels. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.

End point type	Secondary
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End point timeframe:

Pre-Chronocort Baseline, 6 years

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: ng/dl				
arithmetic mean (standard deviation)	-3907.3 ($\pm$ 5036.34)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Pre-Chronocort Baseline in 17-OHP Levels at 7 Years

End point title	Change from Pre-Chronocort Baseline in 17-OHP Levels at 7 Years
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End point description:

Change from pre-Chronocort baseline in mean 17-Hydroxyprogesterone (17-OHP) levels. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.

End point type	Secondary
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End point timeframe:

Pre-Chronocort Baseline, 7 years

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: ng/dl				
arithmetic mean (standard deviation)	-4735.5 ($\pm$ 5414.96)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Pre-Chronocort Baseline in 17-OHP Levels at 8 Years

End point title	Change from Pre-Chronocort Baseline in 17-OHP Levels at 8 Years
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End point description:

Change from pre-Chronocort baseline in mean 17-Hydroxyprogesterone (17-OHP) levels. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.

End point type	Secondary
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End point timeframe:

Pre-Chronocort Baseline, 8 years

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: ng/dl				
arithmetic mean (standard deviation)	-6308.3 ($\pm$ 10911.81)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Pre-Chronocort Baseline in A4 Levels at Week 24

End point title	Change from Pre-Chronocort Baseline in A4 Levels at Week 24
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End point description:

Change from pre-Chronocort baseline in mean androstenedione (A4) levels. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.

End point type	Secondary
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End point timeframe:

Pre-Chronocort Baseline, Week 24

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	46			
Units: ng/dl				
arithmetic mean (standard deviation)	-353.1 ($\pm$ 628.72)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Pre-Chronocort Baseline in A4 Levels at 1 Year

End point title	Change from Pre-Chronocort Baseline in A4 Levels at 1 Year
End point description: Change from pre-Chronocort baseline in mean androstenedione (A4) levels. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.	
End point type	Secondary
End point timeframe: Pre-Chronocort Baseline, 1 year	

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	53			
Units: ng/dl				
arithmetic mean (standard deviation)	-355.6 ($\pm$ 681.94)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Pre-Chronocort Baseline in A4 Levels at 2 Years

End point title	Change from Pre-Chronocort Baseline in A4 Levels at 2 Years
End point description: Change from pre-Chronocort baseline in mean androstenedione (A4) levels. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.	
End point type	Secondary

End point timeframe:
Pre-Chronocort Baseline, 2 years

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	36			
Units: ng/dl				
arithmetic mean (standard deviation)	-186.0 ($\pm$ 442.39)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Pre-Chronocort Baseline in A4 Levels at 3 years

End point title	Change from Pre-Chronocort Baseline in A4 Levels at 3 years
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End point description:

Change from pre-Chronocort baseline in mean androstenedione (A4) levels. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.

End point type	Secondary
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End point timeframe:

Pre-Chronocort Baseline, 3 years

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: ng/dl				
arithmetic mean (standard deviation)	29.7 ($\pm$ 211.02)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Pre-Chronocort Baseline in A4 Levels at 4 Years

End point title	Change from Pre-Chronocort Baseline in A4 Levels at 4 Years
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End point description:

Change from pre-Chronocort baseline in mean androstenedione (A4) levels. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.

End point type	Secondary
End point timeframe:	
Pre-Chronocort Baseline, 4 years	

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: ng/dl				
arithmetic mean (standard deviation)	-200.8 (± 439.42)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Pre-Chronocort Baseline in A4 Levels at 5 Years

End point title	Change from Pre-Chronocort Baseline in A4 Levels at 5 Years
End point description:	
Change from pre-Chronocort baseline in mean androstenedione (A4) levels. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.	
End point type	Secondary
End point timeframe:	
Pre-Chronocort Baseline, 5 years	

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: ng/dl				
arithmetic mean (standard deviation)	-183.5 (± 319.25)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Pre-Chronocort Baseline in A4 Levels at 6 Years

End point title	Change from Pre-Chronocort Baseline in A4 Levels at 6 Years
End point description:	
Change from pre-Chronocort baseline in mean androstenedione (A4) levels. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the	

participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.

End point type	Secondary
End point timeframe:	
Pre-Chronocort Baseline, 6 years	

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: ng/dl				
arithmetic mean (standard deviation)	-195.5 ($\pm$ 311.72)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Pre-Chronocort Baseline in A4 Levels at 7 Years

End point title	Change from Pre-Chronocort Baseline in A4 Levels at 7 Years
End point description:	
Change from pre-Chronocort baseline in mean androstenedione (A4) levels. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.	
End point type	Secondary
End point timeframe:	
Pre-Chronocort Baseline, 7 years	

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: ng/dl				
arithmetic mean (standard deviation)	-278.7 ($\pm$ 345.99)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Pre-Chronocort Baseline in A4 Levels at 8 Years

End point title	Change from Pre-Chronocort Baseline in A4 Levels at 8 Years
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End point description:

Change from pre-Chronocort baseline in mean androstenedione (A4) levels. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.

End point type	Secondary
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End point timeframe:

Pre-Chronocort Baseline, 8 years

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: ng/dl				
arithmetic mean (standard deviation)	-183.0 (± 317.44)			

Statistical analyses

No statistical analyses for this end point

Secondary: Menstrual regularity in pre-menopausal females without hysterectomy and not using hormonal contraceptives at pre-Chronocort baseline

End point title	Menstrual regularity in pre-menopausal females without hysterectomy and not using hormonal contraceptives at pre-Chronocort baseline
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End point description:

Data are presented for participants with more than monthly menstrual cycles, monthly menstrual cycles, number of participants with oligomenorrhoea, amenorrhoea or not determinable. Oligomenorrhoea was defined as cycle length >35 days and amenorrhoea as absent menses for ≥ 3 months. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.

End point type	Secondary
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End point timeframe:

Pre-Chronocort Baseline

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Participants				
More than monthly	3			
Monthly	9			
Oligomenorrhoea	1			
Amenorrhoea	4			
Not Determinable	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Menstrual regularity in pre-menopausal females without hysterectomy and not using hormonal contraceptives at Week 24

End point title	Menstrual regularity in pre-menopausal females without hysterectomy and not using hormonal contraceptives at Week 24
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End point description:

Data are presented for participants with more than monthly menstrual cycles, monthly menstrual cycles, number of participants with oligomenorrhoea, amenorrhoea or not determinable. Oligomenorrhoea was defined as cycle length >35 days and amenorrhoea as absent menses for ≥ 3 months. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.

End point type	Secondary
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End point timeframe:

Week 24

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: Participants				
More than monthly	0			
Monthly	7			
Oligomenorrhoea	1			
Amenorrhoea	4			
Not Determinable	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Menstrual regularity in pre-menopausal females without hysterectomy and not using hormonal contraceptives at 1 Year

End point title	Menstrual regularity in pre-menopausal females without hysterectomy and not using hormonal contraceptives at 1 Year
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End point description:

Data are presented for participants with more than monthly menstrual cycles, monthly menstrual cycles, number of participants with oligomenorrhoea, amenorrhoea or not determinable. Oligomenorrhoea was defined as cycle length >35 days and amenorrhoea as absent menses for ≥ 3 months. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort

received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.

End point type	Secondary
End point timeframe:	
1 Year	

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Participants				
More than monthly	1			
Monthly	9			
Oligomenorrhoea	2			
Amenorrhoea	5			
Not Determinable	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Menstrual regularity in pre-menopausal females without hysterectomy and not using hormonal contraceptives at 2 Year

End point title	Menstrual regularity in pre-menopausal females without hysterectomy and not using hormonal contraceptives at 2 Year
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End point description:

Data are presented for participants with more than monthly menstrual cycles, monthly menstrual cycles, number of participants with oligomenorrhoea, amenorrhoea or not determinable. Oligomenorrhoea was defined as cycle length >35 days and amenorrhoea as absent menses for ≥ 3 months. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.

End point type	Secondary
End point timeframe:	
2 Years	

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: Participants				
More than monthly	0			
Monthly	6			
Oligomenorrhoea	4			
Amenorrhoea	2			
Not Determinable	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Menstrual regularity in pre-menopausal females without hysterectomy and not using hormonal contraceptives at 3 Years

End point title	Menstrual regularity in pre-menopausal females without hysterectomy and not using hormonal contraceptives at 3 Years
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End point description:

Data are presented for participants with more than monthly menstrual cycles, monthly menstrual cycles, number of participants with oligomenorrhoea, amenorrhoea or not determinable. Oligomenorrhoea was defined as cycle length >35 days and amenorrhoea as absent menses for ≥ 3 months. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.

End point type	Secondary
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End point timeframe:

3 Years

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: Participants				
More than monthly	0			
Monthly	1			
Oligomenorrhoea	2			
Amenorrhoea	0			
Not Determinable	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Menstrual regularity in pre-menopausal females without hysterectomy and not using hormonal contraceptives at 4 Years

End point title	Menstrual regularity in pre-menopausal females without hysterectomy and not using hormonal contraceptives at 4 Years
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End point description:

Data are presented for participants with more than monthly menstrual cycles, monthly menstrual cycles, number of participants with oligomenorrhoea, amenorrhoea or not determinable. Oligomenorrhoea was defined as cycle length >35 days and amenorrhoea as absent menses for ≥ 3 months. Pre-Chronocort

baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.

End point type	Secondary
End point timeframe:	
4 years	

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: Participants				
More than monthly	0			
Monthly	3			
Oligomenorrhoea	0			
Amenorrhoea	0			
Not Determinable	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Menstrual regularity in pre-menopausal females without hysterectomy and not using hormonal contraceptives at 5 Years

End point title	Menstrual regularity in pre-menopausal females without hysterectomy and not using hormonal contraceptives at 5 Years
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End point description:

Data are presented for participants with more than monthly menstrual cycles, monthly menstrual cycles, number of participants with oligomenorrhoea, amenorrhoea or not determinable. Oligomenorrhoea was defined as cycle length >35 days and amenorrhoea as absent menses for ≥ 3 months. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.

End point type	Secondary
End point timeframe:	
5 Years	

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: Participants				
More than monthly	0			
Monthly	2			
Oligomenorrhoea	0			
Amenorrhoea	0			
Not Determinable	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Menstrual regularity in pre-menopausal females without hysterectomy and not using hormonal contraceptives at 6 Years

End point title	Menstrual regularity in pre-menopausal females without hysterectomy and not using hormonal contraceptives at 6 Years
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End point description:

Data are presented for participants with more than monthly menstrual cycles, monthly menstrual cycles, number of participants with oligomenorrhoea, amenorrhoea or not determinable. Oligomenorrhoea was defined as cycle length >35 days and amenorrhoea as absent menses for ≥ 3 months. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.

End point type	Secondary
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End point timeframe:

6 years

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: Participants				
More than monthly	0			
Monthly	2			
Oligomenorrhoea	0			
Amenorrhoea	0			
Not Determinable	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Menstrual regularity in pre-menopausal females without hysterectomy and not using hormonal contraceptives at 7 Years

End point title	Menstrual regularity in pre-menopausal females without hysterectomy and not using hormonal contraceptives at 7 Years
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End point description:

Data are presented for participants with more than monthly menstrual cycles, monthly menstrual cycles, number of participants with oligomenorrhoea, amenorrhoea or not determinable. Oligomenorrhoea was defined as cycle length >35 days and amenorrhoea as absent menses for ≥ 3 months. Pre-Chronocort

baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.

End point type	Secondary
End point timeframe:	
7 Years	

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: Participants				
More than monthly	0			
Monthly	2			
Oligomenorrhoea	0			
Amenorrhoea	0			
Not Determinable	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Menstrual regularity in pre-menopausal females without hysterectomy and not using hormonal contraceptives at 8 Years

End point title	Menstrual regularity in pre-menopausal females without hysterectomy and not using hormonal contraceptives at 8 Years
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End point description:

Data are presented for participants with more than monthly menstrual cycles, monthly menstrual cycles, number of participants with oligomenorrhoea, amenorrhoea or not determinable. Oligomenorrhoea was defined as cycle length >35 days and amenorrhoea as absent menses for ≥ 3 months. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.

End point type	Secondary
End point timeframe:	
8 years	

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: Participants				
More than monthly	0			
Monthly	0			
Oligomenorrhoea	0			
Amenorrhoea	0			
Not Determinable	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Pre-Chronocort Baseline in mean LH Levels for males only at 24 Weeks

End point title	Change from Pre-Chronocort Baseline in mean LH Levels for males only at 24 Weeks
End point description: Change from pre-Chronocort baseline in mean Luteinizing Hormone (LH) levels. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.	
End point type	Secondary
End point timeframe: Pre-Chronocort Baseline, 24 Weeks	

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: IU/L				
arithmetic mean (standard deviation)	0.57 ($\pm$ 1.455)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Pre-Chronocort Baseline in mean LH Levels for males only at 1 Year

End point title	Change from Pre-Chronocort Baseline in mean LH Levels for males only at 1 Year
End point description: Change from pre-Chronocort baseline in mean Luteinizing Hormone (LH) levels. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.	
End point type	Secondary
End point timeframe: Pre-Chronocort Baseline, 1 year	

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: IU/L				
arithmetic mean (standard deviation)	1.01 ($\pm$ 2.624)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Pre-Chronocort Baseline in mean LH Levels for males only at 2 Years

End point title	Change from Pre-Chronocort Baseline in mean LH Levels for males only at 2 Years
End point description: Change from pre-Chronocort baseline in mean Luteinizing Hormone (LH) levels. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.	
End point type	Secondary
End point timeframe: Pre-Chronocort Baseline, 2 years	

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: IU/L				
arithmetic mean (standard deviation)	1.77 ($\pm$ 1.821)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Pre-Chronocort Baseline in mean LH Levels for males only at 3 Years

End point title	Change from Pre-Chronocort Baseline in mean LH Levels for males only at 3 Years
End point description: Change from pre-Chronocort baseline in mean Luteinizing Hormone (LH) levels. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.	

End point type	Secondary
End point timeframe:	
Pre-Chronocort Baseline, 3 years	

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: IU/L				
arithmetic mean (standard deviation)	0.34 ($\pm$ 1.270)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Pre-Chronocort Baseline in mean LH Levels for males only at 4 Years

End point title	Change from Pre-Chronocort Baseline in mean LH Levels for males only at 4 Years
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End point description:

Change from pre-Chronocort baseline in mean Luteinizing Hormone (LH) levels. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.

End point type	Secondary
End point timeframe:	
Pre-Chronocort Baseline, 4 years	

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[93]			
Units: IU/L				
arithmetic mean (standard deviation)	()			

Notes:

[93] - No data is available from 4 years onwards

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Pre-Chronocort Baseline in mean T Levels in Females at Week 24

End point title	Change from Pre-Chronocort Baseline in mean T Levels in Females at Week 24
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End point description:

Change from pre-Chronocort baseline in mean Testosterone (T) levels. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.

End point type	Secondary
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End point timeframe:

Pre-Chronocort Baseline, week 24

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: ng/dl				
arithmetic mean (standard deviation)	-10.3 (± 67.33)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Pre-Chronocort Baseline in mean T Levels in Females at 1 Year

End point title	Change from Pre-Chronocort Baseline in mean T Levels in Females at 1 Year
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End point description:

Change from pre-Chronocort baseline in mean Testosterone (T) levels. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.

End point type	Secondary
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End point timeframe:

Pre-Chronocort Baseline, 1 year

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: ng/dl				
arithmetic mean (standard deviation)	-17.4 (± 54.23)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Pre-Chronocort Baseline in mean T Levels in Females at 2 Years

End point title	Change from Pre-Chronocort Baseline in mean T Levels in Females at 2 Years
End point description: Change from pre-Chronocort baseline in mean Testosterone (T) levels. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.	
End point type	Secondary
End point timeframe: Pre-Chronocort Baseline, 2 years	

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: ng/dl				
arithmetic mean (standard deviation)	5.5 ($\pm$ 50.18)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Pre-Chronocort Baseline in mean T Levels in Females at 3 years

End point title	Change from Pre-Chronocort Baseline in mean T Levels in Females at 3 years
End point description: Change from pre-Chronocort baseline in mean Testosterone (T) levels. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.	
End point type	Secondary
End point timeframe: Pre-Chronocort Baseline, 3 years	

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: ng/dl				
arithmetic mean (standard deviation)	21.3 ($\pm$ 69.77)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Pre-Chronocort Baseline in mean T Levels in Females at 4 Years

End point title	Change from Pre-Chronocort Baseline in mean T Levels in Females at 4 Years
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End point description:

Change from pre-Chronocort baseline in mean Testosterone (T) levels. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.

End point type	Secondary
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End point timeframe:

Pre-Chronocort Baseline, 4 years

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: ng/dl				
arithmetic mean (standard deviation)	-20.2 (± 62.58)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Pre-Chronocort Baseline in mean T Levels in Females at 5 Years

End point title	Change from Pre-Chronocort Baseline in mean T Levels in Females at 5 Years
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End point description:

Change from pre-Chronocort baseline in mean Testosterone (T) levels. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.

End point type	Secondary
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End point timeframe:

Pre-Chronocort Baseline, 5 years

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: ng/dl				
arithmetic mean (standard deviation)	-18.5 (± 47.77)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Pre-Chronocort Baseline in mean T Levels in Females at 6 Years

End point title	Change from Pre-Chronocort Baseline in mean T Levels in Females at 6 Years
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End point description:

Change from pre-Chronocort baseline in mean Testosterone (T) levels. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.

End point type	Secondary
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End point timeframe:

Pre-Chronocort Baseline, 6 years

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: ng/dl				
arithmetic mean (standard deviation)	-21.6 (± 42.48)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Pre-Chronocort Baseline in mean T Levels in Females at 7 Years

End point title	Change from Pre-Chronocort Baseline in mean T Levels in Females at 7 Years
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End point description:

Change from pre-Chronocort baseline in mean Testosterone (T) levels. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the

participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.

End point type	Secondary
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End point timeframe:

Pre-Chronocort Baseline, 7 years

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: ng/dl				
arithmetic mean (standard deviation)	-27.5 (± 64.93)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Pre-Chronocort Baseline in mean T Levels in Females at 8 Years

End point title	Change from Pre-Chronocort Baseline in mean T Levels in Females at 8 Years
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End point description:

Change from pre-Chronocort baseline in mean Testosterone (T) levels. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.

End point type	Secondary
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End point timeframe:

Pre-Chronocort Baseline, 8 years

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: ng/dl				
arithmetic mean (standard deviation)	22.0 (± 0.000)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Pre-Chronocort Baseline in mean T Levels in Males at week

End point title	Change from Pre-Chronocort Baseline in mean T Levels in Males at week 24
End point description:	
Change from pre-Chronocort baseline in mean Testosterone (T) levels. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.	
End point type	Secondary
End point timeframe:	
Pre-Chronocort Baseline, week 24	

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: ng/dl				
arithmetic mean (standard deviation)	-9.4 (± 176.12)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Pre-Chronocort Baseline in mean T Levels in Males at 1 Year

End point title	Change from Pre-Chronocort Baseline in mean T Levels in Males at 1 Year
End point description:	
Change from pre-Chronocort baseline in mean Testosterone (T) levels. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.	
End point type	Secondary
End point timeframe:	
Pre-Chronocort Baseline, 1 year	

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: ng/dl				
arithmetic mean (standard deviation)	-37.2 (± 157.64)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Pre-Chronocort Baseline in mean T Levels in Males at 2 Years

End point title	Change from Pre-Chronocort Baseline in mean T Levels in Males at 2 Years
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End point description:

Change from pre-Chronocort baseline in mean Testosterone (T) levels. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.

End point type	Secondary
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End point timeframe:

Pre-Chronocort Baseline, 2 years

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: ng/dl				
arithmetic mean (standard deviation)	1.7 (± 149.55)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Pre-Chronocort Baseline in mean T Levels in Males at 3 Years

End point title	Change from Pre-Chronocort Baseline in mean T Levels in Males at 3 Years
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End point description:

Change from pre-Chronocort baseline in mean Testosterone (T) levels. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.

End point type	Secondary
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End point timeframe:

Pre-Chronocort Baseline, 3 years

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: ng/dl				
arithmetic mean (standard deviation)	91.8 ($\pm$ 76.12)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Pre-Chronocort Baseline in mean T Levels in Males at 4 Years

End point title	Change from Pre-Chronocort Baseline in mean T Levels in Males at 4 Years
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End point description:

Change from pre-Chronocort baseline in mean Testosterone (T) levels. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.

End point type	Secondary
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End point timeframe:

Pre-Chronocort Baseline, 4 years

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: ng/dl				
arithmetic mean (standard deviation)	245.3 ($\pm$ 19.86)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Pre-Chronocort Baseline in mean T Levels in Males at 5 Years

End point title	Change from Pre-Chronocort Baseline in mean T Levels in Males at 5 Years
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End point description:

Change from pre-Chronocort baseline in mean Testosterone (T) levels. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.

End point type	Secondary
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End point timeframe:

Pre-Chronocort Baseline, 5 years

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: ng/dl				
arithmetic mean (standard deviation)	55.9 (± 267.22)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Pre-Chronocort Baseline in mean T Levels in Males at 6 Years

End point title	Change from Pre-Chronocort Baseline in mean T Levels in Males at 6 Years
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End point description:

Change from pre-Chronocort baseline in mean Testosterone (T) levels. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.

End point type	Secondary
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End point timeframe:

Pre-Chronocort Baseline, 6 years

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: ng/dl				
arithmetic mean (standard deviation)	17.5 (± 218.55)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Pre-Chronocort Baseline in mean T Levels in Males at 7 Years

End point title	Change from Pre-Chronocort Baseline in mean T Levels in Males at 7 Years
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End point description:

Change from pre-Chronocort baseline in mean Testosterone (T) levels. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the

participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.

End point type	Secondary
End point timeframe:	
Pre-Chronocort Baseline, 7 years	

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: ng/dl				
arithmetic mean (standard deviation)	0.6 ($\pm$ 172.72)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Pre-Chronocort Baseline in mean T Levels in Males at 8 Years

End point title	Change from Pre-Chronocort Baseline in mean T Levels in Males at 8 Years
End point description:	
Change from pre-Chronocort baseline in mean Testosterone (T) levels. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.	
End point type	Secondary
End point timeframe:	
Pre-Chronocort Baseline, 8 years	

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: ng/dl				
arithmetic mean (standard deviation)	-126.5 ($\pm$ 65.76)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from pre-Chronocort baseline in mean waist circumference at Week 24

End point title	Change from pre-Chronocort baseline in mean waist circumference at Week 24
End point description: Change from pre-Chronocort baseline in mean waist circumference. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.	
End point type	Secondary
End point timeframe: Pre-Chronocort Baseline, week 24	

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: cm				
arithmetic mean (standard deviation)	0.40 ($\pm$ 5.134)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from pre-Chronocort baseline in mean waist circumference at 1 Year

End point title	Change from pre-Chronocort baseline in mean waist circumference at 1 Year
End point description: Change from pre-Chronocort baseline in mean waist circumference. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.	
End point type	Secondary
End point timeframe: Pre-Chronocort Baseline, 1 year	

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: ng/dl				
arithmetic mean (standard deviation)	1.23 ($\pm$ 5.466)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from pre-Chronocort baseline in mean waist circumference at 2 Years

End point title	Change from pre-Chronocort baseline in mean waist circumference at 2 Years
End point description: Change from pre-Chronocort baseline in mean waist circumference. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.	
End point type	Secondary
End point timeframe: Pre-Chronocort Baseline, 2 years	

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: cm				
arithmetic mean (standard deviation)	1.82 ($\pm$ 7.387)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from pre-Chronocort baseline in mean waist circumference at 3 Years

End point title	Change from pre-Chronocort baseline in mean waist circumference at 3 Years
End point description: Change from pre-Chronocort baseline in mean waist circumference. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.	
End point type	Secondary
End point timeframe: Pre-Chronocort Baseline, 3 years	

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: cm				
arithmetic mean (standard deviation)	1.32 ($\pm$ 10.581)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from pre-Chronocort baseline in mean waist circumference at 4 years

End point title	Change from pre-Chronocort baseline in mean waist circumference at 4 years
End point description: Change from pre-Chronocort baseline in mean waist circumference. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.	
End point type	Secondary
End point timeframe: Pre-Chronocort Baseline, 4 years	

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: cm				
arithmetic mean (standard deviation)	0.83 ($\pm$ 3.215)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from pre-Chronocort baseline in mean waist circumference at 5 Years

End point title	Change from pre-Chronocort baseline in mean waist circumference at 5 Years
End point description: Change from pre-Chronocort baseline in mean waist circumference. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.	
End point type	Secondary
End point timeframe: Pre-Chronocort Baseline, 5 years	

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: cm				
arithmetic mean (standard deviation)	3.87 ($\pm$ 5.547)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from pre-Chronocort baseline in mean waist circumference at 6 Years

End point title	Change from pre-Chronocort baseline in mean waist circumference at 6 Years
End point description: Change from pre-Chronocort baseline in mean waist circumference. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.	
End point type	Secondary
End point timeframe: Pre-Chronocort Baseline, 6 years	

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: cm				
arithmetic mean (standard deviation)	3.82 ($\pm$ 7.190)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from pre-Chronocort baseline in mean waist circumference at 7 Years

End point title	Change from pre-Chronocort baseline in mean waist circumference at 7 Years
End point description: Change from pre-Chronocort baseline in mean waist circumference. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.	

End point type	Secondary
End point timeframe:	
Pre-Chronocort Baseline, 7 years	

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: cm				
arithmetic mean (standard deviation)	2.05 ($\pm$ 7.233)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from pre-Chronocort baseline in mean waist circumference at 8 Years

End point title	Change from pre-Chronocort baseline in mean waist circumference at 8 Years
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End point description:

Change from pre-Chronocort baseline in mean waist circumference. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.

End point type	Secondary
End point timeframe:	
Pre-Chronocort Baseline, 8 years	

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: cm				
arithmetic mean (standard deviation)	0.75 ($\pm$ 7.425)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from pre-Chronocort baseline in mean body weight at week 24

End point title	Change from pre-Chronocort baseline in mean body weight at week 24
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End point description:

Change from pre-Chronocort baseline in mean body weight. Pre-Chronocort baseline is defined as the

last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.

End point type	Secondary
End point timeframe:	
Pre-Chronocort Baseline, 24 weeks	

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	47			
Units: kg				
arithmetic mean (standard deviation)	1.05 ($\pm$ 2.866)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from pre-Chronocort baseline in mean body weight at 1 Year

End point title	Change from pre-Chronocort baseline in mean body weight at 1 Year
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End point description:

Change from pre-Chronocort baseline in mean body weight. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.

End point type	Secondary
End point timeframe:	
Pre-Chronocort Baseline, 1 year	

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	54			
Units: kg				
arithmetic mean (standard deviation)	2.27 ($\pm$ 3.409)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from pre-Chronocort baseline in mean body weight at 2 Years

End point title	Change from pre-Chronocort baseline in mean body weight at 2 Years
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End point description:

Change from pre-Chronocort baseline in mean body weight. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.

End point type	Secondary
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End point timeframe:

Pre-Chronocort Baseline, 2 years

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	36			
Units: kg				
arithmetic mean (standard deviation)	3.44 (± 5.004)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from pre-Chronocort baseline in mean body weight at 3 Years

End point title	Change from pre-Chronocort baseline in mean body weight at 3 Years
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End point description:

Change from pre-Chronocort baseline in mean body weight. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.

End point type	Secondary
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End point timeframe:

Pre-Chronocort Baseline, 3 years

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: kg				
arithmetic mean (standard deviation)	1.48 (± 7.261)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from pre-Chronocort baseline in mean body weight at 4 Years

End point title	Change from pre-Chronocort baseline in mean body weight at 4 Years
End point description: Change from pre-Chronocort baseline in mean body weight. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.	
End point type	Secondary
End point timeframe: Pre-Chronocort Baseline, 4 years	

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: kg				
arithmetic mean (standard deviation)	1.94 ($\pm$ 5.900)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from pre-Chronocort baseline in mean body weight at 5 years

End point title	Change from pre-Chronocort baseline in mean body weight at 5 years
End point description: Change from pre-Chronocort baseline in mean body weight. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.	
End point type	Secondary
End point timeframe: Pre-Chronocort Baseline, 5 years	

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: kg				
arithmetic mean (standard deviation)	4.36 ($\pm$ 6.580)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from pre-Chronocort baseline in mean body weight at 6 Years

End point title	Change from pre-Chronocort baseline in mean body weight at 6 Years
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End point description:

Change from pre-Chronocort baseline in mean body weight. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.

End point type	Secondary
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End point timeframe:

Pre-Chronocort Baseline, 6 years

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: kg				
arithmetic mean (standard deviation)	5.61 ($\pm$ 7.243)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from pre-Chronocort baseline in mean body weight at 7 Years

End point title	Change from pre-Chronocort baseline in mean body weight at 7 Years
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End point description:

Change from pre-Chronocort baseline in mean body weight. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.

End point type	Secondary
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End point timeframe:

Pre-Chronocort Baseline, 7 years

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: kg				
arithmetic mean (standard deviation)	4.58 ($\pm$ 5.664)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from pre-Chronocort baseline in mean body weight at 8 Years

End point title	Change from pre-Chronocort baseline in mean body weight at 8 Years
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End point description:

Change from pre-Chronocort baseline in mean body weight. Pre-Chronocort baseline is defined as the last non-missing value prior to the first dose of continuous Chronocort received by the participant, from either the feeder study or from DIUR-015. Analysis visits were assigned using windowing, by calculating time relative to the pre-Chronocort baseline.

End point type	Secondary
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End point timeframe:

Pre-Chronocort Baseline, 8 years

End point values	Chronocort			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: kg				
arithmetic mean (standard deviation)	5.27 (± 0.907)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 30 days after last study dose (maximum treatment duration of approximately 3 years)

Adverse event reporting additional description:

Assessed using the safety analysis set that included all participants who were randomized and received at least 1 dose of study drug

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	28.1
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Reporting groups

Reporting group title	Chronocort
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Reporting group description:

Open-label treatment with Chronocort

Serious adverse events	Chronocort		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 76 (10.53%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Shock			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Torsade de pointes			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			

subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Adrenocortical insufficiency acute			
subjects affected / exposed	3 / 76 (3.95%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	2 / 76 (2.63%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal viral infection			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Influenza			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Chronocort		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	68 / 76 (89.47%)		
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 76 (9.21%)		
occurrences (all)	8		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	10 / 76 (13.16%)		
occurrences (all)	17		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	5 / 76 (6.58%)		
occurrences (all)	6		
Vomiting			
subjects affected / exposed	5 / 76 (6.58%)		
occurrences (all)	9		
Abdominal pain			
subjects affected / exposed	4 / 76 (5.26%)		
occurrences (all)	4		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 76 (9.21%)		
occurrences (all)	13		
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	14 / 76 (18.42%)		
occurrences (all)	16		
COVID-19			

subjects affected / exposed	13 / 76 (17.11%)		
occurrences (all)	14		
Influenza			
subjects affected / exposed	7 / 76 (9.21%)		
occurrences (all)	8		
Urinary tract infection			
subjects affected / exposed	6 / 76 (7.89%)		
occurrences (all)	7		
Nasopharyngitis			
subjects affected / exposed	5 / 76 (6.58%)		
occurrences (all)	8		
Upper respiratory tract infection			
subjects affected / exposed	4 / 76 (5.26%)		
occurrences (all)	7		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 September 2021	1) Titration visit at Week 4 for participants entering from study DIUR-014 moved to Week 6 and second titration visit at Week 12 made optional to reduce the number of times participants have to attend clinic visits. 2) Alertness visual analogue scale removed from the efficacy assessments and the study objectives and endpoints since this was no longer considered necessary. 3) Added at the request of some Investigators that participants who became pregnant could remain in the study but discontinue study treatment and can restart study treatment 6 weeks post pregnancy/post-lactation. 4) Electronic diary changed to a paper diary.
17 January 2022	1) Information on drug interactions and dose modifications added from the Summary of Product Characteristics (SmPC) at the request of the French Regulatory Authority. 2) Information on remote monitoring visits added at the request of the French Regulatory Authority.
26 January 2022	Exclusion criterion added to exclude participants with a body weight of 50 kg or less in France.
23 February 2022	1) Clarified that baseline androgen results for participants entering from study DIUR 014 would not be available to the Investigator and local androgen testing must not be conducted in order to maintain the blinding of the DIUR-014 study. 2) BMI added to the assessments. 3) Assessment of demographic details moved from the baseline visit to the screening visit since this assessment is needed to check eligibility into the study. 4) Measurement plasma renin removed since no longer required. 5) Concomitant therapy requirements clarified. 6) Additional details added on the assessments required for domiciliary and off-site clinic/laboratory visits. 7) Pharmacovigilance provider changed. 8) Urinalysis removed from the required laboratory assessments (but noted that this can be performed locally if indicated).
05 April 2022	1) Bulgaria removed since it was no longer included in the DIUR-014 feeder study. 2) Added that screening and baseline visits can be combined for participants who entered this extension study from their feeder study without a gap to reduce the number of visits required for participants that rolled straight into the study from their feeder study. 3) Clarified that informed consent was to be obtained up to 14 days before, or at the baseline visit for this DIUR-015 study. 4) Clarified that AESIs were to be reported using the SAE form, which was renamed the SAE/AESI form. Events causing implementation of 'stress dosing rules' were also removed from the list of AESIs since these are captured elsewhere.

13 April 2023	1) Removed the requirement for informed consent to be taken within 14 days of the baseline visit and clarified informed consent needed before any screening or baseline procedures. 2) Added that the exploratory plasma/serum research samples are optional. 3) Turkey removed since it was no longer included in the DIUR-014 feeder study. 4) Added that the total amount of blood collected would not exceed each site's policy, and that the amount of blood collected at each visit would not exceed 40 mL. 5) Added that participants would continue in the study until December 2024, when a decision would be made to either switch the participant onto Chronocort commercial supply, extend the study, or return the participant to standard of care therapy. 6) Details of the transfer of the participant's total daily dose details from the DIUR 014 IRT clarified. 7) Added that dose changes should be made in 5 mg increments. 8) Added that the baseline testosterone sample can be taken from the last visit of the feeder study. 9) Window around the annual visits has been increased to 4 weeks to allow flexibility of scheduling the annual visits. 10) Added that participants from study DIUR-014 were instructed to take a 10 mg hydrocortisone dose from their emergency treatment pack between 15:00 and 17:00 on Day 1 to avoid under replacement of cortisol and unblinding the DIUR 014 study. 11) Table of blood volumes at each visit added. 12) Changed to specify that the EQ-5D-5L QoL questionnaire should be completed on paper not through the participant diary. 13) Follow-up on pregnancies in female partners of male participants changed from 6-8 weeks to 30 days.
31 July 2024	(US-specific amendment) 1) Trial extended until December 2025 in USA only to collect long-term data in USA participants. 2) The definition of pre-Chronocort baseline revised to specify the screening visit (Visit 1) for DIUR-014 so that the pre-Chronocort baseline is captured before the run-in medication is given in study DIUR-014. 3) Added that there may be exceptions to the recommended dosing split of approximately to $\frac{1}{4}$ of the total daily dose in the morning on waking and to $\frac{3}{4}$ of the total daily dose at night just prior to bed to allow flexibility if a participant did not tolerate the higher dose at night. 4) Added that assessment of menstrual changes was needed in pre-menopausal females without hysterectomy and that these are required on a weekly basis. 5) Clarified that only participants who had a dose change were required to have a follow up phone call 1 week later. 6) Statement added about increased fertility with Chronocort which could lead to unexpected pregnancies to align with the SmPC. 7) 5 mg oral hydrocortisone tablets added to allow provision of 5 mg or 10 mg oral hydrocortisone tablets. 8) Definition of Addisonian crisis updated to bring it in line with the definition used in other studies. 9) Clarified that not all clinically significant laboratory changes had to be recorded as an AE – only if they were considered an AE by the investigator.

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 reported

Notes: