Clinical trial results:
A Phase III study of efficacy, safety and tolerability of Chronocort® compared with standard glucocorticoid replacement therapy in the treatment of congenital adrenal hyperplasia.

Summary

EudraCT number	2015-000711-40
Trial protocol	GB DE SE NL DK
Global end of trial date	28 July 2018

Results information

Result version number	v1 (current)
This version publication date	26 July 2019
First version publication date	26 July 2019

Trial information

Trial identification

Sponsor protocol code	DIUR-005

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02716818
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Diurnal Ltd
Sponsor organisation address	Cardiff Medicentre, Cardiff, United Kingdom, CF14 4UJ
Public contact	Clinical Trials Information, Diurnal Ltd, info@diurnal.co.uk
Scientific contact	Clinical Trials Information, Diurnal Ltd, info@diurnal.co.uk

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 July 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 July 2018
Global end of trial reached?	Yes
Global end of trial date	28 July 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the superior efficacy of Chronocort compared with standard glucocorticoid replacement therapy in the treatment of congenital adrenal hyperplasia (CAH). This will be assessed by establishing whether Chronocort can provide improved control of serum androgen levels compared to current glucocorticoid treatment regimens.

Protection of trial subjects:

The principles of informed consent in the Declaration of Helsinki, in the current requirements of Good Clinical Practice, (published by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) and local regulation, whichever afforded the greater participant protection, were implemented before any protocol-specified procedures or interventions were carried out. At Dutch centres only, potential participants were approached by their own treating physician. If the treating physician was also the study Investigator, the participant information sheet was provided immediately. If this was not the case, then the treating physician asked the participant for permission for the Investigator to approach them about study participation.

All data computer-processed by Diurnal Ltd. was identified by participant number/study code. Extra precautions were taken to preserve confidentiality and prevent genetic information being linked to the identity of the participant. This involved coding of the samples and data. For coded samples this meant that there was segregation of the databases containing coded genotypic and clinical information, with protection of confidentiality achieved by limited access.

Background therapy:

Fludrocortisone was prescribed to patients with the salt-wasting form of CAH.

Evidence for comparator:

The comparator used in this trial was standard glucocorticoid therapy, according to the patient's normal standard of care. Standard glucocorticoid therapy consists of hydrocortisone, prednisone, prednisolone and/or dexamethasone, or any combination of the aforementioned drugs.

Actual start date of recruitment	30 September 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 15
Country: Number of subjects enrolled	Sweden: 20
Country: Number of subjects enrolled	United Kingdom: 31
Country: Number of subjects enrolled	Denmark: 3
Country: Number of subjects enrolled	France: 32
Country: Number of subjects enrolled	Germany: 29
Country: Number of subjects enrolled	United States: 8

Worldwide total number of subjects	138
EEA total number of subjects	130

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	136
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 11 study sites in 7 countries: Denmark 1, France 2, Germany 1, Netherlands 1, Sweden 1, UK 4, and USA 1.

Pre-assignment

Screening details:

Following written informed consent and screening tests (Visit 0), eligible participants were called back for the baseline visit. As part of the baseline assessment, participants were admitted overnight for a 24-hour endocrine profile whilst remaining on their standard GC therapy. Participants were then randomised to Chronocort or standard therapy.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Chronocort

Arm description: -

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

Dosage and administration details:

Patients randomised to the Chronocort arm were provided a total daily dose that was equivalent to their previous daily dose of standard glucocorticoid therapy, up to a maximum of 30mg per day.

Arm title	Standard Glucocorticoid Therapy

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Hydrocortisone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients randomised to the standard glucocorticoid therapy arm continued taking the same dose that they had taken prior to study participation.

Investigational medicinal product name	Prednisone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients randomised to the standard glucocorticoid therapy arm continued taking the same dose that they had taken prior to study participation.

Investigational medicinal product name	Prednisolone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients randomised to the standard glucocorticoid therapy arm continued taking the same dose that they had taken prior to study participation.

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients randomised to the standard glucocorticoid therapy arm continued taking the same dose that they had taken prior to study participation.

Number of subjects in period 1[1]	Chronocort	Standard Glucocorticoid Therapy
Started	61	61
Completed	58	59
Not completed	3	2
Consent withdrawn by subject	2	1
Physician decision	-	1
Adverse event, non-fatal	1	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: There are 122 subjects overall reported in the baseline period (61 in Chronocort arm, 61 in standard GC therapy). The number of subjects entering the treatment period is the same as this, but the number of "Completed" subjects is lower due to dropouts.

Baseline characteristics

Reporting groups	
Reporting group title	Chronocort
Reporting group description: -	
Reporting group title	Standard Glucocorticoid Therapy
Reporting group description: -	

Reporting group values	Chronocort	Standard Glucocorticoid Therapy	Total
Number of subjects	61	61	122
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	61	59	120
From 65-84 years	0	2	2
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	42	36	78
Male	19	25	44

End points

End points reporting groups

Reporting group title	Chronocort
Reporting group description: -	
Reporting group title	Standard Glucocorticoid Therapy
Reporting group description: -	
Subject analysis set title	Pre-Baseline - Hydrocortisone - 17-OHP
Subject analysis set type	Per protocol
Subject analysis set description:	
Secondary efficacy analysis of 17-OHP (17-Hydroxyprogesterone) by pre-treatment strata, change from baseline to 24 weeks in primary efficacy variable, analysis of covariance model (Efficacy evaluable analysis set).	
Subject analysis set title	Pre-Baseline - Prednisone/Prednisolone - 17-OHP
Subject analysis set type	Per protocol
Subject analysis set description:	
Secondary efficacy analysis of 17-OHP by pre-treatment strata, change from baseline to 24 weeks in primary efficacy variable, analysis of covariance model (Efficacy evaluable analysis set).	
Subject analysis set title	Pre-Baseline - Dexamethasone - 17-OHP
Subject analysis set type	Per protocol
Subject analysis set description:	
Secondary efficacy analysis of 17-OHP by pre-treatment strata, change from baseline to 24 weeks in primary efficacy variable, analysis of covariance model (Efficacy evaluable analysis set).	
Subject analysis set title	Pre-Baseline - Chronocort vs. Hydrocortisone - 17-OHP
Subject analysis set type	Per protocol
Subject analysis set description:	
Secondary efficacy analysis of 17-OHP by pre-treatment strata, change from baseline to 24 weeks in primary efficacy variable, analysis of covariance model (Efficacy evaluable analysis set).	
Subject analysis set title	Pre-Baseline - Chronocort vs. Prednisone/Prednisolone - 17-OHP
Subject analysis set type	Per protocol
Subject analysis set description:	
Secondary efficacy analysis of 17-OHP by pre-treatment strata, change from baseline to 24 weeks in primary efficacy variable, analysis of covariance model (Efficacy evaluable analysis set)	
Subject analysis set title	Pre-Baseline - Chronocort vs. Dexamethasone - 17-OHP
Subject analysis set type	Per protocol
Subject analysis set description:	
Secondary efficacy analysis of 17-OHP by pre-treatment strata, change from baseline to 24 weeks in primary efficacy variable, analysis of covariance model (Efficacy evaluable analysis set)	
Subject analysis set title	Pre-Baseline - Hydrocortisone - Androstenedione (A4)
Subject analysis set type	Per protocol
Subject analysis set description:	
Secondary efficacy analysis of A4 by pre-treatment strata, change from baseline to 24 weeks in primary efficacy variable, analysis of covariance model (Efficacy evaluable analysis set)	
Subject analysis set title	Pre-Baseline - Prednisone/Prednisolone - A4
Subject analysis set type	Per protocol
Subject analysis set description:	
Secondary efficacy analysis of A4 by pre-treatment strata, change from baseline to 24 weeks in primary efficacy variable, analysis of covariance model (Efficacy evaluable analysis set)	
Subject analysis set title	Pre-Baseline - Dexamethasone - A4
Subject analysis set type	Per protocol
Subject analysis set description:	
Secondary efficacy analysis of A4 by pre-treatment strata, change from baseline to 24 weeks in primary efficacy variable, analysis of covariance model (Efficacy evaluable analysis set)	

Subject analysis set title	Pre-Baseline - Chronocort vs. Hydrocortisone - A4
Subject analysis set type	Per protocol

Subject analysis set description:

Secondary efficacy analysis of A4 by pre-treatment strata, change from baseline to 24 weeks in primary efficacy variable, analysis of covariance model (Efficacy evaluable analysis set)

Subject analysis set title	Pre-Baseline - Chronocort vs. Prednisone/Prednisolone - A4
Subject analysis set type	Per protocol

Subject analysis set description:

Secondary efficacy analysis of A4 by pre-treatment strata, change from baseline to 24 weeks in primary efficacy variable, analysis of covariance model (Efficacy evaluable analysis set)

Subject analysis set title	Pre-Baseline - Chronocort vs. Dexamethasone - A4
Subject analysis set type	Per protocol

Subject analysis set description:

Secondary efficacy analysis of A4 by pre-treatment strata, change from baseline to 24 weeks in primary efficacy variable, analysis of covariance model (Efficacy evaluable analysis set)

Subject analysis set title	Chronocort - 09:00h response - 17-OHP
Subject analysis set type	Per protocol

Subject analysis set description:

A subject will be considered a responder if their 09:00h results at week 24 are in the optimal range for 17-OHP.

Subject analysis set title	Chronocort - 09:00h response - A4
Subject analysis set type	Per protocol

Subject analysis set description:

A subject will be considered a responder if their 09:00h results at week 24 are in the optimal range for A4.

Subject analysis set title	Standard GC Therapy - 09:00h response - 17-OHP
Subject analysis set type	Per protocol

Subject analysis set description:

A subject will be considered a responder if their 09:00h results at week 24 are in the optimal range for 17-OHP.

Subject analysis set title	Standard GC Therapy - 09:00h response - A4
Subject analysis set type	Per protocol

Subject analysis set description:

A subject will be considered a responder if their 09:00h results at week 24 are in the optimal range for A4.

Subject analysis set title	Chronocort - DEXA - Fat Mass
Subject analysis set type	Per protocol

Subject analysis set description:

Secondary efficacy analysis of change from baseline to 24 weeks in body composition (fat mass) - Dual Energy X-ray Absorptiometry (DEXA), analysis of covariance model (Efficacy evaluable analysis set)

Subject analysis set title	Standard GC Therapy - DEXA - Fat Mass
Subject analysis set type	Per protocol

Subject analysis set description:

Secondary efficacy analysis of change from baseline to 24 weeks in body composition - DEXA; analysis of covariance model (Efficacy evaluable analysis set).

Subject analysis set title	Chronocort - DEXA - Lean Mass
Subject analysis set type	Per protocol

Subject analysis set description:

Secondary efficacy analysis of change from baseline to 24 weeks in body composition - DEXA; analysis of covariance model (Efficacy evaluable analysis set).

Subject analysis set title	Standard GC Therapy - DEXA - Lean Mass
Subject analysis set type	Per protocol

Subject analysis set description:

Secondary efficacy analysis of change from baseline to 24 weeks in body composition - DEXA; analysis of covariance model (Efficacy evaluable analysis set).

Subject analysis set title	Chronocort - DEXA - Bone Mineral Density
Subject analysis set type	Per protocol

Subject analysis set description:

Secondary efficacy analysis of change from baseline to 24 weeks in body composition - DEXA; analysis of covariance model (Efficacy evaluable analysis set).

Subject analysis set title	Standard GC Therapy - DEXA - Bone Mineral Density
Subject analysis set type	Per protocol

Subject analysis set description:

Secondary efficacy analysis of change from baseline to 24 weeks in body composition - DEXA; analysis of covariance model (Efficacy evaluable analysis set).

Primary: Change from baseline to 24 weeks of the mean of the 24-hour standard deviation score (SDS) profile for 17-OHP

End point title	Change from baseline to 24 weeks of the mean of the 24-hour standard deviation score (SDS) profile for 17-OHP

End point description:

The primary efficacy endpoint was the change from baseline to 24 weeks of the mean of the 24-hour standard deviation score (SDS) profile for 17-OHP (efficacy evaluable analysis set). The SDS profile was calculated as the SDS of log transformed 17-OHP concentration unsigned. A negative value indicates better hormonal control versus baseline, and a difference in LS means < 0 favours Chronocort.

End point type	Primary

End point timeframe:

24 weeks.

End point values	Chronocort	Standard Glucocorticoid Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	52		
Units: N/A - SDS				
arithmetic mean (standard deviation)	-0.403 (± 0.8499)	-0.172 (± 0.7776)		

Statistical analyses

Statistical analysis title	Primary efficacy analysis for 17-OHP

Statistical analysis description:

The primary efficacy variable was the natural logarithm of the mean of the 24-hour SDS profile for the natural logarithm of 17-OHP. The SDS profile was calculated as the SDS of log transformed 17-OHP concentration unsigned. The mean of the 24-hour SDS profile for each visit was the arithmetic mean of all the SDSs, with the first and last (13th) weighted one half relative to the intermediate SDSs.

Comparison groups	Chronocort v Standard Glucocorticoid Therapy
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5521
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.069

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.299
upper limit	0.161

Secondary: Change from baseline to 24 weeks of the mean of the 24-hour SDS profile for A4.

End point title	Change from baseline to 24 weeks of the mean of the 24-hour SDS profile for A4.

End point description:

The change from baseline to 24 weeks of the mean of the 24-hour SDS profile for A4 (calculated in the same way as the primary endpoint).

End point type	Secondary

End point timeframe:

24 weeks

End point values	Chronocort	Standard Glucocorticoid Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	52		
Units: N/A - SDS				
arithmetic mean (standard deviation)	0.113 (± 0.9221)	-0.041 (± 0.7731)		

Statistical analyses

Statistical analysis title	Change from Baseline to 24 Weeks in A4

Statistical analysis description:

Change from Baseline to 24 Weeks in A4 Using an ANCOVA Model - The analysis conducted for the primary endpoint variable analysis of 17-OHP was repeated for A4.

Comparison groups	Standard Glucocorticoid Therapy v Chronocort
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7405
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.047
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.234
upper limit	0.329

Secondary: 17-OHP and A4 by individual baseline treatment strata

End point title	17-OHP and A4 by individual baseline treatment strata

End point description:

17-OHP and A4 by individual baseline treatment strata presented in the same manner as the primary endpoint (using 24-hour SDS profile at 24 weeks).

End point type	Secondary

End point timeframe:

24 weeks

End point values	Pre-Baseline - Hydrocortisone - 17-OHP	Pre-Baseline - Prednisone/Prednisolone - 17-OHP	Pre-Baseline - Dexamethasone - 17-OHP	Pre-Baseline - Chronocort vs. Hydrocortisone - 17-OHP
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	27	21	4	31
Units: N/A - SDS				
arithmetic mean (standard deviation)	-0.248 (± 0.7661)	-0.061 (± 0.8051)	-0.245 (± 0.8522)	-0.431 (± 0.8727)

End point values	Pre-Baseline - Chronocort vs. Prednisone/Prednisolone - 17-OHP	Pre-Baseline - Chronocort vs. Dexamethasone - 17-OHP	Pre-Baseline - Hydrocortisone - Androstenedione (A4)	Pre-Baseline - Prednisone/Prednisolone - A4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	18	4	27	21
Units: N/A - SDS				
arithmetic mean (standard deviation)	-0.320 (± 0.7627)	-0.565 (± 1.2343)	-0.211 (± 0.7426)	0.100 (± 0.8339)

End point values	Pre-Baseline - Dexamethasone - A4	Pre-Baseline - Chronocort vs. Hydrocortisone - A4	Pre-Baseline - Chronocort vs. Prednisone/Prednisolone - A4	Pre-Baseline - Chronocort vs. Dexamethasone - A4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	4	31	18	4
Units: N/A - SDS				
arithmetic mean (standard deviation)	0.368 (± 0.3521)	0.015 (± 1.0128)	0.328 (± 0.7256)	-0.092 (± 1.0310)

Statistical analyses

Statistical analysis title	Chronocort vs. Hydrocortisone - 17-OHP
Comparison groups	Pre-Baseline - Hydrocortisone - 17-OHP v Pre-Baseline - Chronocort vs. Hydrocortisone - 17-OHP
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8186
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.037
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.354
upper limit	0.281

Statistical analysis title	Chronocort vs. Prednisone/Prednisolone - 17-OHP
Comparison groups	Pre-Baseline - Prednisone/Prednisolone - 17-OHP v Pre-Baseline - Chronocort vs. Prednisone/Prednisolone - 17-OHP
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4655
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.135
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.508
upper limit	0.237

Statistical analysis title	Chronocort vs. Dexamethasone - 17-OHP
Comparison groups	Pre-Baseline - Dexamethasone - 17-OHP v Pre-Baseline - Chronocort vs. Dexamethasone - 17-OHP
Number of subjects included in analysis	8
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9081
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.065
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.32
upper limit	1.451

Statistical analysis title	Chronocort vs. Hydrocortisone - A4
Comparison groups	Pre-Baseline - Hydrocortisone - Androstenedione (A4) v Pre-Baseline - Chronocort vs. Hydrocortisone - A4
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6729
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.092
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.343
upper limit	0.527

Statistical analysis title	Chronocort vs. Prednisone/Prednisolone - A4
Comparison groups	Pre-Baseline - Prednisone/Prednisolone - A4 v Pre-Baseline - Chronocort vs. Prednisone/Prednisolone - A4
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5322
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.116
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.257
upper limit	0.489

Statistical analysis title	Chronocort vs. Dexamethasone - A4
Comparison groups	Pre-Baseline - Dexamethasone - A4 v Pre-Baseline - Chronocort vs. Dexamethasone - A4
Number of subjects included in analysis	8
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2885
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.568

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.799
upper limit	0.662

Secondary: 17-OHP and A4 levels at 09:00 as a responder analysis

End point title	17-OHP and A4 levels at 09:00 as a responder analysis
End point description:	
17-OHP and A4 levels at 09:00 as a responder analysis (i.e. the number of participants achieving results in the optimal range).	
End point type	Secondary
End point timeframe:	
24 weeks	

End point values	Chronocort - 09:00h response - 17-OHP	Chronocort - 09:00h response - A4	Standard GC Therapy - 09:00h response - 17-	Standard GC Therapy - 09:00h response - A4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	53	53	52	52
Units: Number of subjects with a response	30	25	30	30

Statistical analyses

Statistical analysis title	Responders at 09:00 - 17-OHP
Comparison groups	Chronocort - 09:00h response - 17-OHP v Standard GC Therapy - 09:00h response - 17-OHP
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9877
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	2.19

Statistical analysis title	Responders at 09:00 - A4

Comparison groups	Chronocort - 09:00h response - A4 v Standard GC Therapy - 09:00h response - A4
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8498
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	2.02

Secondary: Changes relative to standard GC therapy in body composition (DEXA) (fat mass, lean mass) - measured at all sites except Germany.

End point title	Changes relative to standard GC therapy in body composition (DEXA) (fat mass, lean mass) - measured at all sites except Germany.

End point description:

Changes relative to standard GC therapy in body composition (DEXA) (fat mass and lean mass) - measured at all sites except Germany.

End point type	Secondary

End point timeframe:

24 weeks

End point values	Chronocort - DEXA - Fat Mass	Standard GC Therapy - DEXA - Fat Mass	Chronocort - DEXA - Lean Mass	Standard GC Therapy - DEXA - Lean Mass
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	43	39	43	39
Units: kilograms				
arithmetic mean (standard deviation)	-0.575 (± 3.2744)	0.445 (± 2.4660)	0.640 (± 2.3304)	0.234 (± 1.3689)

Statistical analyses

Statistical analysis title	Change in Fat Mass - Chronocort vs. Standard GC

Statistical analysis description:

German subjects have been excluded from this analysis as DEXA scans were not performed at the German site.

Comparison groups	Chronocort - DEXA - Fat Mass v Standard GC Therapy - DEXA - Fat Mass

Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.156
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.294
upper limit	0.374

Statistical analysis title	Change in Lean Mass - Chronocort vs. Standard GC
Statistical analysis description:	
German subjects have been excluded from this analysis as DEXA scans were not performed at the German site.	
Comparison groups	Chronocort - DEXA - Lean Mass v Standard GC Therapy - DEXA - Lean Mass
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3392
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.425
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.455
upper limit	1.305

Secondary: Changes relative to standard GC therapy in body composition (DEXA) (bone mineral density) - measured at all sites except Germany.

End point title	Changes relative to standard GC therapy in body composition (DEXA) (bone mineral density) - measured at all sites except Germany.
End point description:	
Secondary efficacy analysis of change from baseline to 24 weeks in body composition (DEXA), analysis of covariance model (Efficacy evaluable analysis set)	
End point type	Secondary
End point timeframe:	
24 weeks	

End point values	Chronocort - DEXA - Bone Mineral Density	Standard GC Therapy - DEXA - Bone Mineral Density		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	35	36		
Units: g/cm2				
arithmetic mean (standard deviation)	-0.001 (± 0.0250)	-0.008 (± 0.0399)		

Statistical analyses

Statistical analysis title	Change in Bone Mineral Density - Chronocort vs GC

Statistical analysis description:

German subjects have been excluded from the analysis as DEXA scans are not performed at German sites.

Comparison groups	Chronocort - DEXA - Bone Mineral Density v Standard GC Therapy - DEXA - Bone Mineral Density
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2614
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.009
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.007
upper limit	0.025

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events were reported from enrolment to study completion (24 weeks).	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20

Reporting groups	
Reporting group title	Chronocort
Reporting group description: -	
Reporting group title	Standard Glucocorticoid Therapy
Reporting group description: -	

Serious adverse events	Chronocort	Standard Glucocorticoid Therapy	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 61 (11.48%)	5 / 61 (8.20%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
General disorders and administration site conditions			
Odema Peripheral			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal Insufficiency			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Andrenocortical Insufficiency Acute			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	3 / 61 (4.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 61 (3.28%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis Viral			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes Zoster			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salpingitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsilitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Chronocort	Standard Glucocorticoid Therapy	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	59 / 61 (96.72%)	48 / 61 (78.69%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Vascular disorders			
Haematoma			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Hypertension			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Hypotension			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Pallor			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Asthenia			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 61 (6.56%)	3 / 61 (4.92%)	
occurrences (all)	6	3	
Chest pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences (all)	1	0	

Fat tissue increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences (all)	2	0	
Fatigue			
alternative assessment type: Non-systematic			
subjects affected / exposed	9 / 61 (14.75%)	10 / 61 (16.39%)	
occurrences (all)	13	20	
Inflammation			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Influenza like illness			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 61 (3.28%)	4 / 61 (6.56%)	
occurrences (all)	3	4	
Malaise			
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 61 (8.20%)	2 / 61 (3.28%)	
occurrences (all)	5	2	
Oedema peripheral			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	3	
Peripheral swelling			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Pyrexia			
alternative assessment type: Non-systematic			
subjects affected / exposed	9 / 61 (14.75%)	4 / 61 (6.56%)	
occurrences (all)	9	4	
Sensation of foreign body			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Therapeutic response unexpected			
alternative assessment type: Non-systematic			
subjects affected / exposed	10 / 61 (16.39%)	1 / 61 (1.64%)	
occurrences (all)	15	1	
Thirst			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Erectile dysfunction			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Menstruation irregular			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Cough			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 61 (4.92%)	0 / 61 (0.00%)	
occurrences (all)	4	0	
Dyspnoea			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	1 / 61 (1.64%)	
occurrences (all)	1	1	
Nasal congestion			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Oropharyngeal pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	1 / 61 (1.64%)	
occurrences (all)	1	1	
Rhinorrhoea			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	1 / 61 (1.64%)	
occurrences (all)	1	1	
Psychiatric disorders			
Affect lability			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Agitation			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	2 / 61 (3.28%)	
occurrences (all)	0	3	
Anxiety			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences (all)	2	0	
Burnout syndrome			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Depressed mood			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 61 (3.28%)	1 / 61 (1.64%)	
occurrences (all)	2	1	
Depression			
alternative assessment type: Non-systematic			

subjects affected / exposed	2 / 61 (3.28%)	2 / 61 (3.28%)	
occurrences (all)	3	2	
Emotional distress			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Insomnia			
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 61 (8.20%)	4 / 61 (6.56%)	
occurrences (all)	6	4	
Irritability			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Libido decreased			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	1 / 61 (1.64%)	
occurrences (all)	1	1	
Sleep disorder			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	2 / 61 (3.28%)	
occurrences (all)	0	2	
Stress			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	3 / 61 (4.92%)	
occurrences (all)	1	3	
Investigations			
Alanine aminotransferase increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Aspartate aminotransferase increased			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Blood creatine phosphokinase increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Blood glucose increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Blood sodium decreased			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Body temperature increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 61 (3.28%)	0 / 61 (0.00%)	
occurrences (all)	2	0	
C-telopeptide increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Haematocrit decreased			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Haemoglobin decreased			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Liver function test abnormal			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	

Osteocalcin decreased			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Renin increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 61 (4.92%)	7 / 61 (11.48%)	
occurrences (all)	3	7	
Urine output decreased			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Weight increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
White blood cell count increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Auricular haematoma			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Contusion			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Ear injury			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Hand fracture			
alternative assessment type: Non-			

systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Ligament sprain			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Limb injury			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Procedural complication			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Procedural pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Sunburn			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Toxicity to various agents			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Wound			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Cardiac disorders			
Palpitations			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 61 (1.64%)	3 / 61 (4.92%)	
occurrences (all)	1	3	
Sinus tachycardia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Tachycardia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Carpal tunnel syndrome			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 61 (3.28%)	0 / 61 (0.00%)	
occurrences (all)	2	0	
Circadian rhythm sleep disorder			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Dizziness			
alternative assessment type: Non-systematic			
subjects affected / exposed	7 / 61 (11.48%)	4 / 61 (6.56%)	
occurrences (all)	13	5	
Dizziness postural			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Headache			
alternative assessment type: Non-systematic			
subjects affected / exposed	15 / 61 (24.59%)	15 / 61 (24.59%)	
occurrences (all)	19	22	
Lethargy			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Memory impairment			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Migraine			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	1 / 61 (1.64%)	
occurrences (all)	2	1	
Paraesthesia			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 61 (3.28%)	1 / 61 (1.64%)	
occurrences (all)	2	1	
Peripheral nerve lesion			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Poor quality sleep			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Psychomotor hyperactivity			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Sensory loss			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Somnolence			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	1 / 61 (1.64%)	
occurrences (all)	1	1	

Syncope			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Tension headache			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	2 / 61 (3.28%)	
occurrences (all)	0	2	
Tremor			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 61 (6.56%)	3 / 61 (4.92%)	
occurrences (all)	4	3	
Iron deficiency anaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Ear deformity acquired			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	2	
Ear pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Tinnitus			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Tympanic membrane perforation			

alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Vertigo			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Vertigo positional			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Eye disorders			
Chalazion			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Foreign body sensation in eyes			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Lacrimation increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Vision blurred			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 61 (4.92%)	1 / 61 (1.64%)	
occurrences (all)	3	1	
Gastrointestinal disorders			
Abdominal pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 61 (3.28%)	2 / 61 (3.28%)	
occurrences (all)	2	3	
Abdominal pain lower			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)		
occurrences (all)	0	1		
Abdominal pain upper				
alternative assessment type: Non-systematic				
subjects affected / exposed	4 / 61 (6.56%)	0 / 61 (0.00%)		
occurrences (all)	7	0		
Constipation				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)		
occurrences (all)	1	0		
Dental caries				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)		
occurrences (all)	1	0		
Diarrhoea				
alternative assessment type: Non-systematic				
subjects affected / exposed	4 / 61 (6.56%)	3 / 61 (4.92%)		
occurrences (all)	6	3		
Diverticulum intestinal				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)		
occurrences (all)	0	1		
Dyspepsia				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)		
occurrences (all)	0	1		
Epigastric discomfort				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)		
occurrences (all)	2	0		
Faeces soft				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)		
occurrences (all)	0	1		

Food poisoning			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Gastrooesophageal reflux disease			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Inguinal hernia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Nausea			
alternative assessment type: Non-systematic			
subjects affected / exposed	8 / 61 (13.11%)	4 / 61 (6.56%)	
occurrences (all)	9	5	
Vomiting			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 61 (6.56%)	3 / 61 (4.92%)	
occurrences (all)	4	4	
Skin and subcutaneous tissue disorders			
Acne			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 61 (3.28%)	0 / 61 (0.00%)	
occurrences (all)	2	0	
Alopecia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Blister			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Chloasma			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)		
occurrences (all)	0	1		
Cold sweat				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)		
occurrences (all)	1	0		
Eczema				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 61 (1.64%)	1 / 61 (1.64%)		
occurrences (all)	1	1		
Erythema				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)		
occurrences (all)	1	0		
Hair growth abnormal				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)		
occurrences (all)	1	0		
Hyperhidrosis				
alternative assessment type: Non-systematic				
subjects affected / exposed	2 / 61 (3.28%)	1 / 61 (1.64%)		
occurrences (all)	2	1		
Psoriasis				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)		
occurrences (all)	1	0		
Rash				
alternative assessment type: Non-systematic				
subjects affected / exposed	3 / 61 (4.92%)	0 / 61 (0.00%)		
occurrences (all)	3	0		
Urticaria				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)		
occurrences (all)	1	0		

Endocrine disorders			
Mineralocorticoid deficiency			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 61 (3.28%)	2 / 61 (3.28%)	
occurrences (all)	3	2	
Back pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 61 (6.56%)	3 / 61 (4.92%)	
occurrences (all)	4	3	
Joint stiffness			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Muscle fatigue			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Muscle spasms			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Muscle tightness			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	1 / 61 (1.64%)	
occurrences (all)	1	1	
Muscular weakness			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 61 (3.28%)	0 / 61 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal pain			

alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 61 (3.28%)	1 / 61 (1.64%)	
occurrences (all)	2	1	
Myalgia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	1 / 61 (1.64%)	
occurrences (all)	1	1	
Neck pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Osteoarthritis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Pain in extremity			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	1 / 61 (1.64%)	
occurrences (all)	2	1	
Infections and infestations			
Acute sinusitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Bronchitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Conjunctivitis viral			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Cystitis			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Diarrhoea infectious			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Ear infection fungal			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	4 / 61 (6.56%)	
occurrences (all)	1	4	
Gastroenteritis viral			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	1 / 61 (1.64%)	
occurrences (all)	1	1	
Influenza			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 61 (3.28%)	1 / 61 (1.64%)	
occurrences (all)	2	1	
Lower respiratory tract infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences (all)	2	0	
Nasopharyngitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Oral candidiasis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	

Otitis media			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Otitis media acute			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Paronychia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Pharyngitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 61 (3.28%)	0 / 61 (0.00%)	
occurrences (all)	2	0	
Sinusitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 61 (3.28%)	1 / 61 (1.64%)	
occurrences (all)	2	1	
Tonsilitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences (all)	2	0	
Tooth infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	3 / 61 (4.92%)	
occurrences (all)	1	3	
Urinary tract infection			
alternative assessment type: Non-systematic			

subjects affected / exposed	4 / 61 (6.56%)	2 / 61 (3.28%)	
occurrences (all)	4	2	
Viral infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Viral rash			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Viral upper respiratory tract infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	12 / 61 (19.67%)	13 / 61 (21.31%)	
occurrences (all)	16	15	
Salpingitis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences (all)	2	0	
Herpes zoster			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Abnormal loss of weight			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Abnormal weight gain			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 61 (4.92%)	2 / 61 (3.28%)	
occurrences (all)	3	2	
Alcohol intolerance			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Decreased appetite			
alternative assessment type: Non-systematic			

subjects affected / exposed	2 / 61 (3.28%)	0 / 61 (0.00%)	
occurrences (all)	2	0	
Fluid retention			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	2 / 61 (3.28%)	
occurrences (all)	1	2	
Gluten sensitivity			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Hyperglycaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Hyperinsulinaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 61 (4.92%)	1 / 61 (1.64%)	
occurrences (all)	3	1	
Impaired fasting glucose			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 61 (4.92%)	1 / 61 (1.64%)	
occurrences (all)	3	1	
Increased appetite			
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 61 (8.20%)	2 / 61 (3.28%)	
occurrences (all)	5	2	
Weight fluctuation			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 September 2015	Protocol v2.0 dated 03 September 2015: The protocol was amended to address MHRA comments on the protocol and to make a small administrative change to the Adrenal Insufficiency Checklist. The following changes were made: 1) Modification of the RSI in the Investigator's Brochure (IB) necessitated an update to Appendix 3 (Expected Adverse Events) in the protocol. 2) Clarification was added that the DSMB is independent. 3) The inclusion criteria of PRA less than 2 x ULN was reduced to PRA less than 1.5 x ULN. 4) Appendix 5 was updated to a newer version of the Adrenal Insufficiency Checklist (minor administrative change).
03 December 2015	Protocol v3.0 dated 03 December 2015: The protocol was amended to address the Swedish Medicines Agency and the US National Institutes of Health comments on the protocol that a separate benefit/risk assessment should be added. The following changes were made: 1) Section 5: new section added at the end of Section 5 titled Benefit/Risk Assessment.
28 May 2016	Protocol v4.0 dated 28 May 2016: The following changes were made to the protocol: 1) Sponsor signatory changed. 2) Added a maximum possible dose of 30mg hydrocortisone (or equivalent when calculating the dose using conversion factors for other glucocorticoid medications used in the trial; prednisone, prednisolone and dexamethasone). 3) Added a clarification that consent must be taken from the patients in order to access genotyping information for the subject that was taken prior to study involvement. 4) Subjects who routinely work night shifts and so do not sleep during the usual nighttime hours was added to the exclusion criteria. 5) At the request of the Dutch ethics committee, the following sentence has been added to the procedures for the screening visit (Section 11.1.1) and also in Section 11.4 (Informed Consent): At Dutch centres only, potential subjects will be approached by their own treating physician. If the treating physician is also the investigator the subject information sheet can be provided immediately. If this is not the case then the treating physician will ask the patient for permission for the investigator to approach them about study participation. 6) It was noted that the terminology for the independent blinded physician was not consistent throughout the protocol so this was corrected throughout. 7) The text in Section 8 (Study Design) and Section 10.4 (Dose Adjustment) was updated to state 'No dose adjustments outside of the protocol-defined dose adjustments should be conducted, unless clinical signs and symptoms indicate an immediate need. In such cases the Sponsor's medical monitor must be contacted (preferably before any dose changes are implemented). Any such unscheduled dose adjustments should be based on clinical symptoms only, with repeated androgen testing discouraged and must be pre-approved by the Sponsor's medical monitor.'

23 September 2016	Protocol v5.0 dated 23 September 2016: The following changes were made to the protocol: 1) Sponsor signatory changed. 2) The Chronocort® capsules may now be supplied in either blister packs or bottles. Therefore, Section 10.2.2 (Packaging and Labelling) and Appendix 9 (Labelling) were updated.
13 April 2017	Protocol v6.0 dated 13 April 2017: The following changes were made to the protocol: 1) The statistician was changed. 2) The sample size was increased from 110 to 120 patients due to a higher level of protocol deviations than originally anticipated. As such, the inevaluability rate has been increased from 7% to 15%. 3) The titration instructions in Section 8 (Dose Adjustment) were modified to provide guidance to state that if the independent blinded physician states that a change to the midday dose is needed but the patient is either receiving Chronocort or is receiving twice daily dosing of standard therapy. In such cases the local investigator is instructed to decide whether to adjust the morning or evening dose, based on their judgement, in addition to any changes already advised for morning and evening doses, thus ensuring that the total change advised is accommodated within the day. 4) The screening period has been extended by 1 week (21 days) to allow extra time for the study site to obtain the results of the screening PRA test. 5) Clarification added to Sections 9.2 and 11.7 and the synopsis that female subjects presenting with oligomenorrhoea or amenorrhoea who are aged ≤55 years of age should be considered potentially fertile and therefore, as well as undergoing pregnancy testing like all other female subjects, will be expected to be using an acceptable method of contraception, as listed in Section 11.7. 6) Some events may occur during the study that represent an improvement in the subject's condition e.g. restoration of menses. To ensure sufficient details of such events are recorded, Section 12.9 has been updated to state that these events will be reported in the same manner as SAEs in order to capture the data in real time, together with additional data, if this should be required. However these events will not be reported to the regulatory authorities as SAEs.

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.

A limitation of the pre-defined primary endpoint was that it included an unsigned SDS score over a 24-hour period.

Notes: