Clinical trial results:
A Randomized, Double-Blind, Active-Controlled, Phase 3 Study of Chronocort Compared With Immediate-Release Hydrocortisone Replacement Therapy in Participants Aged 16 Years and Over With Congenital Adrenal Hyperplasia

Summary

EudraCT number	2021-003668-29
Trial protocol	FR
Global end of trial date	02 February 2024

Results information

Result version number	v1 (current)
This version publication date	17 August 2024
First version publication date	17 August 2024

Trial information

Trial identification

Sponsor protocol code	DIUR-014

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05063994
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Diurnal Limited
Sponsor organisation address	Cardiff Medicentre, Heath Park, Cardiff, United Kingdom, CF14 4UJ
Public contact	Clinical Trials Information, Diurnal Limited, +44 0 292 068 2069, info@diurnal.co.uk
Scientific contact	Clinical Trials Information, Diurnal Limited, +44 0 292 068 2069, 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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	25 April 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 February 2024
Global end of trial reached?	Yes
Global end of trial date	02 February 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study is a randomized, double-blind, active-controlled, phase III study of Chronocort® compared with immediate-release hydrocortisone replacement therapy in participants aged 16 years and over with Congenital Adrenal Hyperplasia.

Protection of trial subjects:

The study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki, the Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines, in accordance with ICH GCP requirements, and in accordance with the United States of America (USA) Code of Federal Regulations on Protection of Human Rights (21 CFR 50) (for USA sites only).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 May 2022
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	France: 21
Country: Number of subjects enrolled	Japan: 9
Country: Number of subjects enrolled	United States: 23
Worldwide total number of subjects	53
EEA total number of subjects	21

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)	7
Adults (18-64 years)	46
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants received IRHC (Cortef) during the run-in therapy for 4 weeks prior to randomization. Once eligibility for the study was confirmed at the Baseline visit, participants were randomized on a 1:1 basis (Chronocort:Cortef). 55 participants entered the run-in period and 53 were randomized to treatment.

Pre-assignment period milestones

Number of subjects started	55[1]
Number of subjects completed	53

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 1
Reason: Number of subjects	Did not meet the inclusion/exclusion criteria: 1

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Two participants discontinued prior to randomization.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Chronocort

Arm description:

Participants received Chronocort at a starting dose of 30 milligrams (mg), with dose adjustments down to 25, 20, or 15 mg based on adrenal insufficiency symptoms and androgen levels. Placebo was used for dose adjustment to maintain blinding.

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

Dosage and administration details:

Participants received dosage and administration as specified in the arm description.

Arm title	Cortef

Arm description:

Participants received Cortef at a starting dose of 30 mg, with dose adjustments down to 25, 20, or 15 mg based on adrenal insufficiency symptoms and androgen levels. Placebo was used for dose adjustment to maintain blinding.

Arm type	Active comparator

Investigational medicinal product name	Cortef
Investigational medicinal product code	
Other name	Immediate-release hydrocortisone, IRHC
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received dosage and administration as specified in the arm description.

Number of subjects in period 1	Chronocort	Cortef
Started	25	28
Full Analysis Set (FAS) Population	25	28
Completed	25	25
Not completed	0	3
Withdrawal of Consent	-	1
Physician decision	-	1
Consent withdrawn by subject	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Chronocort
Reporting group description:	
Participants received Chronocort at a starting dose of 30 milligrams (mg), with dose adjustments down to 25, 20, or 15 mg based on adrenal insufficiency symptoms and androgen levels. Placebo was used for dose adjustment to maintain blinding.	
Reporting group title	Cortef
Reporting group description:	
Participants received Cortef at a starting dose of 30 mg, with dose adjustments down to 25, 20, or 15 mg based on adrenal insufficiency symptoms and androgen levels. Placebo was used for dose adjustment to maintain blinding.	

Reporting group values	Chronocort	Cortef	Total
Number of subjects	25	28	53
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age Continuous Units: years			
arithmetic mean	36.7	31.6	
standard deviation	± 14.68	± 13.02	-
Sex: Female, Male Units: participants			
Female	16	16	32
Male	9	12	21
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	2	3	5
Not Hispanic or Latino	15	16	31
Unknown or Not Reported	8	9	17
Race/Ethnicity, Customized Units: Subjects			
White	13	12	25
Black or African American	1	2	3
Asian	4	5	9
Not Reportable	6	6	12
Unknown	1	3	4

17-Hydroxyprogesterone (17-OHP) Level			
Units: nanograms (ng)/deciliters (dL)			
arithmetic mean	3470.48	5595.36	
full range (min-max)	43.5 to 16968.5	10.0 to 14641.5	-
Androstenedione (A4) Level			
Analysis Population: Participants in the FAS population who had an A4 assessment at the baseline visit. n = 25 for Chronocort and n = 27 for Cortef.			
Units: ng/dL			
arithmetic mean	173.30	483.09	
full range (min-max)	5.0 to 1040.5	5.0 to 2516.5	-

End points

End points reporting groups

Reporting group title	Chronocort
Reporting group description:	
Participants received Chronocort at a starting dose of 30 milligrams (mg), with dose adjustments down to 25, 20, or 15 mg based on adrenal insufficiency symptoms and androgen levels. Placebo was used for dose adjustment to maintain blinding.	
Reporting group title	Cortef
Reporting group description:	
Participants received Cortef at a starting dose of 30 mg, with dose adjustments down to 25, 20, or 15 mg based on adrenal insufficiency symptoms and androgen levels. Placebo was used for dose adjustment to maintain blinding.	

Primary: Percentage of participants who were biochemical responders at Week 28

End point title	Percentage of participants who were biochemical responders at Week 28
End point description:	
Biochemical response was defined as a participant who a) was in biochemical control at the 08:00 assessment and b) was receiving a total daily dose of hydrocortisone of not more than 25 mg if the participant was in biochemical control at baseline or not more than 30 mg if the participant was not in biochemical control at baseline. Biochemical control was defined as both a 17-OHP concentration equal to or below the upper limit for optimal control (1200 ng/dL [36.4 nmol/L]) and an A4 concentration equal to or below the upper limit of the reference range (150 ng/dL [5.2 nmol/L] for men and 200 ng/dL [7.0 nmol/L] for women). Assessment of efficacy at Week 28 was a composite of each participant's on-treatment visit closest in time to 28 weeks post randomisation. FAS: All participants with CAH who were randomized into the study and who received at least 1 dose of study drug.	
End point type	Primary
End point timeframe:	
Week 28	

End point values	Chronocort	Cortef		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	28		
Units: percentage of participants				
number (not applicable)	40.0	14.3		

Statistical analyses

Statistical analysis title	Analysis of Biochemical Responders
Comparison groups	Chronocort v Cortef

Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	= 0.0003 [2]
Method	Regression, Logistic
Parameter estimate	Treatment Difference
Point estimate	25.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.5
upper limit	48.9
Variability estimate	Standard error of the mean
Dispersion value	11.82

Notes:

[1] - Non-inferiority of Chronocort to Cortef was declared if the 95% CI for the difference in biochemical response rates between the 2 treatment arms (Chronocort minus Cortef) was wholly above minus 15 percentage points.
[2] - One-sided non-inferiority.
The Ge et al (2011) method was used to calculate the estimate, standard error, confidence interval and P-value for the treatment difference from the results of a logistic regression analysis.

Secondary: Total daily dose of hydrocortisone at Week 28

End point title	Total daily dose of hydrocortisone at Week 28

End point description:

Least squares (LS) mean was assessed using mixed model repeated measures (MMRM).
Assessment of efficacy at Week 28 was a composite of each participant's on-treatment visit closest in time to 28 weeks post randomisation.
FAS: All participants with CAH who were randomized into the study and who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Week 28

End point values	Chronocort	Cortef		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	28		
Units: mg				
least squares mean (confidence interval 95%)	20.2 (17.8 to 22.6)	26.0 (23.7 to 28.3)		

Statistical analyses

Statistical analysis title	Analysis of Total Daily Dose of Hydrocortisone
Comparison groups	Chronocort v Cortef

Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.0005 [4]
Method	MMRM
Parameter estimate	Treatment Difference
Point estimate	-5.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.2
upper limit	-2.5
Variability estimate	Standard error of the mean
Dispersion value	1.66

Notes:

[3] - Superiority of Chronocort to Cortef was declared if the two-sided 95% CI for difference in means between the 2 treatment arms (Chronocort minus Cortef) was wholly below zero, provided that non-inferiority of Chronocort to Cortef in terms of biochemical response had been declared under the primary efficacy objective, and superiority of Chronocort to Cortef in terms of dose response has been declared.
[4] - One sided-superiority.

Secondary: Percentage of participants who were dose responders at Week 28

End point title	Percentage of participants who were dose responders at Week 28

End point description:

Dose response was defined as a participant who a) was receiving a total daily dose of hydrocortisone of not more than 25 mg and b) was in biochemical control at the 08:00 assessment.
Assessment of efficacy at Week 28 was a composite of each participant's on-treatment visit closest in time to 28 weeks post randomisation.
FAS: All participants with CAH who were randomized into the study and who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Week 28

End point values	Chronocort	Cortef		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	28		
Units: percentage of participants				
number (not applicable)	36.0	10.7		

Statistical analyses

Statistical analysis title	Analysis of Dose Responders
Comparison groups	Chronocort v Cortef

Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.012 [6]
Method	Regression, Logistic
Parameter estimate	Treatment Difference
Point estimate	25.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.3
upper limit	47.3
Variability estimate	Standard error of the mean
Dispersion value	11.24

Notes:

[5] - Superiority of Chronocort to Cortef with respect to the dose response after 28 weeks of randomized treatment was declared if the two-sided 95% CI for the difference in response rates between the 2 treatment arms (Chronocort minus Cortef) was wholly above zero, provided that non-inferiority of Chronocort to Cortef with respect to the biochemical response had been declared under the primary efficacy objective.
[6] - One-sided superiority.
The Ge et al (2011) method was used to calculate the estimate, standard error, confidence interval and P-value for the treatment difference from the results of a logistic regression analysis.

Secondary: Percentage of participants in biochemical control

End point title	Percentage of participants in biochemical control

End point description:

Biochemical control was defined as both a 17-OHP concentration (assessed at 08:00) equal to or below the upper limit for optimal control (1200 ng/dL [36.4 nmol/L]) and an A4 concentration equal to or below the upper limit of the reference range (150 ng/dL [5.2 nmol/L] for men and 200 ng/dL [7.0 nmol/L] for women).
Assessment of efficacy at Week 28 was a composite of each participant's on-treatment visit closest in time to 28 weeks post randomisation.
FAS: All participants with CAH who were randomized into the study and who received at least 1 dose of study drug. Participants with evaluable data for the endpoint were analyzed for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline and Week 28

End point values	Chronocort	Cortef		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	25[7]		
Units: percentage of participants				
number (not applicable)				
Baseline	52.0	28.6		
Week 28	40.0	16.0		

Notes:

[7] - Baseline: n=27
Week 28: n=25

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in mean of 08:00 and 13:00 A4 levels at Week 28

End point title	Change from baseline in mean of 08:00 and 13:00 A4 levels at Week 28

End point description:

LS mean was assessed using ANCOVA.
Assessment of efficacy at Week 28 was a composite of each participant's on-treatment visit closest in time to 28 weeks post randomisation.
FAS: All participants with CAH who were randomized into the study and who received at least 1 dose of study drug. Participants with evaluable data for the endpoint were analyzed for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, Week 28

End point values	Chronocort	Cortef		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	25		
Units: ng/dL				
least squares mean (confidence interval 95%)	-4.85 (-115.57 to 105.86)	146.13 (35.42 to 256.85)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in mean of 08:00 and 13:00 17-OHP levels at Week 28

End point title	Change from baseline in mean of 08:00 and 13:00 17-OHP levels at Week 28

End point description:

LS mean was assessed using analysis of covariance (ANCOVA).
Assessment of efficacy at Week 28 was a composite of each participant's on-treatment visit closest in time to 28 weeks post randomisation.
FAS: All participants with CAH who were randomized into the study and who received at least 1 dose of study drug. Participants with evaluable data for the endpoint were analyzed for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, Week 28

End point values	Chronocort	Cortef		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	25		
Units: ng/dL				
least squares mean (confidence interval 95%)	-1223.91 (-2897.42 to 449.6)	1612.17 (-61.34 to 3285.68)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with menstrual regularity (females of childbearing potential only)

End point title	Percentage of participants with menstrual regularity (females of childbearing potential only)

End point description:

Data are presented for the number of participants with more than monthly menstrual cycles, monthly menstrual cycles, and number of participants with oligomenorrhoea and amenorrhoea. Oligomenorrhoea was defined as fewer than 9 menstrual cycles per year or cycle length >35 days and amenorrhoea as absent menses for ≥ 3 months.
Assessment of efficacy at Week 28 was a composite of each participant's on-treatment visit closest in time to 28 weeks post randomisation.
FAS: All participants with CAH who were randomized into the study and who received at least 1 dose of study drug. Only female participants of childbearing potential with evaluable data for the endpoint were analyzed for this outcome measure.

End point type	Secondary

End point timeframe:

Week 28

End point values	Chronocort	Cortef		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	12		
Units: percentage of participants				
number (not applicable)				
More than Monthly	0	0		
Monthly	64.3	16.7		
Oligomenorrhoea	14.3	33.3		
Amenorrhoea	21.4	50.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in size of testicular adrenal rest tumors (males Only) at Week 28

End point title	Percent Change From Baseline in size of testicular adrenal rest

	tumors (males Only) at Week 28

End point description:

Assessment of efficacy at Week 28 was a composite of each participant's on-treatment visit closest in time to 28 weeks post randomisation.
FAS: All participants with CAH who were randomized into the study and who received at least 1 dose of study drug. Only male participants with evaluable data for the endpoint were analyzed for this outcome measure.

End point type	Secondary

End point timeframe:

Week 28

End point values	Chronocort	Cortef		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: percent change				
arithmetic mean (standard deviation)	-7.67 (± 9.220)	-0.90 (± 1.810)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in luteinizing hormone levels (males only) at Week 28

End point title	Change from baseline in luteinizing hormone levels (males only) at Week 28

End point description:

LS mean was assessed using ANCOVA.
Assessment of efficacy at Week 28 was a composite of each participant's on-treatment visit closest in time to 28 weeks post randomisation.
FAS: All participants with CAH who were randomized into the study and who received at least 1 dose of study drug. Only male participants with evaluable data for the endpoint were analyzed for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, Week 28

End point values	Chronocort	Cortef		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	10		
Units: mIU/mL				
least squares mean (confidence interval 95%)	0.15 (-0.71 to 1.02)	-1.19 (-2.01 to -0.37)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in hirsutism at Week 28 using the Ferriman-Gallwey score (females only) at Week 28

End point title	Change from baseline in hirsutism at Week 28 using the Ferriman-Gallwey score (females only) at Week 28

End point description:

Ferriman-Gallwey score is a method used to assess and quantify hirsutism in women. A total score < 8 is considered normal whereas a score of 8 to 15 indicates mild hirsutism. A score >15 indicates moderate or severe hirsutism. The Ferriman-Gallwey score ranged from 0 to 36. Higher score indicated more hirsutism. Change from baseline is reported (negative change from baseline indicated improvement).
LS mean was assessed using ANCOVA.
Assessment of efficacy at Week 28 was a composite of each participant's on-treatment visit closest in time to 28 weeks post randomisation.
FAS: All participants with CAH who were randomized into the study and who received at least 1 dose of study drug. Only female participants with evaluable data for the endpoint were analyzed for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, Week 28

End point values	Chronocort	Cortef		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	13		
Units: score on a scale				
least squares mean (confidence interval 95%)	-1.0 (-2.5 to 0.6)	-1.2 (-3.0 to 0.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in acne using the Global Evaluation Acne (GEA) scale (females only) at Week 28

End point title	Change from baseline in acne using the Global Evaluation Acne (GEA) scale (females only) at Week 28

End point description:

Acne severity was assessed according to GEA scale, which ranged from 0 (Clear. No lesions) to 5 (Very severe). Higher score indicated higher severity of acne. Change from baseline is reported (negative change from baseline indicated improvement).
LS mean was assessed using ANCOVA.
Assessment of efficacy at Week 28 was a composite of each participant's on-treatment visit closest in time to 28 weeks post randomisation.
FAS: All participants with CAH who were randomized into the study and who received at least 1 dose of study drug. Only female participants with evaluable data for the endpoint were analyzed for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, Week 28

End point values	Chronocort	Cortef		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	13		
Units: score on a scale				
least squares mean (confidence interval 95%)	-0.3 (-0.5 to -0.1)	-0.2 (-0.4 to 0.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in waist circumference at Week 28

End point title	Change from baseline in waist circumference at Week 28

End point description:

LS mean was assessed using ANCOVA.
Assessment of efficacy at Week 28 was a composite of each participant's on-treatment visit closest in time to 28 weeks post randomisation.
FAS: All participants with CAH who were randomized into the study and who received at least 1 dose of study drug. Participants with evaluable data for the endpoint were analyzed for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, Week 28

End point values	Chronocort	Cortef		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	24		
Units: centimeters				
least squares mean (confidence interval 95%)	0.867 (-1.387 to 3.121)	-1.242 (-3.496 to 1.012)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in glycated hemoglobin (HbA1c) percent levels at Week 28

End point title	Change from baseline in glycated hemoglobin (HbA1c) percent levels at Week 28

End point description:

LS mean was assessed by ANCOVA. Assessment of efficacy at Week 28 was a composite of each participant's on-treatment visit closest in time to 28 weeks post randomisation.
FAS: All participants with CAH who were randomized into the study and who received at least 1 dose of

study drug. Participants with evaluable data for the endpoint were analyzed for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, Week 28

End point values	Chronocort	Cortef		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	24		
Units: percent HbA1c				
least squares mean (confidence interval 95%)	-0.01 (-0.09 to 0.06)	-0.06 (-0.13 to 0.01)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in body weight at Week 28

End point title	Change from baseline in body weight at Week 28

End point description:

LS mean was assessed by ANCOVA.
Assessment of efficacy at Week 28 was a composite of each participant's on-treatment visit closest in time to 28 weeks post randomisation.
FAS: All participants with CAH who were randomized into the study and who received at least 1 dose of study drug. Participants with evaluable data for the endpoint were analyzed for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, Week 28

End point values	Chronocort	Cortef		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	25		
Units: kilograms				
least squares mean (confidence interval 95%)	1.29 (0.00 to 2.58)	-1.67 (-2.96 to -0.38)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline quality of life using the self-completed Medical Outcome Study 36-Item Short Form Health Survey (SF-36) total score for the physical and mental components and the sub-domain of vitality at Week 28

End point title	Change from baseline quality of life using the self-completed Medical Outcome Study 36-Item Short Form Health Survey (SF-36) total score for the physical and mental components and the sub-domain of vitality at Week 28

End point description:

SF-36 evaluates aspects of functional health and well-being. Physical component has 4 sub-scales: physical function, role limitations due to physical problems, pain, and general health perception; and mental component has 4 sub-scales: vitality, social function, role limitations due to emotional problems, and mental health. Total scores for the physical and mental component are presented as well as the sub-scale score for vitality. Scores were summarized and transformed into a range from 0 to 100; 0=worst, and 100=best outcome. Higher scores indicated better outcome. Change from baseline is reported (positive change from baseline indicated improvement.
LS mean was assessed by ANCOVA.
Assessment of efficacy at Week 28 was a composite of each participant's on-treatment visit closest in time to 28 weeks post randomisation.
FAS: All participants with CAH who were randomized into the study and received at least 1 dose of study drug. Participants with evaluable data were analyzed.

End point type	Secondary

End point timeframe:

Baseline, Week 28

End point values	Chronocort	Cortef		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	15		
Units: score on a scale				
least squares mean (confidence interval 95%)				
Physical Component	-3.313 (-5.801 to -0.824)	-1.031 (-3.976 to 1.913)		
Mental Component	0.772 (-3.209 to 4.752)	0.685 (-4.034 to 5.403)		
Vitality Sub-domain	-0.847 (-4.354 to 2.660)	-0.002 (-4.157 to 4.153)		

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 53 weeks; median exposure = 255.0 days for Chronocort and 230.5 days for Cortef)

Adverse event reporting additional description:

The Cortef and Chronocort reporting groups were assessed using the safety analysis set that included all participants who were randomized and received at least 1 dose of study drug in the treatment period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups

Reporting group title	Cortef

Reporting group description:

Participants received Cortef at a starting dose of 30 mg, with dose adjustments down to 25, 20, or 15 mg based on adrenal insufficiency symptoms and androgen levels. Placebo was used for dose adjustment to maintain blinding.

Reporting group title	Chronocort

Reporting group description:

Participants received Chronocort at a starting dose of 30 mg, with dose adjustments down to 25, 20, or 15 mg based on adrenal insufficiency symptoms and androgen levels. Placebo was used for dose adjustment to maintain blinding.

Serious adverse events	Cortef	Chronocort	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 28 (3.57%)	2 / 25 (8.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant melanoma			
subjects affected / exposed	0 / 28 (0.00%)	1 / 25 (4.00%)	
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			
Pneumonia			
subjects affected / exposed	1 / 28 (3.57%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

COVID-19			
subjects affected / exposed	0 / 28 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Cortef	Chronocort	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 28 (85.71%)	22 / 25 (88.00%)	
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	3 / 28 (10.71%)	1 / 25 (4.00%)	
occurrences (all)	4	1	
Alanine aminotransferase increased			
subjects affected / exposed	1 / 28 (3.57%)	2 / 25 (8.00%)	
occurrences (all)	1	2	
Weight increased			
subjects affected / exposed	0 / 28 (0.00%)	3 / 25 (12.00%)	
occurrences (all)	0	3	
Injury, poisoning and procedural complications			
Ligament sprain			
subjects affected / exposed	0 / 28 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	2	
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 28 (10.71%)	4 / 25 (16.00%)	
occurrences (all)	4	4	
Dizziness			
subjects affected / exposed	1 / 28 (3.57%)	2 / 25 (8.00%)	
occurrences (all)	1	2	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	2 / 28 (7.14%)	1 / 25 (4.00%)	
occurrences (all)	2	1	
Fatigue			

subjects affected / exposed	5 / 28 (17.86%)	4 / 25 (16.00%)	
occurrences (all)	5	6	
Pyrexia			
subjects affected / exposed	6 / 28 (21.43%)	0 / 25 (0.00%)	
occurrences (all)	6	0	
Gastrointestinal disorders			
Diarrhea			
subjects affected / exposed	2 / 28 (7.14%)	0 / 25 (0.00%)	
occurrences (all)	2	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 28 (7.14%)	2 / 25 (8.00%)	
occurrences (all)	2	2	
Psychiatric disorders			
Stress			
subjects affected / exposed	0 / 28 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	2	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 28 (7.14%)	0 / 25 (0.00%)	
occurrences (all)	3	0	
Arthralgia			
subjects affected / exposed	2 / 28 (7.14%)	3 / 25 (12.00%)	
occurrences (all)	2	3	
Infections and infestations			
Sinusitis			
subjects affected / exposed	1 / 28 (3.57%)	2 / 25 (8.00%)	
occurrences (all)	1	2	
Ear infection			
subjects affected / exposed	0 / 28 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	2	
Nasopharyngitis			
subjects affected / exposed	2 / 28 (7.14%)	1 / 25 (4.00%)	
occurrences (all)	2	1	
Gastroenteritis			

subjects affected / exposed	2 / 28 (7.14%)	2 / 25 (8.00%)	
occurrences (all)	2	2	
Upper respiratory tract infection			
subjects affected / exposed	2 / 28 (7.14%)	2 / 25 (8.00%)	
occurrences (all)	3	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 May 2021	• Amended blinding procedure to avoid inadvertent unblinding • Allowed access to commercial Chronocort, depending on the territory
27 January 2022	• Added additional exclusion criteria • Changed maximum blood volume to be drawn during the study • Clarified concomitant therapy • Added section for interactions with other medicinal product • Expended on Dose Modification reasons • Added section for COVID-19 Procedures • New section added on remote monitoring visits
04 March 2022	• Revised schedule of assessment • Clarified exclusion criteria • Clarified rescue medication • Clarified participant discontinuation • Clarified dosing schedule • Amended serious adverse event reporting procedure • Clarified fasting requirements • Revised Clinical Laboratory Tests
23 March 2022	• Correction made to schedule of assessments • Clarified study assessments and procedures • Clarified adverse event definition
09 February 2023	• Duration of the fixed-dose period has been reduced from 36 weeks to 12 weeks and the number of patients reduced from approximately 150 to approximately 50 (or an enrolment cut-off date of 30 April 2023, whichever is reached first)
30 October 2023	• Revised non-inferiority margin • Clarified when last dose of study medication will be taken • Clarified EOS visit sample analysis • Clarified procedure for recording of physical examination findings

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: