Clinical trial results:
A Double-Blind, Double-Dummy, Two-Way Cross-Over, Randomised, Phase II Study of Efficacy, Safety and Tolerability of Modified-Release Hydrocortisones: Chronocort® Versus Plenadren®, in Adrenal Insufficiency (The CHAMPAIN Study)

Summary

EudraCT number	2021-000144-21
Trial protocol	DE
Global end of trial date	18 October 2023

Results information

Result version number	v1 (current)
This version publication date	02 November 2024
First version publication date	02 November 2024

Trial information

Trial identification

Sponsor protocol code	DIUR-016-AI

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05222152
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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 October 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 October 2023
Global end of trial reached?	Yes
Global end of trial date	18 October 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The study aimed to compare the efficacy, safety and tolerability of twice daily Chronocort, a modified-release hydrocortisone, with once daily Plenadren, a modified-release hydrocortisone.

Protection of trial subjects:

The study was conducted in accordance with the ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organisations of Medical Sciences (CIOMS) international ethical guidelines, applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, and applicable laws and regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 January 2022
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 19
Country: Number of subjects enrolled	United Kingdom: 39
Worldwide total number of subjects	58
EEA total number of subjects	19

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)	49
From 65 to 84 years	9
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants were randomly assigned on a 1:1 basis to either Chronocort then Plenadren or Plenadren then Chronocort. A total of 86 participants were screened, with 58 participants subsequently being enrolled into the study.

Period 1

Period 1 title	Treatment Period 1 (4 Weeks)
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 then Plenadren

Arm description:

Participants received Chronocort 15 milligrams (mg) just prior to going to bed (typically between 22:00 hours and midnight) and Chronocort 10 mg and Plenadren placebo on waking up (typically between 06:00 and 08:00 hours) for 4 weeks during Treatment Period 1. Participants received Chronocort placebo just prior to going to bed (typically between 22:00 hours and midnight) and Plenadren 25 mg and Chronocort placebo on waking up (typically between 06:00 and 08:00 hours) for 4 weeks during Treatment Period 2.

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

Dosage and administration details:

Hydrocortisone modified-release hard gelatin capsules for oral administration - 5 mg and 10 mg

Investigational medicinal product name	Plenadren
Investigational medicinal product code	
Other name	Hydrocortisone modified-release tablet
Pharmaceutical forms	Modified-release tablet
Routes of administration	Oral use

Dosage and administration details:

Hydrocortisone modified-release tablets for oral administration - 5 mg and 20 mg

Investigational medicinal product name	Chronocort Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Placebo hard gelatin capsules for oral administration

Investigational medicinal product name	Plenadren Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet

Routes of administration	Oral use

Dosage and administration details:

Placebo tablets for oral administration

Arm title	Plenadren then Chronocort

Arm description:

Participants received Chronocort placebo just prior to going to bed (typically between 22:00 hours and midnight) and Plenadren 25 mg and Chronocort placebo on waking up (typically between 06:00 and 08:00 hours) for 4 weeks during Treatment Period 1. Participants received Chronocort 15 mg just prior to going to bed (typically between 22:00 hours and midnight) and Chronocort 10 mg and Plenadren placebo on waking up (typically between 06:00 and 08:00 hours) for 4 weeks during Treatment Period 2.

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

Dosage and administration details:

Hydrocortisone modified-release hard gelatin capsules for oral administration - 5 mg and 10 mg

Investigational medicinal product name	Plenadren
Investigational medicinal product code	
Other name	Hydrocortisone modified-release tablet
Pharmaceutical forms	Modified-release tablet
Routes of administration	Oral use

Dosage and administration details:

Hydrocortisone modified-release tablets for oral administration - 5 mg and 20 mg

Investigational medicinal product name	Chronocort Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Placebo hard gelatin capsules for oral administration

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

Dosage and administration details:

Placebo tablets for oral administration

Number of subjects in period 1	Chronocort then Plenadren	Plenadren then Chronocort
Started	29	29
Received at Least 1 Dose of Study Drug	29	29
Completed	27	29
Not completed	2	0

Consent withdrawn by subject	2	-

Period 2

Period 2 title	Treatment Period 2 (4 Weeks)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Chronocort then Plenadren

Arm description:

Participants received Chronocort 15 milligrams (mg) just prior to going to bed (typically between 22:00 hours and midnight) and Chronocort 10 mg and Plenadren placebo on waking up (typically between 06:00 and 08:00 hours) for 4 weeks during Treatment Period 1. Participants received Chronocort placebo just prior to going to bed (typically between 22:00 hours and midnight) and Plenadren 25 mg and Chronocort placebo on waking up (typically between 06:00 and 08:00 hours) for 4 weeks during Treatment Period 2.

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

Dosage and administration details:

Hydrocortisone modified-release hard gelatin capsules for oral administration - 5 mg and 10 mg

Investigational medicinal product name	Plenadren
Investigational medicinal product code	
Other name	Hydrocortisone modified-release tablet
Pharmaceutical forms	Modified-release tablet
Routes of administration	Oral use

Dosage and administration details:

Hydrocortisone modified-release tablets for oral administration - 5 mg and 20 mg

Investigational medicinal product name	Chronocort Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Placebo hard gelatin capsules for oral administration

Investigational medicinal product name	Plenadren Placebo
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo tablets for oral administration

Arm title	Plenadren then Chronocort

Arm description:

Participants received Chronocort placebo just prior to going to bed (typically between 22:00 hours and midnight) and Plenadren 25 mg and Chronocort placebo on waking up (typically between 06:00 and 08:00 hours) for 4 weeks during Treatment Period 1. Participants received Chronocort 15 mg just prior to going to bed (typically between 22:00 hours and midnight) and Chronocort 10 mg and Plenadren placebo on waking up (typically between 06:00 and 08:00 hours) for 4 weeks during Treatment Period 2.

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

Dosage and administration details:

Hydrocortisone modified-release hard gelatin capsules for oral administration - 5 mg and 10 mg

Investigational medicinal product name	Plenadren
Investigational medicinal product code	
Other name	Hydrocortisone modified-release tablet
Pharmaceutical forms	Modified-release tablet
Routes of administration	Oral use

Dosage and administration details:

Hydrocortisone modified-release tablets for oral administration - 5 mg and 20 mg

Investigational medicinal product name	Chronocort Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Placebo hard gelatin capsules for oral administration

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

Dosage and administration details:

Placebo tablets for oral administration

Number of subjects in period 2	Chronocort then Plenadren	Plenadren then Chronocort
Started	27	29
Received at Least 1 Dose of Study Drug	27	29
Completed	26	28
Not completed	1	1

Consent withdrawn by subject	-	1
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Chronocort then Plenadren
Reporting group description:	
Participants received Chronocort 15 milligrams (mg) just prior to going to bed (typically between 22:00 hours and midnight) and Chronocort 10 mg and Plenadren placebo on waking up (typically between 06:00 and 08:00 hours) for 4 weeks during Treatment Period 1. Participants received Chronocort placebo just prior to going to bed (typically between 22:00 hours and midnight) and Plenadren 25 mg and Chronocort placebo on waking up (typically between 06:00 and 08:00 hours) for 4 weeks during Treatment Period 2.	
Reporting group title	Plenadren then Chronocort
Reporting group description:	
Participants received Chronocort placebo just prior to going to bed (typically between 22:00 hours and midnight) and Plenadren 25 mg and Chronocort placebo on waking up (typically between 06:00 and 08:00 hours) for 4 weeks during Treatment Period 1. Participants received Chronocort 15 mg just prior to going to bed (typically between 22:00 hours and midnight) and Chronocort 10 mg and Plenadren placebo on waking up (typically between 06:00 and 08:00 hours) for 4 weeks during Treatment Period 2.	

Reporting group values	Chronocort then Plenadren	Plenadren then Chronocort	Total
Number of subjects	29	29	58
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 49.4 ± 14.88	 49.3 ± 14.59	 -
Gender categorical Units: Subjects			
Female	20	22	42
Male	9	7	16
Race Units: Subjects			
White	29	28	57
Other	0	1	1

End points

End points reporting groups

Reporting group title	Chronocort then Plenadren

Reporting group description:

Participants received Chronocort 15 milligrams (mg) just prior to going to bed (typically between 22:00 hours and midnight) and Chronocort 10 mg and Plenadren placebo on waking up (typically between 06:00 and 08:00 hours) for 4 weeks during Treatment Period 1. Participants received Chronocort placebo just prior to going to bed (typically between 22:00 hours and midnight) and Plenadren 25 mg and Chronocort placebo on waking up (typically between 06:00 and 08:00 hours) for 4 weeks during Treatment Period 2.

Reporting group title	Plenadren then Chronocort

Reporting group description:

Participants received Chronocort placebo just prior to going to bed (typically between 22:00 hours and midnight) and Plenadren 25 mg and Chronocort placebo on waking up (typically between 06:00 and 08:00 hours) for 4 weeks during Treatment Period 1. Participants received Chronocort 15 mg just prior to going to bed (typically between 22:00 hours and midnight) and Chronocort 10 mg and Plenadren placebo on waking up (typically between 06:00 and 08:00 hours) for 4 weeks during Treatment Period 2.

Reporting group title	Chronocort then Plenadren

Reporting group description:

Participants received Chronocort 15 milligrams (mg) just prior to going to bed (typically between 22:00 hours and midnight) and Chronocort 10 mg and Plenadren placebo on waking up (typically between 06:00 and 08:00 hours) for 4 weeks during Treatment Period 1. Participants received Chronocort placebo just prior to going to bed (typically between 22:00 hours and midnight) and Plenadren 25 mg and Chronocort placebo on waking up (typically between 06:00 and 08:00 hours) for 4 weeks during Treatment Period 2.

Reporting group title	Plenadren then Chronocort

Reporting group description:

Participants received Chronocort placebo just prior to going to bed (typically between 22:00 hours and midnight) and Plenadren 25 mg and Chronocort placebo on waking up (typically between 06:00 and 08:00 hours) for 4 weeks during Treatment Period 1. Participants received Chronocort 15 mg just prior to going to bed (typically between 22:00 hours and midnight) and Chronocort 10 mg and Plenadren placebo on waking up (typically between 06:00 and 08:00 hours) for 4 weeks during Treatment Period 2.

Subject analysis set title	Chronocort
Subject analysis set type	Full analysis

Subject analysis set description:

Participants received Chronocort 15 mg just prior to going to bed (typically between 22:00 hours and midnight) and Chronocort 10 mg on waking up (typically between 06:00 and 08:00 hours) for 4 weeks during Treatment Period 1 or 2.

Subject analysis set title	Plenadren
Subject analysis set type	Full analysis

Subject analysis set description:

Participants received Plenadren 25 mg on waking up (typically between 06:00 and 08:00 hours) for 4 weeks during Treatment Period 1 or 2.

Primary: 07:00 Hour Serum Cortisol Level After 4 Weeks of Treatment

End point title	07:00 Hour Serum Cortisol Level After 4 Weeks of Treatment

End point description:

07:00 hour serum cortisol level after 4 weeks of treatment has been reported. Efficacy evaluable analysis set (EEAS) included participants with morning serum cortisol assessed at baseline and after each treatment period, with no 'major significant' protocol deviations.

End point type	Primary

End point timeframe:

At the end of each 4-week Treatment Period

End point values	Chronocort	Plenadren		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	49	49		
Units: nanomoles (nmol)/liter (L)				
least squares mean (confidence interval 95%)	369.38 (263.68 to 517.45)	8.14 (5.81 to 11.41)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Cross-over design: Actual number of participants analyzed = 49	
Comparison groups	Chronocort v Plenadren
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Linear Mixed Model
Parameter estimate	Least Square (LS) Mean Ratio
Point estimate	45.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	28.86
upper limit	71.32

Secondary: Multidimensional Assessment of Fatigue (MAF) Global Fatigue Index (GFI)

End point title	Multidimensional Assessment of Fatigue (MAF) Global Fatigue Index (GFI)

End point description:

MAF questionnaire contains 16 items that measure 4 dimensions of fatigue: severity (items 1 & 2), distress (item 3), degree of interference in activities of daily living (items 4 to 14), and timing (items 15 & 16). First 14 questions answered on a scale from 1 (best case) to 10 (worst case). Last 2 had multiple-choices responses that were converted to a numeric scale of 1 (best) to 4 (worst). GFI was obtained based on item 1 to 15 by summing the following: a) responses to items 1 to 3; b) average of items 4 to 14; c) response to item 15 multiplied by 2.5. GFI ranges between 1 (no fatigue) and 50 (severe fatigue). If answer to item 1 (To what degree have you experienced fatigue?) was 1 (not at all) then all the following items were not answered and total GFI = 1. EEAS = participants with morning serum cortisol assessed at baseline and after each treatment period, with no major significant protocol deviations. Number of participants analyzed = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

At the end of each 4-week Treatment Period

End point values	Chronocort	Plenadren		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	42	40		
Units: units on a scale				
arithmetic mean (standard deviation)	17.37 (± 9.701)	19.97 (± 10.055)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Achieving a Physiological Morning Cortisol Level After 4 Weeks of Treatment

End point title	Number of Participants Achieving a Physiological Morning Cortisol Level After 4 Weeks of Treatment

End point description:

A physiological morning cortisol level was defined as a value >140 nmol/L at the 07:00 hour pre-dose timepoint after 4 weeks of treatment in Treatment Period 1. The EEAS included participants with morning serum cortisol assessed at baseline and after Treatment Period 1, with no 'major significant' protocol deviations. Number of participants analyzed = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

At the end of each 4-week Treatment Period

End point values	Chronocort then Plenadren	Plenadren then Chronocort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	26		
Units: participants				
Period 1 Only	20	0		
Period 2 Only	0	23		
Both Periods	2	0		
Neither Periods	1	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Salivary Cortisone Profile Score After 4 Weeks of Treatment

End point title	Salivary Cortisone Profile Score After 4 Weeks of Treatment

End point description:

Salivary profile score was obtained by summing 5 components that relate to how salivary cortisone

compared vs quartiles of salivary cortisone in healthy participants: 1. 2-points if on-study morning predose salivary cortisone was >first quartile (Q1) of healthy participant salivary cortisone at 07:00 hrs. 2. 1-point if on-study 1.5 hrs post morning dose salivary cortisone was <third quartile (Q3) of healthy participant salivary cortisone at 07:00 hrs. 3. 1-point if on-study midday salivary cortisone was >Q1 of healthy participant salivary cortisone at 12:00 hrs. 4. 1-point if on-study 15:00 hrs salivary cortisone was >Q1 of healthy participants salivary cortisone at 15:00 hrs. 5. 1-point if on-study evening predose salivary cortisone was <Q3 of healthy participant salivary cortisone at 22:00 hrs. Quartiles were based on 14 healthy participants' data available from literature. Higher score=more physiological salivary cortisone profile. N= EEAS participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

At the end of each 4-week Treatment Period

End point values	Chronocort	Plenadren		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	46	45		
Units: units on a scale				
arithmetic mean (standard deviation)	3.33 (± 1.012)	2.49 (± 0.968)		

Statistical analyses

No statistical analyses for this end point

Secondary: 07:00 Hour Plasma Adrenocorticotropic Hormone (ACTH) Level After 4 Weeks of Treatment

End point title	07:00 Hour Plasma Adrenocorticotropic Hormone (ACTH) Level After 4 Weeks of Treatment

End point description:

07:00 hour plasma ACTH level after 4 weeks of treatment has been reported. EEAS included participants with morning serum cortisol assessed at baseline and after each treatment period, with no 'major significant' protocol deviations. Number of participants analyzed = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

At the end of each 4-week Treatment Period

End point values	Chronocort	Plenadren		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	48	45		
Units: picomoles (pmol)/L				
arithmetic mean (standard deviation)	61.360 (± 80.6612)	184.776 (± 135.7575)		

Statistical analyses

No statistical analyses for this end point

Secondary: Osteocalcin Levels After 4 Weeks of Treatment

End point title	Osteocalcin Levels After 4 Weeks of Treatment

End point description:

Osteocalcin level after 4 weeks of treatment has been reported. EEAS included participants with morning serum cortisol assessed at baseline and after each treatment period, with no 'major significant' protocol deviations. Number of participants analyzed = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

At the end of each 4-week Treatment Period

End point values	Chronocort	Plenadren		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	48	48		
Units: micrograms (µg)/L				
arithmetic mean (standard deviation)	23.150 (± 7.0789)	27.181 (± 9.9398)		

Statistical analyses

No statistical analyses for this end point

Secondary: Patient-Reported Outcomes Measurement Information System (PROMIS) 7b Standardised Total Score After 4 Weeks of Treatment

End point title	Patient-Reported Outcomes Measurement Information System (PROMIS) 7b Standardised Total Score After 4 Weeks of Treatment

End point description:

The PROMIS 7b is a short questionnaire that aims to define the levels of fatigue in participants. It uses 7 questions on fatigue experience and impact on daily activities measured on a 5-point rating scale, with possible answers ranging from 1 (never) to 5 (always). The PROMIS 7b after 4 weeks of treatment was derived as the average of the scores in the 4th week of a Treatment Period (Day 22 to 28), provided that there were at least 4 evaluable measurements. The total score was obtained by summing results across items, with scores ranging between 7 and 35. Based on this raw score, a standardised T-score was obtained mapping to a distribution with a mean of 50 and a standard deviation of 10. EEAS included participants with morning serum cortisol assessed at baseline and after each treatment period, with no 'major significant' protocol deviations. Number of participants analyzed = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

At the end of each 4-week Treatment Period

End point values	Chronocort	Plenadren		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44	42		
Units: T-score				
arithmetic mean (standard deviation)	42.875 (± 8.5895)	45.388 (± 9.3964)		

Statistical analyses

No statistical analyses for this end point

Secondary: European Quality of Life (EuroQol) 5-level Standardised Health Questionnaire (EQ-5D-5L) Index Score After 4 Weeks of Treatment

End point title	European Quality of Life (EuroQol) 5-level Standardised Health Questionnaire (EQ-5D-5L) Index Score After 4 Weeks of Treatment

End point description:

EQ-5D-5L is a multi-attribute instrument used in assessing the health-related quality of life (HRQoL). The EQ-5D descriptive system contains 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: 1= no problems, 2= slight problems, 3= moderate problems, 4 =severe problems, 5 =extreme problems. Responses to 5 EQ-5D dimensions were converted into a 5-digit number (for example 12112) called a 'health state'. The health state reflects how good or bad the health state was according to the preferences of the general population of a country/region. In order to convert the health state to a continuous index value, value sets (that is, weights ranging from 1 for a health state of 11111 to negative values for health states reflective of a poor condition such as 55555) as derived for Germany and the UK from the cross-walk approach available on the EuroQoL website was adopted. N = EEAS participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

At the end of each 4-week Treatment Period

End point values	Chronocort	Plenadren		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	43	41		
Units: units on a scale				
arithmetic mean (standard deviation)	0.887 (± 0.1624)	0.818 (± 0.1820)		

Statistical analyses

No statistical analyses for this end point

Secondary: EuroQol Visual Analogue Scale (EQ-VAS) Score After 4 Weeks of Treatment

End point title	EuroQol Visual Analogue Scale (EQ-VAS) Score After 4 Weeks of Treatment

End point description:

The EQ VAS recorded the participants' self-rated health on a vertical VAS, where participants were asked to mark their self-rated health on a scale from 0 (the worst health you can imagine) to 100 (the best health you can imagine). EEAS included participants with morning serum cortisol assessed at baseline and after each treatment period, with no 'major significant' protocol deviations. Number of participants analyzed = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

At the end of each 4-week Treatment Period

End point values	Chronocort	Plenadren		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	43	41		
Units: units on a scale				
arithmetic mean (standard deviation)	80.95 (± 15.221)	76.49 (± 19.828)		

Statistical analyses

No statistical analyses for this end point

Secondary: Health-related Quality of Life in Addison's disease (AddiQoL) Total Score After 4 Weeks of Treatment

End point title	Health-related Quality of Life in Addison's disease (AddiQoL) Total Score After 4 Weeks of Treatment

End point description:

A 30-item questionnaire version of AddiQoL was developed to measure HRQoL in participants with Addison's disease undergoing replacement therapy that maps to 4 sub-dimensions: fatigue, symptoms, emotions and miscellaneous. The AddiQoL total score was obtained by summing up the scores for each individual item and ranged from 30 to 120, with higher scores suggesting better overall quality of life. EEAS included participants with morning serum cortisol assessed at baseline and after each treatment period, with no 'major significant' protocol deviations. Number of participants analyzed = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

At the end of each 4-week Treatment Period

End point values	Chronocort	Plenadren		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	43	41		
Units: units on a scale				
arithmetic mean (standard deviation)	89.09 (± 12.528)	84.76 (± 14.522)		

Statistical analyses

No statistical analyses for this end point

Secondary: Short Form Health Survey (SF-36) Questionnaire Domain and Component Scores After 4 Weeks of Treatment

End point title	Short Form Health Survey (SF-36) Questionnaire Domain and Component Scores After 4 Weeks of Treatment

End point description:

The SF-36 v2 is a multipurpose short-form heath survey which measures 8 different health domains using 36 items: physical functioning (10 items), role limitations due to physical problems (4 items), bodily pain (2 items), general health (5 items), vitality (4 items), social functioning (2 items), role limitations due to emotional problems (3 items), and mental health (5 items). A final item, termed self-reported health transition was not included in the scoring process. A separate score was derived for each domain and, in addition, also a physical (PCS) and mental (MCS) component summary was derived. Domain and summary components scores ranged from 0 to 100, with higher scores suggesting better overall health. EEAS included participants with morning serum cortisol assessed at baseline and after each treatment period, with no 'major significant' protocol deviations. Number of participants analyzed = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

At the end of each 4-week Treatment Period

End point values	Chronocort	Plenadren		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	43	41		
Units: units on a scale				
arithmetic mean (standard deviation)				
Physical Functioning	51.621 (± 8.6185)	48.391 (± 10.7967)		
Role Limitations Due to Physical Health	48.435 (± 9.9614)	45.106 (± 9.6026)		
Bodily Pain	52.229 (± 9.6349)	49.549 (± 8.9333)		
General Health Perceptions	45.202 (± 11.0073)	42.065 (± 11.3526)		
Vitality	51.631 (± 10.8619)	48.252 (± 10.5265)		
Social Functioning	49.994 (± 9.8673)	50.248 (± 9.2428)		
Role Limitations Due to Emotional Problems	52.849 (± 5.6334)	51.838 (± 8.0832)		
Mental Health	53.727 (± 7.5269)	53.484 (± 8.3755)		
PCS	48.325 (± 10.1773)	44.302 (± 10.6918)		
MCS	53.108 (± 7.2616)	53.287 (± 8.6201)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 30 days after the end of study (Day 87)

Adverse event reporting additional description:

The Safety Analysis Set included all participants randomized into the study who received any dose of study drug. As pre-specified, data are presented per treatment received.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups

Reporting group title	Chronocort

Reporting group description:

Participants received Chronocort 15 mg just prior to going to bed (typically between 22:00 hours and midnight) and Chronocort 10 mg on waking up (typically between 06:00 and 08:00 hours) for 4 weeks during Treatment Period 1 or 2.

Reporting group title	Plenadren

Reporting group description:

Participants received Plenadren 25 mg on waking up (typically between 06:00 and 08:00 hours) for 4 weeks during Treatment Period 1 or 2.

Serious adverse events	Chronocort	Plenadren	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 58 (5.17%)	1 / 56 (1.79%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Endocrine disorders			
Adrenocortical insufficiency acute			
subjects affected / exposed	3 / 58 (5.17%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Influenza			
subjects affected / exposed	1 / 58 (1.72%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			

subjects affected / exposed	1 / 58 (1.72%)	0 / 56 (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	Plenadren	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	43 / 58 (74.14%)	47 / 56 (83.93%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign breast neoplasm			
subjects affected / exposed	1 / 58 (1.72%)	0 / 56 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Hot flush			
subjects affected / exposed	2 / 58 (3.45%)	0 / 56 (0.00%)	
occurrences (all)	2	0	
Hypertension			
subjects affected / exposed	1 / 58 (1.72%)	0 / 56 (0.00%)	
occurrences (all)	1	0	
Hypotension			
subjects affected / exposed	0 / 58 (0.00%)	1 / 56 (1.79%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 58 (1.72%)	2 / 56 (3.57%)	
occurrences (all)	1	2	
Fatigue			
subjects affected / exposed	12 / 58 (20.69%)	25 / 56 (44.64%)	
occurrences (all)	13	35	
Malaise			
subjects affected / exposed	0 / 58 (0.00%)	4 / 56 (7.14%)	
occurrences (all)	0	5	
Oedema peripheral			

subjects affected / exposed	1 / 58 (1.72%)	1 / 56 (1.79%)	
occurrences (all)	1	1	
Therapeutic response unexpected			
subjects affected / exposed	1 / 58 (1.72%)	0 / 56 (0.00%)	
occurrences (all)	1	0	
Thirst			
subjects affected / exposed	0 / 58 (0.00%)	1 / 56 (1.79%)	
occurrences (all)	0	1	
Vaccination site pain			
subjects affected / exposed	1 / 58 (1.72%)	0 / 56 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	1 / 58 (1.72%)	0 / 56 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Breast mass			
subjects affected / exposed	1 / 58 (1.72%)	0 / 56 (0.00%)	
occurrences (all)	1	0	
Breast pain			
subjects affected / exposed	1 / 58 (1.72%)	0 / 56 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 58 (3.45%)	1 / 56 (1.79%)	
occurrences (all)	2	1	
Epistaxis			
subjects affected / exposed	1 / 58 (1.72%)	0 / 56 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal pain			
subjects affected / exposed	2 / 58 (3.45%)	3 / 56 (5.36%)	
occurrences (all)	2	3	
Rhinorrhoea			
subjects affected / exposed	1 / 58 (1.72%)	0 / 56 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			

Anxiety			
subjects affected / exposed	1 / 58 (1.72%)	0 / 56 (0.00%)	
occurrences (all)	6	0	
Depressed mood			
subjects affected / exposed	1 / 58 (1.72%)	0 / 56 (0.00%)	
occurrences (all)	1	0	
Emotional distress			
subjects affected / exposed	0 / 58 (0.00%)	1 / 56 (1.79%)	
occurrences (all)	0	1	
Insomnia			
subjects affected / exposed	3 / 58 (5.17%)	1 / 56 (1.79%)	
occurrences (all)	3	1	
Nervousness			
subjects affected / exposed	0 / 58 (0.00%)	1 / 56 (1.79%)	
occurrences (all)	0	1	
Sleep disorder			
subjects affected / exposed	1 / 58 (1.72%)	0 / 56 (0.00%)	
occurrences (all)	1	0	
Stress			
subjects affected / exposed	1 / 58 (1.72%)	2 / 56 (3.57%)	
occurrences (all)	5	2	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 58 (0.00%)	1 / 56 (1.79%)	
occurrences (all)	0	1	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 58 (0.00%)	1 / 56 (1.79%)	
occurrences (all)	0	1	
Blood bilirubin increased			
subjects affected / exposed	1 / 58 (1.72%)	0 / 56 (0.00%)	
occurrences (all)	1	0	
Blood glucose increased			
subjects affected / exposed	1 / 58 (1.72%)	0 / 56 (0.00%)	
occurrences (all)	1	0	
Blood phosphorus increased			

subjects affected / exposed	1 / 58 (1.72%)	0 / 56 (0.00%)	
occurrences (all)	1	0	
Blood thyroid stimulating hormone increased			
subjects affected / exposed	0 / 58 (0.00%)	1 / 56 (1.79%)	
occurrences (all)	0	1	
Blood urine present			
subjects affected / exposed	1 / 58 (1.72%)	0 / 56 (0.00%)	
occurrences (all)	2	0	
Haematocrit decreased			
subjects affected / exposed	0 / 58 (0.00%)	1 / 56 (1.79%)	
occurrences (all)	0	1	
Haemoglobin decreased			
subjects affected / exposed	0 / 58 (0.00%)	1 / 56 (1.79%)	
occurrences (all)	0	1	
Hepatic enzyme increased			
subjects affected / exposed	1 / 58 (1.72%)	0 / 56 (0.00%)	
occurrences (all)	1	0	
Low density lipoprotein increased			
subjects affected / exposed	0 / 58 (0.00%)	2 / 56 (3.57%)	
occurrences (all)	0	2	
White blood cells urine			
subjects affected / exposed	2 / 58 (3.45%)	0 / 56 (0.00%)	
occurrences (all)	3	0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 58 (1.72%)	0 / 56 (0.00%)	
occurrences (all)	1	0	
Joint injury			
subjects affected / exposed	1 / 58 (1.72%)	0 / 56 (0.00%)	
occurrences (all)	1	0	
Meniscus injury			
subjects affected / exposed	0 / 58 (0.00%)	1 / 56 (1.79%)	
occurrences (all)	0	1	
Muscle strain			

subjects affected / exposed	1 / 58 (1.72%)	0 / 56 (0.00%)	
occurrences (all)	1	0	
Post vaccination syndrome			
subjects affected / exposed	2 / 58 (3.45%)	0 / 56 (0.00%)	
occurrences (all)	2	0	
Product dose omission in error			
subjects affected / exposed	1 / 58 (1.72%)	0 / 56 (0.00%)	
occurrences (all)	1	0	
Road traffic accident			
subjects affected / exposed	0 / 58 (0.00%)	1 / 56 (1.79%)	
occurrences (all)	0	1	
Vaccination complication			
subjects affected / exposed	1 / 58 (1.72%)	0 / 56 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 58 (1.72%)	1 / 56 (1.79%)	
occurrences (all)	3	1	
Palpitations			
subjects affected / exposed	1 / 58 (1.72%)	0 / 56 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Brain fog			
subjects affected / exposed	2 / 58 (3.45%)	1 / 56 (1.79%)	
occurrences (all)	3	1	
Dizziness			
subjects affected / exposed	5 / 58 (8.62%)	3 / 56 (5.36%)	
occurrences (all)	7	7	
Dysgeusia			
subjects affected / exposed	1 / 58 (1.72%)	1 / 56 (1.79%)	
occurrences (all)	1	1	
Headache			
subjects affected / exposed	14 / 58 (24.14%)	15 / 56 (26.79%)	
occurrences (all)	19	19	
Lethargy			

subjects affected / exposed	1 / 58 (1.72%)	1 / 56 (1.79%)	
occurrences (all)	1	1	
Memory impairment			
subjects affected / exposed	0 / 58 (0.00%)	1 / 56 (1.79%)	
occurrences (all)	0	1	
Migraine			
subjects affected / exposed	1 / 58 (1.72%)	3 / 56 (5.36%)	
occurrences (all)	2	3	
Paraesthesia			
subjects affected / exposed	1 / 58 (1.72%)	1 / 56 (1.79%)	
occurrences (all)	1	1	
Restless legs syndrome			
subjects affected / exposed	1 / 58 (1.72%)	0 / 56 (0.00%)	
occurrences (all)	1	0	
Somnolence			
subjects affected / exposed	0 / 58 (0.00%)	1 / 56 (1.79%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 58 (5.17%)	1 / 56 (1.79%)	
occurrences (all)	3	1	
Abdominal pain upper			
subjects affected / exposed	0 / 58 (0.00%)	3 / 56 (5.36%)	
occurrences (all)	0	4	
Constipation			
subjects affected / exposed	1 / 58 (1.72%)	0 / 56 (0.00%)	
occurrences (all)	1	0	
Dental caries			
subjects affected / exposed	1 / 58 (1.72%)	0 / 56 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	6 / 58 (10.34%)	3 / 56 (5.36%)	
occurrences (all)	7	3	
Dyspepsia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 56 (1.79%)	
occurrences (all)	0	1	

Gastrointestinal disorder			
subjects affected / exposed	0 / 58 (0.00%)	1 / 56 (1.79%)	
occurrences (all)	0	1	
Gingival bleeding			
subjects affected / exposed	0 / 58 (0.00%)	1 / 56 (1.79%)	
occurrences (all)	0	1	
Lip swelling			
subjects affected / exposed	1 / 58 (1.72%)	0 / 56 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	6 / 58 (10.34%)	7 / 56 (12.50%)	
occurrences (all)	8	7	
Toothache			
subjects affected / exposed	0 / 58 (0.00%)	1 / 56 (1.79%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	0 / 58 (0.00%)	2 / 56 (3.57%)	
occurrences (all)	0	2	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 58 (0.00%)	1 / 56 (1.79%)	
occurrences (all)	0	1	
Hyperhidrosis			
subjects affected / exposed	0 / 58 (0.00%)	2 / 56 (3.57%)	
occurrences (all)	0	2	
Night sweats			
subjects affected / exposed	1 / 58 (1.72%)	0 / 56 (0.00%)	
occurrences (all)	1	0	
Pruritus			
subjects affected / exposed	1 / 58 (1.72%)	0 / 56 (0.00%)	
occurrences (all)	1	0	
Rash			
subjects affected / exposed	0 / 58 (0.00%)	1 / 56 (1.79%)	
occurrences (all)	0	1	
Endocrine disorders			

Adrenocortical insufficiency acute			
subjects affected / exposed	1 / 58 (1.72%)	1 / 56 (1.79%)	
occurrences (all)	1	1	
Glucocorticoid deficiency			
subjects affected / exposed	0 / 58 (0.00%)	1 / 56 (1.79%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 58 (5.17%)	1 / 56 (1.79%)	
occurrences (all)	3	2	
Back pain			
subjects affected / exposed	0 / 58 (0.00%)	2 / 56 (3.57%)	
occurrences (all)	0	2	
Flank pain			
subjects affected / exposed	1 / 58 (1.72%)	0 / 56 (0.00%)	
occurrences (all)	1	0	
Muscle tightness			
subjects affected / exposed	0 / 58 (0.00%)	2 / 56 (3.57%)	
occurrences (all)	0	2	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 58 (1.72%)	0 / 56 (0.00%)	
occurrences (all)	1	0	
Myalgia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 56 (1.79%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	2 / 58 (3.45%)	3 / 56 (5.36%)	
occurrences (all)	3	4	
Sacral pain			
subjects affected / exposed	0 / 58 (0.00%)	1 / 56 (1.79%)	
occurrences (all)	0	1	
Synovial cyst			
subjects affected / exposed	0 / 58 (0.00%)	1 / 56 (1.79%)	
occurrences (all)	0	1	
Infections and infestations			

COVID-19			
subjects affected / exposed	5 / 58 (8.62%)	1 / 56 (1.79%)	
occurrences (all)	6	1	
Conjunctivitis			
subjects affected / exposed	1 / 58 (1.72%)	0 / 56 (0.00%)	
occurrences (all)	1	0	
Furuncle			
subjects affected / exposed	0 / 58 (0.00%)	1 / 56 (1.79%)	
occurrences (all)	0	1	
Gastroenteritis			
subjects affected / exposed	1 / 58 (1.72%)	0 / 56 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal infection			
subjects affected / exposed	0 / 58 (0.00%)	1 / 56 (1.79%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	8 / 58 (13.79%)	5 / 56 (8.93%)	
occurrences (all)	9	5	
Oral herpes			
subjects affected / exposed	1 / 58 (1.72%)	1 / 56 (1.79%)	
occurrences (all)	1	1	
Upper respiratory tract infection			
subjects affected / exposed	1 / 58 (1.72%)	1 / 56 (1.79%)	
occurrences (all)	1	1	
Urinary tract infection			
subjects affected / exposed	1 / 58 (1.72%)	1 / 56 (1.79%)	
occurrences (all)	1	1	
Viral infection			
subjects affected / exposed	1 / 58 (1.72%)	1 / 56 (1.79%)	
occurrences (all)	1	1	
Metabolism and nutrition disorders			
Abnormal loss of weight			
subjects affected / exposed	0 / 58 (0.00%)	1 / 56 (1.79%)	
occurrences (all)	0	1	
Decreased appetite			

subjects affected / exposed	0 / 58 (0.00%)	2 / 56 (3.57%)	
occurrences (all)	0	2	
Hyperlipidaemia			
subjects affected / exposed	1 / 58 (1.72%)	0 / 56 (0.00%)	
occurrences (all)	1	0	
Increased appetite			
subjects affected / exposed	0 / 58 (0.00%)	1 / 56 (1.79%)	
occurrences (all)	0	1	
Salt craving			
subjects affected / exposed	0 / 58 (0.00%)	1 / 56 (1.79%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 March 2021	During the feasibility assessment and set-up of the study, some changes to the evaluations specified in the protocol were agreed to ensure the study could be run in line with local practice and in line with the published quality of life (QoL) tools. These comprised the following: 1) Urinalysis added to the safety laboratory tests. 2) Clarified that pregnancy tests should be conducted on a urine sample. 3) Timing of QoL assessments amended to specify when the questionnaires should be completed in relation to waking in the morning. 4) AddiQoL questionnaire changed from weekly assessment to every 4 weeks. 5) Clarification added for what should happen if a participant receives a coronavirus disease 2019 (COVID-19) vaccine. 6) Example VAS updated with specific VASs for each treatment period. 7) Requirement for a blood sample for plasma renin activity or plasma renin concentration removed. 8) The requirement for adverse event of special interests (AESIs) to be reported and followed up in the same way as serious adverse events (SAEs) removed. 9) Clarified that SAE reporting was to be conducted using a paper SAE form not an electronic data collection tool.
04 May 2021	Provisions for remote monitoring were added in the case of continued pandemic procedures. 1) Number of sites increased to 6 sites in 2 countries. 2) Clarified that participants with type 2 diabetes receiving regular insulin were excluded. 3) Clarified that participants receiving daily inhaled, topical, nasal, or oral steroids for any indication other than adrenal insufficiency were excluded. 4) Participants taking sleeping medication added to the exclusion criteria. 5) Requirement for SAEs on Plenadren to be reported to the Marketing Authorisation Holder was removed. 6) New section added on remote monitoring visits.
17 November 2021	Changes to the protocol were made following review of the protocol by the regulatory authorities. Updates to the blood volume were also made following recalculation in the laboratory manual. 1) Non-high-density lipoprotein (HDL) cholesterol was removed from the assessments since this test was not performed by the central laboratory. 2) Added that any visit (home or on-site) should be delayed if the participant was stress dosing. 3) Clarified that only treatment-related SAEs occurring after the 30-day follow-up period needed to be reported and followed up. 4) Windows added for blood and saliva sampling. 5) Clarified that if the Day 29 or 57 visits were delayed, the collection of saliva and urine samples, the completion of QoL questionnaires (except the daily PROMIS 7b) were delayed until the day before the rescheduled visit. 6) Details of approval of Chronocort in the European Union (EU) added, along with the tradename of Efmody. 7) New criterion added to exclude participants with a known hypersensitivity to any of the components of the Chronocort capsules, the Plenadren tablets, the Chronocort placebo, or the Plenadren placebo. 8) Requirement for participants to fast before the 07:00 hour blood sampling point removed. 8) Added that hydrocortisone can interact with cytochrome P3A4 (CYP3A4) inhibitors and inducers so since dose adjustment was not allowed, inclusion of participants taking these medications was to be discussed with the Medical Monitor. 9) Blood volumes required updated in line with updates to the laboratory manual. 10) Clarified that all SAEs had to be reported immediately rather than within 24 hours. 11) Timepoints for the serum cortisol assessments corrected.

30 March 2022	The following changes were made to the protocol: 1) A window of +3 days was added around the Day 29 and Day 57 visits to allow flexibility of visits around weekends etc. 2) Clarified that scheduling delays due to stress dosing were not limited to the window of 3 days noted above, and in these cases the visit should be scheduled at the soonest date feasible for the participant after 48 hours free from any stress doses. 3) Early morning pre-dose serum sample amended to specify collection time of 07:00 hours (±15 minutes). 4) Clarified that osteocalcin, Apo A-I, Apo-B and Lp(a) were not required at the Screening Visit. 5) Added that on Days 20, 21, 27, and 28 of Treatment Period 1 and Days 48, 49, 55 and 56 of Treatment Period 2, the morning dose of study drug was to be taken at 07:00 hours and the evening dose of study drug taken at 23:00 hours to ensure accurate pharmacokinetic (PK) measurements could be taken. 6) Added that if the Day 29 and Day 57 study visits were delayed, then the completion of QoL questionnaires (with the exception of the daily PROMIS 7b which was to continue to be completed daily), were also to be delayed until the day before the rescheduled visit. These assessments were then also moved out accordingly at subsequent visits. 7) Added that participants took their last dose of standard of care in the afternoon of Day 1, and the first dose of their allocated Treatment Period 1 investigational medicinal product (IMP) in the evening of Day 1. 8) Added that participants were to take their last dose of Treatment Period 1 IMP in the morning of Day 29, and the first dose of their allocated Treatment Period 2 IMP in the morning of Day 29, and the first dose of their allocated Treatment Period 2 IMP in the evening of Day 29.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported