Title Page

Protocol Title: 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

Study Name: CONnECT

Protocol Number: DIUR-014

Compound: Chronocort®

Study Phase: 3

Short Title: Double-blind comparison of Chronocort versus standard hydrocortisone replacement therapy in participants aged 16 years and over with congenital adrenal hyperplasia

Sponsor Name: Diurnal Ltd

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This protocol is based on the TransCelerate protocol template:
https://www.transceleratebiopharmainc.com/assets/clinical-content-reuse-solutions/

Sponsor Signatory:

[redacted]

03-Nov-2023 | 10:27 GMT

[redacted]

Date

The Investigator agreement pages are provided as stand-alone documents.

The medical monitor's name and contact information will be provided separately.

Protocol Amendment Summary of Changes

DOCUMENT HISTORY	
Document	**Date**
Amendment 6	30-Oct-2023
Amendment 5	09-Feb-2023
Amendment 4	23-Mar-2022
Amendment 3	04-Mar-2022
Amendment 2	27-Jan-2022
Amendment 1	04-May-2021
Original Protocol	16-Apr-2021

Amendment 6 (30-Oct-2023)

Overall Rationale for the Amendment:

After finalization of amendment 5, it was noted that in some places the non-inferiority margin still stated 10% instead of the updated 15%, so this was corrected. In addition, a few small clarifications were made to reflect the study procedures. All the changes are marked in the tracked changes version of the protocol, with the key changes summarized below:

Section # and Name	Description of Change	Brief Rationale
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Section # and Name	Description of Change	Brief Rationale
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

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1. Protocol Summary

1.1. Synopsis

Protocol Title: 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

Study Name: CONnECT

Short Title: Double-blind comparison of Chronocort versus standard hydrocortisone replacement therapy in participants aged 16 years and over with congenital adrenal hyperplasia

Rationale: Congenital adrenal hyperplasia (CAH) is most commonly caused by 21-hydroxylase deficiency that results in cortisol deficiency and androgen excess, with or without aldosterone deficiency. Patients are currently treated with glucocorticoid replacement therapy, but immediate-release formulations fail to replicate the natural cortisol circadian rhythm, and patients often struggle to take an afternoon dose, resulting in patients being poorly controlled. Chronocort is a newly developed modified release oral formulation of hydrocortisone, and it is designed to closely replicate the normal serum levels of the endogenous cortisol circadian rhythm, offering the prospect of an improved treatment outcome and a novel treatment paradigm. The proposed study will evaluate whether a twice daily dosing regimen of Chronocort, with two-thirds of the total daily dose given at night and one-third in the morning (the 'toothbrush regimen'), which can more closely replicate circadian cortisol levels, will improve control of adrenal androgen production (as measured by 17-hydroxyprogesterone [17-OHP] and androstenedione [A4] concentrations) compared to a similarly titrated regimen of twice daily immediate-release hydrocortisone replacement therapy (IRHC) in conditions broadly resembling routine clinical practice.

Objectives, Outcome Variables, and Analyses

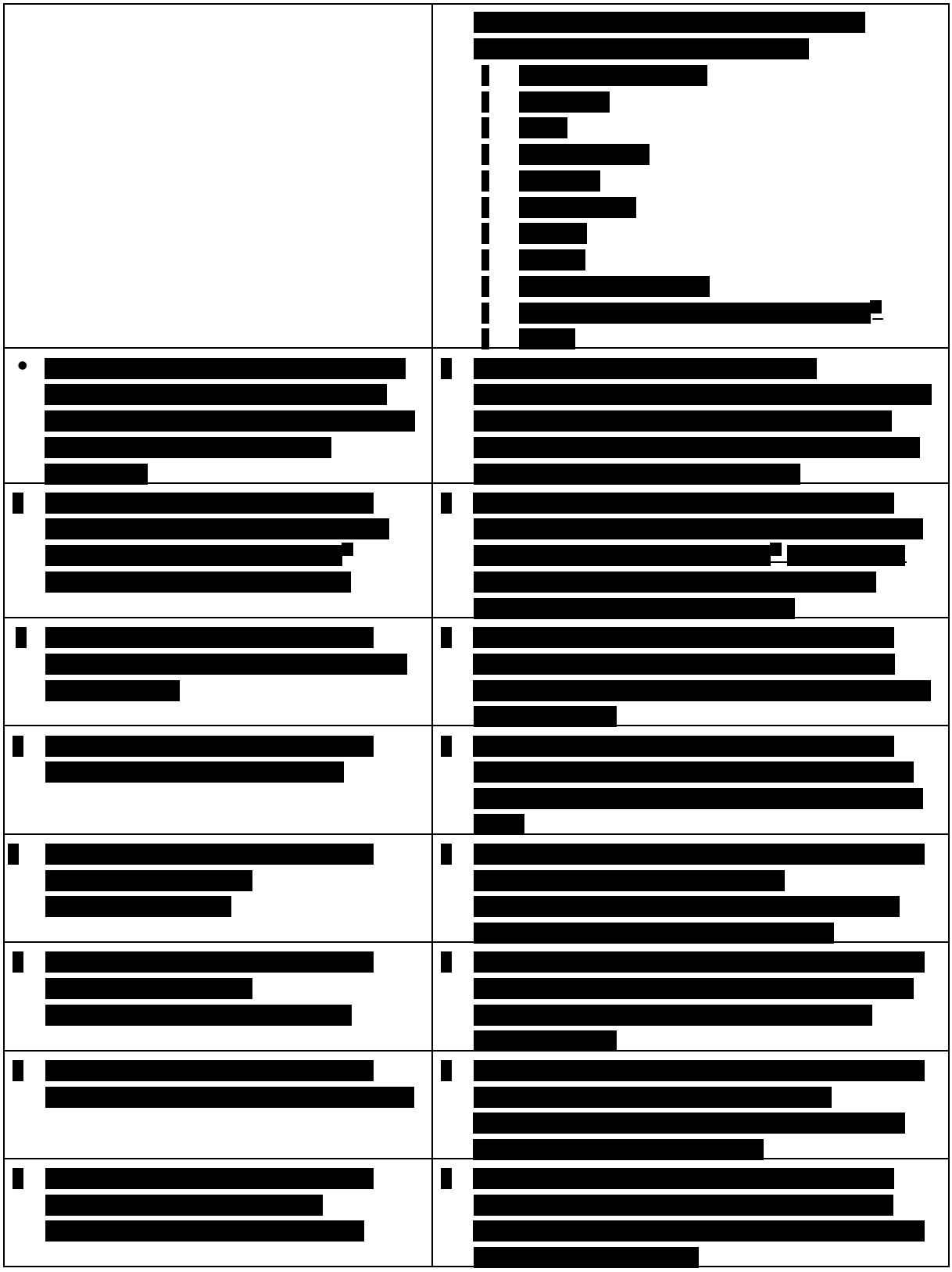
Objectives	Outcome Variable and Analyses Supporting the Objectives
Primary Efficacy	
• To compare Chronocort to IRHC in terms of biochemical responder rate after 28 weeks of randomized treatment.	• The primary efficacy outcome variable is <u>whether or not the participant is a biochemical responder after 28 weeks of randomized treatment.</u> A biochemical responder is a participant who: i) is in biochemical control at the 08:00 hours assessment after 28 weeks of randomized treatment (where in biochemical control is defined as both a 17-OHP concentration equal to or below the upper limit for optimal control and an A4 concentration equal to or below the upper limit of the reference range), and ii) is receiving after 28 weeks of randomized treatment 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). The difference (Chronocort minus IRHC) between the proportion of participants in each treatment arm who are biochemical responders 28 weeks after randomization will be estimated in the full analysis set (FAS). Participants who die or withdraw from treatment before 28 weeks will be classified as not a biochemical responder. Participants receiving rescue medication under the 'stress dosing rules' within 5 days before the scheduled visit at 28 weeks after randomization will have their visit delayed appropriately[1]. Biochemical non-inferiority of Chronocort to IRHC will be declared if the 95% confidence interval (CI) for the difference in proportions lies wholly above minus 15 percentage points.
Key Secondary Efficacy	
• 1) To compare Chronocort to IRHC in terms of dose responder rate after 28 weeks of randomized treatment.	• The first key secondary efficacy outcome variable is <u>whether or not the participant is a dose responder after 28 weeks of randomized treatment.</u> A dose responder is a participant who: i) is receiving after 28 weeks of randomized treatment a total daily dose of hydrocortisone of not more than 25 mg, and ii) is in biochemical control at the 08:00 hours assessment after 28 weeks of randomized treatment (where in biochemical control is defined as both a 17-OHP concentration equal to or below the upper limit for optimal control and an A4 concentration equal to or below the upper limit of the reference range). The difference (Chronocort minus IRHC) between the proportion of participants in each treatment arm who are dose responders 28 weeks after randomization will be estimated in the FAS. Participants who die or withdraw from treatment before 28 weeks will be classified as not a dose responder. Participants receiving rescue medication under the 'stress dosing rules' within 5 days before the scheduled visit at 28 weeks after randomization will have their visit delayed appropriately[1]. Dose superiority of Chronocort to IRHC will be declared if the 95% CI for the difference in proportions lies wholly above zero, provided that biochemical non-inferiority of Chronocort to IRHC has been declared under the primary efficacy objective.

• 2) To compare Chronocort to IRHC in terms of total daily dose after 28 weeks of randomized treatment.	• The second key secondary efficacy outcome variable is the total daily dose (mg) after 28 weeks of randomized treatment. The difference (Chronocort minus IRHC) between the mean total daily dose after 28 weeks of randomized treatment in each treatment arm will be estimated in the FAS. Superiority of Chronocort to IRHC with respect to total daily dose after 28 weeks of randomized treatment will be declared if the 95% CI for the difference in means lies wholly below zero, provided that dose superiority of Chronocort to IRHC has been declared under the first key secondary efficacy objective.
Other Secondary Efficacy	
• To compare Chronocort to IRHC in terms of biochemical responders at 4, 10, and 16 weeks after randomization.	• The outcome variables whether or not the participant is a biochemical responder at 08:00 hours at 4, 10, and 16 after randomization are compared between treatment arms by calculating the difference in proportion of participants responding. These outcome variables are to be analyzed in the same manner as the primary efficacy outcome variable.
• To compare Chronocort to IRHC in terms of dose responders at 10 and 16 weeks after randomization.	• The outcome variables whether or not the participant is a dose responder at 08:00 hours at 10 and 16 weeks after randomization are compared between treatment arms by calculating the difference in proportion of participants responding. These outcome variables are to be analyzed in the same manner as the first key secondary outcome variable.
• To compare Chronocort to IRHC in terms of total daily dose at 10 and 16 weeks after randomization.	• The outcome variables total daily dose at 10 and 16 weeks after randomization are compared between treatment arms by calculating the difference in mean total daily dose. These outcome variables are to be analyzed in the same manner as the second key secondary outcome variable.
• To compare Chronocort to IRHC in terms of biochemical control at 4, 10, 16, and 28 weeks after randomization.	• The outcome variables whether or not the participant is in biochemical control (provided total daily dose is not more than 30 mg) at 08:00 hours at 4, 10, 16, and 28 weeks after randomization are compared between treatment arms by calculating the difference in proportion of participants in control.

• To compare Chronocort to IRHC in terms of the impact on 17-OHP range.	• The difference in range as calculated as the difference between the 08:00 and 13:00 measurements of 17-OHP levels at 4, 10, 16, and 28 weeks after randomization and their changes from baseline will be summarized and compared between treatment arms.
• To compare Chronocort to IRHC in terms of the impact on A4 range.	• The difference in range as calculated as the difference between the 08:00 and 13:00 measurements of A4 levels at 4, 10, 16, and 28 weeks after randomization and their changes from baseline will be summarized and compared between treatment arms.
• To compare Chronocort to IRHC in terms of the impact on mean 17-OHP and A4.	• The mean of the 08:00 and 13:00 measurements of 17-OHP levels and A4 levels at 4, 10, 16, and 28 weeks after randomization and their changes from baseline will be summarized and compared between treatment arms.
• To compare Chronocort to IRHC in terms of the impact on glucocorticoid dose.	• The total daily glucocorticoid dose at 4, 10, 16, and 28 weeks after randomization will be summarized and compared between treatment arms. • The relationship between daily glucocorticoid dose and biochemical control at 28 weeks after randomization will be explored.
• To compare Chronocort to IRHC in terms of changes in menstrual regularity.	• The change from baseline to 4, 10, 16, and 28 weeks of randomized treatment in menstrual regularity (only in pre-menopausal women without hysterectomy and not using hormonal contraception) will be summarized and compared between treatment arms.
• To compare Chronocort to IRHC in terms of the impact on luteinizing hormone (LH) levels.	• The change from baseline to 4, 10, 16, and 28 weeks of randomized treatment in LH levels (men only) will be summarized and compared between treatment arms.
• To compare Chronocort to IRHC in terms of the impact on testicular adrenal rest tumor (TART) size.	• The change from baseline to 28 weeks of randomized treatment in size of TART (men only) will be summarized and compared between treatment arms.
• To compare Chronocort to IRHC in terms of the impact on sperm count.	• The change from baseline to 28 weeks of randomized treatment in sperm count (men only) will be summarized and compared between treatment arms.
• To compare Chronocort to IRHC in terms of the impact on subjective hirsutism in female participants.	• The change from baseline to 4, 10, 16, and 28 weeks of randomized treatment in subjective hirsutism using a visual analog scale (VAS) (women only) will be summarized and compared between treatment arms.

• To compare Chronocort to IRHC in terms of the impact on objective hirsutism in female participants.	• The change from baseline to 4, 10, 16, and 28 weeks of randomized treatment in objective hirsutism using the Ferriman-Gallwey score (women only) will be summarized and compared between treatment arms.
• To compare Chronocort to IRHC in terms of the impact on subjective acne in female participants.	• The change from baseline to 4, 10, 16, and 28 weeks of randomized treatment in subjective acne using a VAS (women only) will be summarized and compared between treatment arms.
• To compare Chronocort to IRHC in terms of the impact on objective acne in female participants.	• The change from baseline to 4, 10, 16, and 28 weeks of randomized treatment in objective acne using the Global Evaluation Acne (GEA) scale (women only) will be summarized and compared between treatment arms.
• To compare Chronocort to IRHC in terms of the impact on glycated hemoglobin (HbA1c) levels.	• The change from screening to 4, 10, 16, and 28 weeks of randomized treatment in HbA1c levels will be summarized and compared between treatment arms.
• To compare Chronocort to IRHC in terms of the impact on waist circumference.	• The change from baseline to 4, 10, 16, and 28 weeks of randomized treatment in waist circumference will be summarized and compared between treatment arms.
• To compare Chronocort to IRHC in terms of the impact on body weight.	• The change from baseline to 4, 10, 16, and 28 weeks of randomized treatment in body weight will be summarized and compared between treatment arms.
• To compare Chronocort to IRHC in terms of the impact on quality of life (QoL) using the self-completed Medical Outcome Study 36-Item Short Form Health Survey (SF-36®) total score and the sub-domain of vitality.	• The change from baseline to 4, 10, 16, and 28 weeks of randomized treatment in QoL using the self-completed SF-36® total score and the sub-domain of vitality will be summarized and compared between treatment arms.
• To compare Chronocort to IRHC in terms of the impact on QoL using the Multidimensional Assessment of Fatigue (MAF).	• The change from baseline to 4, 10, 16, and 28 weeks of randomized treatment in QoL using the MAF will be summarized and compared between treatment arms.
• To compare Chronocort to IRHC in terms of the impact on QoL using the 5-level Standardized Health Questionnaire (EQ-5D-5L™).	• The change from baseline to 4, 10, 16, and 28 weeks of randomized treatment in QoL using the EQ-5D-5L™ will be summarized and compared between treatment arms.
Compliance	
• To assess compliance over the study period.	• The percentage treatment compliance between visits and overall will be summarized.
Exploratory Efficacy	
• [redacted]	[redacted]



• [redacted]	[redacted]
[redacted]	[redacted]
Safety	
• To assess the safety and tolerability of Chronocort relative to IRHC.	• The incidence, nature, severity, relatedness, duration, outcome, seriousness and expectedness of treatment-emergent adverse events (TEAEs) will be tabulated by treatment arm. Adverse events (AEs) of special interest will additionally be tabulated separately, with particular note of adrenal crises.
• To assess the need for use of additional glucocorticoid doses (stress dosing rules).	• The use of medication from the stress dosing packs or use of any additional glucocorticoid treatment during the study will be tabulated by treatment arm.
• To evaluate the safety of Chronocort compared to IRHC by assessment of routine safety laboratory assessments, physical examination, vital signs, and electrocardiogram (ECG).	• Safety hematology, biochemistry, urinalysis, and vital signs conducted at each post-randomization visit and the physical examination and ECG assessments conducted after 28 weeks of randomized treatment, and their changes from baseline, will be summarized by treatment arm.

[1] This description aligns with the International Council for Harmonization (ICH) E9 requirement for the definition of an Estimand.
Outcome variables are underlined.
Note: The reference range for A4 is up to 150 ng/dL (5.2 nmol/L) for men and up to 200 ng/dL (7.0 nmol/L) for women (based on the luteal phase) (based on data from The Mayo Clinic).
The optimal range for 17-OHP in adults (post-pubertal males or females aged >16 years) is up to 1200 ng/dL (36.4 nmol/L).

Overall Design: This study is a randomized, double-blind, active-controlled, titrated, parallel arm, multicenter study. It will compare the efficacy, safety and tolerability of twice daily Chronocort with twice daily IRHC (Cortef®) over a randomized treatment period of up to 28 weeks in participants aged 16 years and over with known classic CAH due to 21-hydroxylase deficiency. The primary efficacy assessment of biochemical responder rate and the key secondary assessments of dose responder rate and mean total daily dose will be assessed after 28 weeks of randomized treatment.

Participants will attend a screening visit 4 weeks prior to the baseline visit. Participants will be asked to take their usual medication at the usual times up until the screening visit, with details of the dosing regimen and the timing of doses of CAH medication recorded throughout the screening visit and for the previous 24 hours. At this screening visit, informed consent/assent will be obtained and then the screening assessments will be conducted. Participants will then be switched to 20 mg IRHC in the morning on waking (typically between 06:00 and 08:00 hours) and 10 mg in the afternoon (between 15:00 and 17:00 hours) for the next 4 weeks as run-in therapy. This total daily dose is based on the guidelines for adrenal replacement, where the recommended dose is between 15 and 25 mg, plus an

acknowledgement that patients with CAH may need a higher dose [Speiser et al. 2018]. This total daily dose was safely used in the Chronocort Phase 2 and 3 studies and equates to the dose used in large cohort studies [Arlt et al, 2010; Finkielstain et al, 2012].

After 4 weeks on this run-in therapy, participants will attend a baseline visit for all the baseline assessments. If at the end of the 4-week run-in period there are persistent signs of adrenal insufficiency, or the participant does not tolerate treatment, then they should be withdrawn from the study before randomization. Assessment of baseline androgen levels (17-OHP and A4) will be made at 08:00 hours before the morning dose of IRHC and at 13:00 hours, with a window of ±30 minutes allowed around each sampling timepoint. These baseline adrenal androgens will be analyzed by the central laboratory and participants with 17-OHP equal to or below the upper limit for optimal control at 08:00 hours and A4 equal to or below the upper limit of the reference range at 08:00 hours will be subsequently classified as 'in biochemical control' during the analysis. If the measurements are outside these criteria the participant will be classified as 'not in biochemical control' during the analysis. Once eligibility for the study is confirmed, the Investigator will then randomize the participants on a 1:1 basis (Chronocort:IRHC) using an interactive response technology (IRT) system, with randomization being stratified within each treatment arm based on fludrocortisone replacement status (requires fludrocortisone or does not require fludrocortisone). Note: the results of the baseline androgen tests are NOT needed prior to the participant being randomized to the study. The IRT will also be programmed with blind-breaking instructions.

Participants randomized to Chronocort will change to a dosing regimen of 10 mg in the morning on waking (typically between 06:00 and 08:00 hours) and 20 mg at night just prior to going to bed (typically between 22:00 hours and midnight). Participants randomized to IRHC will continue the same dosing regimen as they were receiving during the run-in period (20 mg in the morning on waking [typically between 06:00 and 08:00 hours] and 10 mg in the afternoon [between 15:00 and 17:00 hours]). To ensure blinding of the study, both study treatments will be over-encapsulated and placebo capsules will also be used, so participants will take a combination of capsules (active and placebo) in the morning on waking, in the afternoon, and in the evening before going to bed (i.e., three times daily). The time of the first dose of randomized medication on Day 1 will be recorded in an electronic participant diary.

Participants will return to the study site for titration visits at 4, 10, and 16 weeks after randomization, with androgen levels assessed at each of these visits at 08:00 hours (before the morning dose of study medication) and 13:00 hours (±30 minutes). After each of these 3 visits, dose reductions (in 5 mg steps at each visit) can be conducted if required, based on androgen results (17-OHP <300 ng/dL and A4 <150 ng/dL [males] and <200 ng/dL [females]) and adrenal insufficiency symptoms collected using the adrenal insufficiency checklist. The decision to change doses in both treatment groups will be made by an independent blinded physician and the appropriate investigational medicinal product (IMP) packs will be sent to the participant, either to collect from their local study site or sent directly to the participant's home. The treatment packs for each participant will always contain the same number of capsules as the previous supplies (with placebo capsules masking any changes) to maintain the blinding and to ensure the participant is not aware of any dose changes.

Once the titration visit at 16 weeks is complete and the dose subsequently adjusted, if necessary, the dose of study medication will then be fixed and should remain unchanged until

the end of study (EOS) visit (up to 12 weeks of fixed dose treatment) if possible. The last dose of study medication will be taken in the morning of the last dosing day.

The analysis of all 17-OHP and A4 levels will be conducted by a central laboratory and the results will be sent to an independent blinded physician, with the independent blinded physician being unaware of the participant's treatment allocation. The Investigator will also complete an adrenal insufficiency checklist at each visit which will be made available to the independent blinded physician. At the titration visits at 4, 10, and 16 weeks, if the independent blinded physician considers a dose reduction is necessary, the dose should be reduced by a total of 5 mg at each titration visit, as detailed in the dose titration rules in Section 4.2. Each treatment arm will be subject to the same titration rules throughout the study, ensuring that opportunities for optimization and control of androgens are the same in both arms and thus minimizing bias in the management of participants. Note that only dose reductions are permitted at the titration visits at 4, 10, and 16 weeks (unless the dose has previously been reduced, in which case it can be reverted back to the previous higher dose if needed without having to wait until the next titration point). Dose increases can only be made in an urgent situation where the Investigator believes the participant is exhibiting signs of adrenal insufficiency, and in all cases, this should be discussed with the medical monitor before a dose increase is initiated (see Section 4.2 for further details).

The EOS visit will be conducted 28 weeks after randomization or at early withdrawal from the study. The total study duration is up to 40 weeks (screening period up to 4 weeks prior to the screening visit, 4 weeks run-in period on IRHC up to the baseline visit, 16 weeks dose titration on randomized treatment, 12 weeks fixed dose period on randomized treatment, and follow-up phone call 4 weeks/30 days after the EOS visit). In some cases (e.g., if the participant lives a long way from the study site, or if pandemic guidelines dictate) Visits 3 and 4 may be performed as domiciliary visits and IMP shipments can be made directly to the participant's home. However, the following visits must be performed at the study site: Screening (Visit 1), Baseline (Visit 2), Week 16 (Visit 5), and end of treatment/early withdrawal visit (Visit 6). If necessary in some cases, IMP at Visit 5 can also be delivered to the participant's home. If a domiciliary visit is conducted the safety and endocrine blood samples must be sent to the central laboratory for analysis and the Investigator must complete the adrenal insufficiency checklist. The assessment of hirsutism and acne can be conducted via a video call (within ±2 days of the domiciliary visit). If androgen samples are analyzed locally for safety reasons the participant must be withdrawn from treatment.

At the end of the study, participants who have completed the study will be offered the option of continuing in a long-term safety study (DIUR-015) where all participants will receive open-label Chronocort treatment or they will be offered commercial supplies of Chronocort (the options will be dependent on territory), or the participant can return to the standard treatment they were receiving before entry into this study. For participants who agree to enter the long-term safety study DIUR-015, the EOS visit (Visit 6) will be their last assessment in this study. Participants who decide not to enter the long-term safety study or who withdrew from the study early will receive a telephone call 30 days after the last study visit to ask about any AEs that were ongoing and any new serious adverse events (SAEs) that could be related to the study medication. This telephone call will be considered the last assessment for these participants, although ongoing SAEs will be followed until resolution or stabilization, the event is otherwise explained, or the participant is lost to follow-up.

Disclosure Statement: This is a double-blind parallel group treatment study with 2 arms.

Number of Participants: Sufficient participants will be screened to achieve approximately 50 participants randomly assigned to either Chronocort or IRHC (25 participants per treatment arm, regardless of baseline strata), or until a cut-off date of 30 April 2023, whichever is reached first. Individual study sites should not randomize more than 8 participants without first consulting the Sponsor. A sample size of 25 participants per treatment arm will provide at least 80% power to demonstrate non-inferiority of Chronocort to IRHC when the biochemical response rate in the IRHC arm is 40%, the non-inferiority margin is 15% and the biochemical response rate in the Chronocort arm is 68% using a 1-sided continuity corrected z-test with unpooled variance and a 1-sided alpha of 2.5%.

Inclusion/Exclusion Criteria: Participants are eligible to be included in the study only if they meet all the following inclusion criteria and none of the exclusion criteria (note: re-screening is permitted if the Investigator considers that the circumstances leading to screening failure will not be relevant when the participant is re-screened at a later time):

Inclusion Criteria	Exclusion Criteria
Male or female participants must be aged 16 years or older at the time of signing the informed consent/assent.	Clinical or biochemical evidence of hepatic or renal disease e.g., creatinine >2 times the upper limit of normal (ULN) or elevated liver function tests (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] >2 times the ULN).
In participants aged <18 years, height velocity must be less than 2 cm/year in the last year and puberty must be completed (Tanner stage V).	History of bilateral adrenalectomy.
Participants with known classic CAH due to 21-hydroxylase deficiency diagnosed in childhood with documented (at any time) elevated 17-OHP and with or without elevated A4 and currently treated with hydrocortisone, prednisone, prednisolone or dexamethasone (or a combination of the aforementioned glucocorticoids) and on stable glucocorticoid therapy for a minimum of 3 months.	History of malignancy (other than basal cell carcinoma successfully treated >26 weeks prior to entry into the study).
Participants who are receiving fludrocortisone must be on a documented stable dose for a minimum of 3 months prior to enrollment and must have stable renin levels at screening.	Participants who have type 1 diabetes, receive regular insulin, have uncontrolled diabetes, or have a screening HbA1c greater than 8%.
Female participants of childbearing potential and all male participants must agree to the use of an accepted method of contraception during the study.	Persistent signs of adrenal insufficiency or the participant does not tolerate treatment at the end of the 4-week run-in period.

Inclusion Criteria	Exclusion Criteria
A female participant is eligible to participate if she is not pregnant, not breastfeeding, and she is either not a woman of childbearing potential (WOCBP) or has a negative pregnancy test at entry into the study. Note: females presenting with oligomenorrhea or amenorrhea who are aged ≤55 years should be considered potentially fertile and therefore should undergo pregnancy testing like all other female participants.	Participants with any other significant medical or psychiatric conditions that in the opinion of the Investigator would preclude participation in the study.
Capable of giving signed informed consent/assent which includes compliance with requirements and restrictions listed in the informed consent form (ICF) and in this protocol.	Participants on regular daily inhaled, topical, nasal or oral steroids for any indication other than CAH.
	Co-morbid condition requiring daily administration of a medication or consumption of any material that interferes with the metabolism of glucocorticoids.
	Participants who are receiving <10 mg hydrocortisone dose at screening or the hydrocortisone dose equivalent.
	Participants anticipating regular prophylactic use of additional steroids e.g., for strenuous exercise.
	Participation in another clinical study of an investigational or licensed drug or device within the 12 weeks prior to screening.
	Inclusion in any natural history or translational research study that would require evaluation of androgen levels during the study period outside of this protocol's assessments.
	Participants who have previously been exposed to Chronocort in any Diurnal study.
	Participants who routinely work night shifts and so do not sleep during the usual night-time hours.
	Participants, who in the opinion of the Investigator, will be unable to comply with the requirements of the protocol.
	Participants with a known hypersensitivity to any of the components of the Chronocort capsules, the Cortef tablets, or the placebo capsules.
	Participants with congenital galactosemia, malabsorption of glucose and galactose, or who are lactase deficient.
	Participants with a body weight of 45 kg or less.

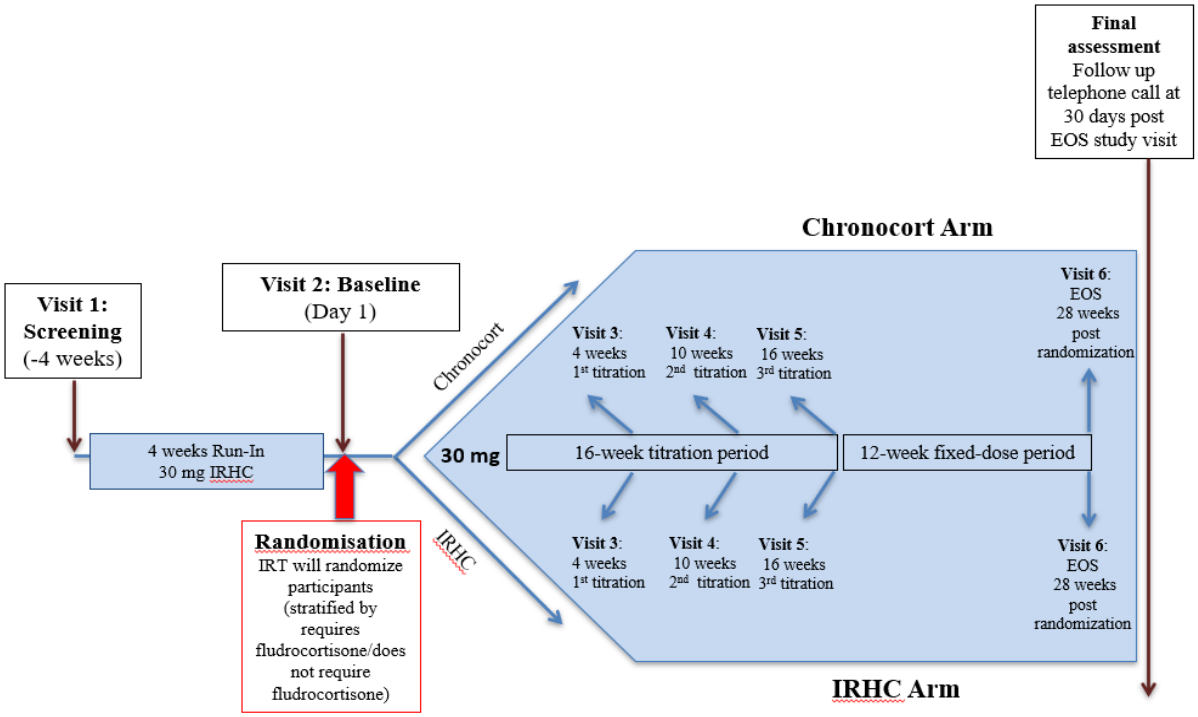
Treatment Groups and Duration: Treatment will continue for a total of 32 weeks (4-week run-in with IRHC, 16-week dose titration to randomized treatment, and 12 weeks fixed dosing period to randomized treatment) or until early withdrawal from the study. Participants will attend the study sites for a total of 6 visits during the study: screening, baseline, Week 4 (titration visit), Week 10 (titration visit), Week 16 (titration visit), and Week 28 (EOS visit). If a participant who was enrolled under an earlier version of the protocol (where the study was up to 52 weeks in duration) had attended Visit 5 at Week 16 and is ongoing treatment, they must continue taking the study medication and must return at 28 weeks for the EOS (Visit 6) assessments. If they have already had more than 28 weeks of treatment then they must return as soon as possible (but not within 4 weeks of previous blood sampling) for the EOS (Visit 6) assessments according to this amendment**.** After completion of the study, participants may join a long-term safety study (Protocol DIUR-015) or they will be offered commercial supplies of Chronocort (the options will be dependent on territory), or they can return to standard glucocorticoid replacement regimen (as determined by the Investigator).

The test IMP for this study is Chronocort (hydrocortisone modified release capsule). In this study Chronocort will be supplied in 2 dose strengths of 5 mg and 10 mg per capsule for oral administration. The capsules will be over-encapsulated to maintain blinding. The comparator IMP for this study is IRHC (Cortef). IRHC will be supplied as 5 mg and 10 mg tablets for oral administration. The tablets will be over-encapsulated to maintain blinding.

In addition, stress dosing packs (Section 6.1.1) will be provided for use in the case of incurrent illness.

Data Safety Management Board: Yes

1.2. Schema



EOS = end of study; IRHC = immediate-release hydrocortisone; IRT = interactive response technology
Note: timelines not to scale

1.3. Schedule of Activities

Description	Screening Visit	Baseline	Titration Visit	Telephone call	Titration Visit	Telephone call	Titration Visit and Start of Fixed Dose Period
Visit Number	**V1**	**V2**	**V3[15]**	**Call T3.1**	**V4[15]**	**Call T4.1**	**V5**
Week	**Week -4**	**Day 1**	**Week 4 + 1 week**	**V3 + 2-5 weeks**	**Week 10 ± 1 week**	**V4 + 2-5 weeks**	**Week 16 ± 1 week**
Consent[1]	X						
Medical history[2]	X						
Concomitant medications[3]	X	X	X	X	X	X	X
Demographic data	X						
Inclusion/exclusion criteria	X	X[13]					
Physical examination	X	X					
Abbreviated physical examination (if indicated by AEs)			X		X		X
Vital signs (blood pressure, heart rate, respiratory rate, temperature)	X	X	X		X		X
17-OHP and A4 (at 08:00 and 13:00 ± 30 minutes)[4]	X	X	X		X		X
Safety laboratory tests (hematology, biochemistry, urinalysis)	X	X	X		X		X
Pregnancy test (females)	X	X	X		X		X
Plasma renin[5]	X						
HbA1c	X		X		X		X
FSH and osteocalcin		X	X		X		X
ECG		X					
QoL (SF-36®, MAF, EQ-5D-5L™)		X	X		X		X
Adrenal insufficiency checklist	X	X	X		X		X
Height, waist circumference, weight	X	X	X		X		X
Assessment of menstrual cycle pattern in females[6] and LH levels in males		X	X		X		X
Hirsutism assessment in female participants using VAS and Ferriman-Gallwey score[7]		X	X		X		X
Acne assessment in female participants[7]		X	X		X		X
TART measurement in male participants by ultrasound[8]		X					
Sperm count in male participants [9]		X					
Treatment preference assessment using VAS[7]							
Alertness assessment using VAS[10]		X	X		X		X
Serum 11-ketotestosterone and DHEA		X					
Serum testosterone		X					
4 weeks run-in IRHC medication	X						
Randomization		X					
Salivary samples for exploratory analysis [11]		X	X		X		X
Dose titration, if required[12]			X		X		X
Recording details of glucocorticoid doses for previous 24 hours and throughout visit	X	X	X		X		X
Adverse events	X	X	X	X	X	X	X
Compliance		X	X		X		X

Description	Telephone call	Telephone Call	End of Study/Early Withrawal Visit	Telephone call
Visit Number	**Call T5.1**	**Call T5.2**	**V6**	**Call T6.1**
Week	**V5 + 2-5 weeks**	**Week 22 ± 2 weeks**	**Week 28 + 1 week from randomization or early termination visit[14]**	**30 days after V6 ± 1 week**
Consent[1]				
Medical history[2]				
Concomitant medications[3]	X	X	X	
Demographic data				
Inclusion/exclusion criteria				
Physical examination			X	
Abbreviated physical examination (if indicated by AEs)				
Vital signs (blood pressure, heart rate, respiratory rate, temperature)			X	
17-OHP and A4 (at 08:00 and 13:00 ± 30 minutes)[4]			X	
Safety laboratory tests (hematology, biochemistry, urinalysis)			X	
Pregnancy test (females)			X	
Plasma renin[5]			X	
HbA1c			X	
FSH and osteocalcin			X	
ECG			X	
QoL (SF-36®, MAF, EQ-5D-5L™)			X	
Adrenal insufficiency checklist			X	
Height, waist circumference, weight			X	
Assessment of menstrual cycle pattern in females[6] and LH levels in males			X	
Hirsutism assessment in female participants using VAS and Ferriman-Gallwey score[7]			X	
Acne assessment in female participants[7]			X	
TART measurement in male participants by ultrasound[8]			X	
Sperm count in male participants [9]			X	
Treatment preference assessment using VAS[7]			X	
Alertness assessment using VAS[10]			X	
Serum 11-ketotestosterone and DHEA			X	
Serum testosterone			X	
4 weeks run-in IRHC medication				
Randomization				
Salivary samples for exploratory analysis [11]			X	
Dose titration, if required[12]				
Recording details of glucocorticoid doses for previous 24 hours and throughout visit			X	
Adverse events	X	X	X	X
Compliance			X	

17-OHP = 17-hydroxyprogesterone; A4 = androstenedione; AE = adverse event; DHEA = dehydroepiandrosterone; ECG = electrocardiogram; EQ-5D-5L™ = 5-level Standardized Health Questionnaire; FSH = follicle stimulating hormone; HbA1c = glycated hemoglobin; IMP = investigational medicinal product; IRHC = immediate-release hydrocortisone; LH = luteinizing hormone; MAF = Multidimensional Assessment of Fatigue; QoL = quality of life; SF-36® = Medical Outcome Study 36-Item Short Form Health Survey; TART = testicular adrenal rest tumors; VAS = visual analog scale.

Notes:

The screening visit can be split over 2 days, if necessary, to help facilitate consent and the conduct of the screening study procedures.

If visits have to be moved (e.g., due to use of 'stress dosing rules') this should be noted in the electronic case report form (eCRF). However, the participant should return to their usual visit schedule as soon as possible (i.e., all subsequent visits should not be moved out as well).

[1] Consent forms will be sent to the participant at least 24 hours prior to the visit so they can review the document and ask any questions. The consent form must be signed at or before the screening visit (Visit 1) prior to any study related procedures.

[2] Including menstrual history, menopausal status and oral contraceptive use for female participants.

[3] Previous treatments for CAH (last 26 weeks) and any other previous treatments (last 4 weeks) will be recorded at the screening visit (Visit 1). At each visit details of the study medication use at each visit and for the 24 hours preceding each visit will be recorded plus any changes in other concomitant medications. CAH medication will be recorded separately from other concomitant medications.

[4] If the participant has been receiving their usual medication for the previous 5 days (i.e. 'stress dosing rules' have not been applied in the 5 days preceding the visit date) they will be admitted to the clinic for androgen testing (17-OHP and A4). If 'stress dosing rules' have been applied in the previous 5 days, then the visit should be postponed until the participant has been receiving their usual medication for 5 days. Samples for androgen testing to be taken at 08:00 (before the morning dose of study medication) and 13:00 hours (±30 minutes). Exact times of sampling to be recorded in eCRF.

[5] Plasma renin concentration or activity will be assessed at screening and at the end of study according to local practice (preferably after the participant has been supine for 30 minutes). Participants who are receiving fludrocortisone must be on a documented stable dose for a minimum of 3 months prior to enrollment and must have stable renin levels at screening.

[6] Electronic participant diary used to record menstrual cycle details in all pre-menopausal women.

[7] Assessed using a 10 cm VAS at each visit (hirsutism also assessed by the Investigator using Ferriman-Gallwey score and acne also assessed by the Investigator using Global Evaluation [GEA] scale).

[8] TARTs measured by ultrasound and results read by central laboratory.

[9] Sperm count measured at home using a testing kit supplied to the male participants (only in participants who agree to this assessment).

[10] Alertness assessed weekly before the morning dose of study medication, and results recorded in the electronic participant diary.

[11] Saliva samples collected for exploratory analysis at 8.00 and 13.00 hours (optional).

[12] Dose titrations based on the adrenal insufficiency checklist and the endocrine profiles at 08:00 and 13:00 hours (±30 minutes) from the central laboratory and dose adjustments made by an independent blinded physician in accordance with the dose titration rules.

[13] Limited check of inclusion/exclusion criteria

[14] The last dose of study medication should be taken in the morning of the last dosing day. If the participant discontinues early from study treatment or from the whole study then androgen measurements and as many other assessments as possible should be completed within 48 hours of the last dose of the study medication. If the participant only discontinues study treatment, they should remain in the study where possible and be followed for safety assessments until the scheduled end of the study.

[15] In some cases (e.g., if the participant lives a long way from the study site or pandemic guidelines are in place) Visits 3 and 4 may be performed as domiciliary visits and IMP shipments can be made directly to the participant's home. However, the following visits must be performed at the study site: Screening (Visit 1), Baseline (Visit 2), Week 16 (Visit 5), and end of study/early withdrawal visit (Visit 6). If necessary in some cases, IMP at Visit 5 can also be delivered to the participant's home. If a domiciliary visit is conducted the safety and endocrine blood samples must be sent to the central laboratory for analysis and the Investigator must complete the adrenal insufficiency checklist. The assessment of hirsutism and acne can be conducted via a video call (within ±2 days of the domiciliary visit). If androgen samples are analyzed locally for safety reasons the participant must be withdrawn from treatment.

2. Introduction

Chronocort® is a newly developed modified-release oral formulation of hydrocortisone. It is designed to replicate the normal serum levels of the endogenous cortisol circadian rhythm with the aim of improving control in patients with congenital adrenal hyperplasia (CAH) who are receiving glucocorticoid replacement therapy.

2.1. Study Rationale

CAH, generally due to 21-hydroxylase deficiency, is a disease of the adrenal cortex characterized by cortisol deficiency and androgen excess, with or without aldosterone deficiency. The severe or classic form occurs in 1 in 15,000 births worldwide [Pang et al, 1993; Therrell, 2001; Merke and Bornstein, 2005]. The discovery of glucocorticoid therapy as a treatment for CAH occurred in the 1950s resulting in patients with classic CAH surviving. However, existing glucocorticoid treatment remains suboptimal and many unresolved clinical problems exist [Han et al, 2014].

There is currently no standard treatment for this condition, with glucocorticoid therapies varying by country and by treating site. Current treatments also often fail to normalize the patient's condition, with abnormal growth and development in children, and iatrogenic Cushing's syndrome, hyperandrogenism, infertility or the development of metabolic syndrome in adults [Arlt et al, 2010]. Chronocort, a newly developed modified-release oral formulation of hydrocortisone, is designed to replicate the normal serum levels of the endogenous cortisol circadian rhythm, offering the prospect of an improved treatment outcome and a novel treatment paradigm. The proposed study aims to build on the results of the Phase 2 study (DIUR-003) and the completed Phase 3 study (DIUR-005), as well as the ongoing Phase 3 extension study (DIUR-006). It is designed to further evaluate whether a twice daily dosing regimen of Chronocort with two-thirds of the total daily dose given at night and one-third in the morning (the 'toothbrush regimen'), which can more closely replicate circadian cortisol levels and also avoids the afternoon dose which can be difficult for some patients, can provide improved long-term control of CAH (using 17-hydroxyprogesterone [17-OHP] and androstenedione [A4] concentrations as markers) compared to the same total daily dose of twice daily (morning and afternoon) immediate-release hydrocortisone (IRHC) replacement therapy in conditions broadly resembling routine clinical practice. Adults and adolescents aged 16 or older who have completed their growth are included in this study, with the adolescent age group being included following feedback from pediatric endocrinologists that this group is particularly challenging to manage with standard care IRHCs, yet improved control at this age may be particularly relevant for future health.

This study should help delineate the benefits derived from a more physiological delivery of cortisol by the modified release Chronocort preparation from benefits due to the potential for reduced daily dose requirements with a more physiological preparation.

2.2. Background

Cortisol is an essential steroid hormone secreted by the adrenal gland, with severe deficiency ultimately resulting in death through an adrenal crisis. Endogenous cortisol is secreted in a circadian rhythm, with levels building up overnight to peak first thing in the morning then falling over the day with a nadir at midnight. Patients with adrenal failure that is either primary (Addison's disease and CAH) or secondary (hypothalamic-pituitary dysfunction) are deficient in cortisol and have to take life-long glucocorticoid replacement (such as hydrocortisone, the synthetic form of cortisol).

Hydrocortisone was first isolated from adrenal glands in 1937 [Reichstein and Steiger, 1937] and is now a well characterized therapeutic molecule widely used in clinical practice to treat adrenal insufficiency [Speiser et al, 2018]. The majority of existing marketed oral formulations of hydrocortisone are provided at doses of 5 mg, 10 mg and 20 mg and are designed to deliver "immediate-release" of the active ingredient. In order to achieve efficacious plasma levels of hydrocortisone, multiple daily dosing is required (typically 2 or 3 times daily [Speiser et al, 2018]), which results in high peak-to-trough fluctuations in plasma concentrations [Maguire et al, 2007]. Furthermore, this results in low early morning cortisol levels and high adrenocorticotropic hormone (ACTH) levels, causing fatigue in patients with Addison's disease and high adrenal androgen levels in patients with CAH. It is therefore not possible to replicate physiological cortisol release using this therapeutic regimen. Thrice daily regimens can also be difficult to manage for busy adults, meaning that many will use twice daily dosing. Treatment is also complicated by the fact that excessive steroid replacement with hydrocortisone or other glucocorticoids causes complications in its own right, by reducing growth in the child and causing osteoporosis and skin atrophy in the adult, so a balance needs to be maintained between under-treatment leading to excessive androgens and ultimately an adrenal crisis but avoiding the side effects of over-treatment.

Diurnal has developed a novel modified-release formulation of hydrocortisone (Chronocort) which closely replicates the physiological circadian profile for cortisol and therefore has the potential to provide optimal control of all forms of adrenal insufficiency. To date, 3 studies evaluating Chronocort in healthy volunteers (DIUR-002, DIUR-004 and DIUR-008) and 2 studies evaluating Chronocort in patients with CAH (DIUR-003 and DIUR-005) have been completed. An extension study allowing participants enrolled into the 2 CAH studies to receive long-term Chronocort treatment is ongoing (DIUR-006). In total, 71 healthy volunteers (65 who received Chronocort) and 138 patients with CAH (120 who received Chronocort) have been evaluated to date.

The results from the studies to date show that the pharmacokinetic (PK) profile of Chronocort after 20 mg at 23:00 hours and 10 mg at 07:00 hours both in healthy subjects and in subjects with CAH is characterized by an overnight rise in cortisol levels, reaching a maximal concentration approximately 8 hours post-dosing, which is consistent with the physiological endogenous profile of cortisol reported in normal individuals. Physiological replacement of cortisol with Chronocort, replicating the cortisol circadian rhythm, improved the control of disease-related biomarker androgens in subjects with CAH when compared to subjects on baseline standard therapy, particularly in the early morning period when androgens typically peak in conventionally-treated patients, with this being achieved with a similar or lower dose of glucocorticoid. PK data indicated that food slightly delayed and reduced the rate of absorption of Chronocort. However, overall exposure was similar in fed and fasted subjects,

so this effect was not considered clinically relevant. In a relative bioequivalence study, Chronocort was bioequivalent to IRHC (Cortef®) with respect to the area under the plasma concentration versus time curve (AUC).

Results of the Phase 3 studies in patients with CAH showed improved control of adrenal androgen precursors (17-OHP and A4) in the critical morning and early afternoon periods following Chronocort treatment, with a similar or lower dose of Chronocort being used to attain better morning and similar evening androgen control compared to standard glucocorticoid therapy. Post-hoc analyses demonstrated reduced variability of disease biomarkers and a reduced AUC for 17-OHP and A4 with Chronocort therapy compared to standard therapy. In CAH, elevated 17-OHP is diagnostic and widely used in monitoring therapy, and it plays a central role in driving excess adrenal androgens. 17-OHP in CAH displays a marked diurnal rhythm that is not seen in the normal population. In CAH patients, elevated 17-OHP drives the production of excess adrenal androgens through the 3 adrenal androgen pathways: The Classic, The Alternative and The 11-Oxygenated [Storbeck et al, 2019]. In the pathophysiology of CAH, the Classic pathway, via dehydroepiandrosterone (DHEA) to A4 is down regulated, as evidenced by normal or low DHEA levels in poorly controlled CAH patients, and it is the raised 17-OHP that directly drives A4 production [Debono et al, 2015]. When 17-OHP is controlled into the optimal range (<1200 ng/dL) throughout 24 hours, as shown in the Diurnal DIUR-005 and DIUR-006 studies, this direct route from 17-OHP to A4 is switched off, meaning that A4 levels are either normal or low as it is neither generated from 17-OHP nor DHEA (Chronocort DIUR-005 Clinical Study Report [CSR]). A4 may be low in well-controlled CAH, even when using adrenal replacement doses of hydrocortisone, i.e., lower than those typically used in CAH, as shown in the DIUR-006 efficacy and safety extension study (DIUR-006 CSR) where a number of patients were treated for extended periods on 10 mg daily Chronocort with low A4. To reduce the glucocorticoid dose below these doses in this situation would put patients at risk of adrenal insufficiency and crisis. Thus, as 17-OHP plays the central role for A4 generation, 17-OHP is the better biomarker for control of androgens in CAH. Interest has been expressed by endocrinologists in using 11-keto androgens as biomarkers for monitoring disease, and there are published [Jones et al, 2017] and unpublished data suggesting that Chronocort can control these markers more effectively than standard therapies, however, there is as yet no universally recognised and validated 11-keto-steroid biomarker and so Diurnal has chosen to include one of these biomarkers (11-ketotestosterone) as an exploratory endpoint rather than as the primary endpoint.

In studies DIUR-005 and DIUR-006 there was a reduced incidence of potentially life-threatening adrenal crises, and a reduction in the need for supplementary steroid stress dosing, with an increased incidence of therapeutic benefits (fatigue reduction, improvement of hirsutes, menstrual benefits) being reported. No safety concerns have been raised in any of the studies and the adverse event (AE) profile resembles that of other hydrocortisone products used at comparable dose levels for glucocorticoid replacement therapy in CAH patients.

Further details on the use of Chronocort in humans is provided in Section 6 of the Investigator's Brochure. Details on the comparator product are provided in the Cortef prescribing information.

2.3. Benefit/Risk Assessment

The participants planned to be included in this study all have classic CAH and, as such, they have an absolute requirement for life-long glucocorticoid replacement therapy. The currently used glucocorticoid replacement therapies do not accurately replicate physiological cortisol profiles. Chronocort is a novel modified-release formulation of hydrocortisone that has been shown to closely replicate the physiological circadian profile of cortisol. Hydrocortisone is an established therapy for CAH that has been used for over 60 years. The safety profile when used in a low dose adrenal replacement regimen is well understood and the development program for Chronocort has shown no differences in safety profile to established IRHC preparations. Results of completed clinical studies using Chronocort have demonstrated that cortisol levels on Chronocort approximated physiological cortisol rhythm over 24 hours, and improved control of androgens (17-OHP and A4) in participants with CAH when compared to their disease control on conventional glucocorticoid therapy. Thus, it is proposed that the formulation of hydrocortisone being evaluated in this study (Chronocort) has characteristics that may improve the outcome in these participants. This hypothesis applies to adults and adolescents who have completed their growth and may benefit from improved control, particularly considering potential positive impacts on fertility and metabolic parameters. There are no formulation-specific concerns regarding the use of this modified-release presentation of hydrocortisone in this age group.

The risks associated with this study include those associated with blood sampling and general involvement with clinical studies. The Investigators in this study are all highly experienced both in clinical studies and in the management of patients with CAH, and so these risks are considered negligible. In addition, to minimize the risk of anemia associated with the withdrawal of multiple blood samples for laboratory testing (as seen in a previous study), the planned blood volume to be drawn during this study has been limited to a maximum of approximately 200 mL.

Other risks relate to the potential under- or over-treatment of participants with glucocorticoids as seen in day-to-day clinical practice. These risks apply to both conventional treatment and Chronocort. All participants included in this study will be informed of the potential for under-treatment (as occurs when there is an intercurrent illness), and the routine teaching on how to manage this with supplemental steroids (emergency pack for ‘stress dosing rules’) and to seek medical assistance will be reinforced. [redacted]

Both under- and over-treatment with hydrocortisone are common as physicians try to balance androgens and clinical symptoms. Regular assessment of the participants (both biochemically

and clinically) and review of these results will identify under- and over-treatment, which will be corrected by the recommendations from an independent blinded physician through a modification in the dose. Thus, the potential risks are minimized and mitigated by the Investigator's oversight, dose modification by the independent blinded physician, use of 'stress dosing rules' by the individual participants when needed, and specific study activities (e.g. identification of AEs).

[redacted]

All participants will be given the relevant information about the risks and potential benefits of the study and all participants have to sign a consent form prior to inclusion in the study that meets all the requirements of Good Clinical Practice (GCP) and national regulations. Thus, the risks of Chronocort are expected to be no greater than the risks of an equivalent dose of hydrocortisone and similar to the risks associated with current glucocorticoid therapy the participant will have received prior to entry into the study. However, the delivery of hydrocortisone with Chronocort has been demonstrated to produce a cortisol profile more similar to the endogenous cortisol profile than current IRHC formulations [redacted]

3. Objectives, Outcome Variables, and Analyses

Objectives	Outcome Variable and Analyses Supporting the Objectives
Primary Efficacy	
• To compare Chronocort to IRHC in terms of biochemical responder rate after 28 weeks of randomized treatment.	• The primary efficacy outcome variable is <u>whether or not the participant is a biochemical responder after 28 weeks of randomized treatment.</u> A biochemical responder is a participant who: i) is in biochemical control at the 08:00 hours assessment after 28 weeks of randomized treatment (where in biochemical control is defined as both a 17-OHP concentration equal to or below the upper limit for optimal control and an A4 concentration equal to or below the upper limit of the reference range), and ii) is receiving after 28 weeks of randomized treatment 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). The difference (Chronocort minus IRHC) between the proportion of participants in each treatment arm who are biochemical responders 28 weeks after randomization will be estimated in the full analysis set (FAS). Participants who die or withdraw from treatment before 28 weeks will be classified as not a biochemical responder. Participants receiving rescue medication under the 'stress dosing rules' within 5 days before the scheduled visit at 28 weeks after randomization will have their visit delayed appropriately[1]. Biochemical non-inferiority of Chronocort to IRHC will be declared if the 95% confidence interval (CI) for the difference in proportions lies wholly above minus 15 percentage points.
Key Secondary Efficacy	
• 1) To compare Chronocort to IRHC in terms of dose responder rate after 28 weeks of randomized treatment.	• The first key secondary efficacy outcome variable is <u>whether or not the participant is a dose responder after 28 weeks of randomized treatment.</u> A dose responder is a participant who: i) is receiving after 28 weeks of randomized treatment a total daily dose of hydrocortisone of not more than 25 mg, and ii) is in biochemical control at the 08:00 hours assessment after 28 weeks of randomized treatment (where in biochemical control is defined as both a 17-OHP concentration equal to or below the upper limit for optimal control and an A4 concentration equal to or below the

	upper limit of the reference range). The difference (Chronocort minus IRHC) between the proportion of participants in each treatment arm who are dose responders 28 weeks after randomization will be estimated in the FAS. Participants who die or withdraw from treatment before 28 weeks will be classified as not a dose responder. Participants receiving rescue medication under the 'stress dosing rules' within 5 days before the scheduled visit at 28 weeks after randomization will have their visit delayed appropriately[1]. Dose superiority of Chronocort to IRHC will be declared if the 95% CI for the difference in proportions lies wholly above zero, provided that biochemical non-inferiority of Chronocort to IRHC has been declared under the primary efficacy objective.
• 2) To compare Chronocort to IRHC in terms of total daily dose after 28 weeks of randomized treatment.	• The second key secondary efficacy outcome variable is the total daily dose (mg) after 28 weeks of randomized treatment. The difference (Chronocort minus IRHC) between the mean total daily dose after 28 weeks of randomized treatment in each treatment arm will be estimated in the FAS. Superiority of Chronocort to IRHC with respect to total daily dose after 28 weeks of randomized treatment will be declared if the 95% CI for the difference in means lies wholly below zero, provided that dose superiority of Chronocort to IRHC has been declared under the first key secondary efficacy objective.
Other Secondary Efficacy	
• To compare Chronocort to IRHC in terms of biochemical responders at 4, 10, and 16 weeks after randomization.	• The outcome variables whether or not the participant is a biochemical responder at 08:00 hours at 4, 10, and 16 weeks after randomization are compared between treatment arms by calculating the difference in proportion of participants responding. These outcome variables are to be analyzed in the same manner as the primary efficacy outcome variable.
• To compare Chronocort to IRHC in terms of dose responders at 10 and 16 weeks after randomization.	• The outcome variables whether or not the participant is a dose responder at 08:00 hours at 10 and 16 weeks after randomization are compared between treatment arms by calculating the difference in proportion of participants responding. These outcome variables are to be analyzed in the same manner as the key secondary outcome variable.

• To compare Chronocort to IRHC in terms of total daily dose at 10 and 16 weeks after randomization.	• The outcome variables total daily dose at 10 and 16 weeks after randomization are compared between treatment arms by calculating the difference in mean total daily dose. These outcome variables are to be analyzed in the same manner as the second key secondary outcome variable.
• To compare Chronocort to IRHC in terms of biochemical control at 4, 10, 16, and 28 weeks after randomization.	• The outcome variables whether or not the participant is in biochemical control (provided total daily dose is not more than 30 mg) at 08:00 hours at 4, 10, 16, and 28 weeks after randomization are compared between treatment arms by calculating the difference in proportion of participants in control.
• To compare Chronocort to IRHC in terms of the impact on 17-OHP range.	• The difference in range as calculated as the difference between the 08:00 and 13:00 measurements of 17-OHP levels at 4, 10, 16, and 28 weeks after randomization and their changes from baseline will be summarized and compared between treatment arms.
• To compare Chronocort to IRHC in terms of the impact on A4 range.	• The difference in range as calculated as the difference between the 08:00 and 13:00 measurements of A4 levels at 4, 10, 16, and 28 weeks after randomization and their changes from baseline will be summarized and compared between treatment arms.
• To compare Chronocort to IRHC in terms of the impact on mean 17-OHP and A4.	• The mean of the 08:00 and 13:00 measurements of 17-OHP levels and A4 levels at 4, 10, 16, and 28 weeks after randomization and their changes from baseline will be summarized and compared between treatment arms.
• To compare Chronocort to IRHC in terms of the impact on glucocorticoid dose.	• The total daily glucocorticoid dose at 4, 10, 16, and 28 weeks after randomization will be summarized and compared between treatment arms. • The relationship between daily glucocorticoid dose and biochemical control at 28 weeks after randomization will be explored.
• To compare Chronocort to IRHC in terms of changes in menstrual regularity.	• The change from baseline to 4, 10, 16, and 28 weeks of randomized treatment in menstrual regularity (only in pre-menopausal women without hysterectomy and not using hormonal contraception) will be summarized and compared between treatment arms.
• To compare Chronocort to IRHC in terms of the impact on luteinizing hormone (LH) levels.	• The change from baseline to 4, 10, 16, and 28 weeks of randomized treatment in LH levels (men only) will be summarized and compared between treatment arms.

• To compare Chronocort to IRHC in terms of the impact on testicular adrenal rest tumors (TART) size.	• The change from baseline to 28 weeks of randomized treatment in size of TART (men only) will be summarized and compared between treatment arms.
• To compare Chronocort to IRHC in terms of the impact on sperm count.	• The change from baseline to 28 weeks of randomized treatment in sperm count (men only) will be summarized and compared between treatment arms.
• To compare Chronocort to IRHC in terms of the impact on subjective hirsutism in female participants.	• The change from baseline to 4, 10, 16, and 28 weeks of randomized treatment in subjective hirsutism using a visual analog scale (VAS) (women only) will be summarized and compared between treatment arms.
• To compare Chronocort to IRHC in terms of the impact on objective hirsutism in female participants.	• The change from baseline to 4, 10, 16, and 28 weeks of randomized treatment in objective hirsutism using the Ferriman-Gallwey score (women only) will be summarized and compared between treatment arms.
• To compare Chronocort to IRHC in terms of the impact on subjective acne in female participants.	• The change from baseline to 4, 10, 16, and 28 weeks of randomized treatment in subjective acne using a VAS (women only) will be summarized and compared between treatment arms.
• To compare Chronocort to IRHC in terms of the impact on objective acne in female participants.	• The change from baseline to 4, 10, 16, and 28 weeks of randomized treatment in objective acne using the Global Evaluation Acne (GEA) scale (women only) will be summarized and compared between treatment arms.
• To compare Chronocort to IRHC in terms of the impact on glycated hemoglobin (HbA1c) levels.	• The change from screening to 4, 10, 16, and 28 weeks of randomized treatment in HbA1c levels will be summarized and compared between treatment arms.
• To compare Chronocort to IRHC in terms of the impact on waist circumference.	• The change from baseline to 4, 10, 16, and 28 weeks of randomized treatment in waist circumference will be summarized and compared between treatment arms.
• To compare Chronocort to IRHC in terms of the impact on body weight.	• The change from baseline to 4, 10, 16, and 28 weeks of randomized treatment in body weight will be summarized and compared between treatment arms.
• To compare Chronocort to IRHC in terms of the impact on quality of life (QoL) using the self-completed Medical Outcome Study 36-Item Short Form Health Survey (SF-36®) total score and the sub-domain of vitality.	• The change from baseline to 4, 10, 16, and 28 weeks of randomized treatment in QoL using the self-completed SF-36® total score and the sub-domain of vitality will be summarized and compared between treatment arms.
• To compare Chronocort to IRHC in terms of the impact on QoL using the Multidimensional Assessment of Fatigue (MAF).	• The change from baseline to 4, 10, 16, and 28 weeks of randomized treatment in QoL using the MAF will be summarized and compared between treatment arms.

• To compare Chronocort to IRHC in terms of the impact on QoL using the 5-level Standardized Health Questionnaire (EQ-5D-5L™).	• The change from baseline to 4, 10, 16, and 28 weeks of randomized treatment in QoL using the EQ-5D-5L™ will be summarized and compared between treatment arms.
Compliance	
• To assess compliance over the study period.	• The percentage treatment compliance between visits and overall will be summarized.
Exploratory Efficacy	
• [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Safety	
• To assess the safety and tolerability of Chronocort relative to IRHC.	• The incidence, nature, severity, relatedness, duration, outcome, seriousness and expectedness of treatment-emergent adverse events (TEAEs) will be tabulated by treatment arm. AEs of special interest will additionally be tabulated separately, with particular note of adrenal crises.
• To assess the need for use of additional glucocorticoid doses (stress dosing rules).	• The use of medication from the stress dosing packs or use of any additional glucocorticoid treatment during the study will be tabulated by treatment arm.
• To evaluate the safety of Chronocort compared to IRHC by assessment of routine safety laboratory assessments, physical examination, vital signs, and electrocardiogram (ECG).	• Safety hematology, biochemistry, urinalysis, and vital signs conducted at each post-randomization visit and the physical examination and ECG assessments conducted after 28 weeks of randomized treatment, and their changes from baseline, will be summarized by treatment arm.

[1] This description aligns with the International Council for Harmonization (ICH) E9 requirement for the definition of an Estimand.
Outcome variables are underlined
Note: The reference range for A4 is up to 150 ng/dL (5.2 nmol/L) for men and up to 200 ng/dL (7.0 nmol/L) for women (based on the luteal phase) (based on data from The Mayo Clinic).
The optimal range for 17-OHP in adults (post-pubertal males or females aged >16 years) is up to 1200 ng/dL (36.4 nmol/L).

4. Study Design

4.1. Overall Design

This study is a randomized, double-blind, active-controlled, titrated, parallel arm, multicenter study. It will compare the efficacy, safety and tolerability of twice daily Chronocort with twice daily IRHC over a randomized treatment period of up to 28 weeks in participants aged 16 years and over with known classic CAH due to 21-hydroxylase deficiency. The primary efficacy assessment of biochemical responder rate and the key secondary assessments of dose responder rate and mean total daily dose will be assessed after 28 weeks of randomized treatment.

Participants will attend a screening visit 4 weeks prior to the baseline visit. Participants will be asked to take their usual medication at the usual times up until the screening visit, with details of the dosing regimen and the timing of doses of CAH medication recorded throughout the screening visit and for the previous 24 hours. At this screening visit, informed consent/assent will be obtained and then the screening assessments will be conducted. Participants will then be switched to 20 mg IRHC in the morning on waking (typically between 06:00 and 08:00 hours) and 10 mg in the afternoon (between 15:00 and 17:00 hours) for the next 4 weeks as run-in therapy. This total daily dose is based on the guidelines for adrenal replacement, where the recommended dose is between 15 and 25 mg, plus an acknowledgement that patients with CAH may need a higher dose [Speiser et al. 2018]. This total daily dose was safely used in the Chronocort Phase 2 and 3 studies and equates to the dose used in large cohort studies [Arlt et al, 2010; Finkielstain et al, 2012].

After 4 weeks on this run-in therapy, participants will attend a baseline visit for all the baseline assessments. If at the end of the 4-week run-in period there are persistent signs of adrenal insufficiency, or the participant does not tolerate treatment, then they should be withdrawn from the study before randomization. Assessment of baseline androgen levels (17-OHP and A4) will be made at 08:00 hours before the morning dose of IRHC and at 13:00 hours, with a window of ±30 minutes allowed around each sampling timepoint. These baseline adrenal androgens will be analyzed by the central laboratory and participants with 17-OHP equal to or below the upper limit for optimal control at 08:00 hours and A4 equal to or below the upper limit of the reference range at 08:00 hours will be classified as ‘in biochemical control’. If the measurements are outside these criteria the participant will be classified as ‘not in biochemical control’. Once eligibility for the study is confirmed, the Investigator will randomize the participants on a 1:1 basis (Chronocort:IRHC) using an interactive response technology (IRT) system, with randomization being stratified within each treatment arm based on fludrocortisone replacement status (requires fludrocortisone or does not require fludrocortisone). Note: the results of the baseline androgen tests are NOT needed prior to the participant being randomized to the study.

Participants randomized to Chronocort will change to a dosing regimen of 10 mg in the morning on waking (typically between 06:00 and 08:00 hours) and 20 mg at night just prior to going to bed (typically between 22:00 hours and midnight). Participants randomized to IRHC will continue the same dosing regimen as they were receiving during the run-in period (20 mg in the morning on waking [typically between 06:00 and 08:00 hours] and 10 mg in the afternoon [between 15:00 and 17:00 hours]). The time of the first dose of randomized medication on Day 1 will be recorded in an electronic participant diary.

Participants will return to the study site for titration visits at 4, 10 and 16 weeks after randomization, with androgen levels assessed at each of these visits at 08:00 hours (before the morning dose of study medication) and 13:00 hours (±30 minutes). At each of these 3 visits dose reductions (in 5 mg steps at each visit) can be conducted if required, based on androgen results and adrenal insufficiency symptoms collected using the adrenal insufficiency checklist. The decision to change doses in both treatment groups will be made by an independent blinded physician and the appropriate investigational medicinal product (IMP) packs will be sent to the participant, either to collect from their local study site or sent directly to the participant's home. The treatment packs for each participant will always contain the same number of capsules as the previous supplies (with placebo capsules masking any changes) to maintain the blinding and to ensure the participant is not aware of any dose changes.

Once the titration visit at 16 weeks is complete and the dose adjusted, if necessary, the dose of study medication will then be fixed and should remain unchanged until the end of study (EOS) visit (up to 12 weeks of fixed dose treatment) if possible. The last dose of study medication will be taken in the morning of the last dosing day.

The analysis of all 17-OHP and A4 levels will be conducted by a central laboratory and the results will be sent to an independent blinded physician, with the independent blinded physician being unaware of the participant's treatment allocation. The Investigator will also complete an adrenal insufficiency checklist at each visit which will be made available to the independent blinded physician. If at the titration visits at Weeks 4, 10, and 16 the independent blinded physician considers a dose reduction is necessary, the dose should be reduced by a total of 5 mg at each titration visit. Each treatment arm will be subject to the same titration rules throughout the study, ensuring that opportunities for optimization and control of androgens are the same in both arms and thus minimizing bias in the management of participants. At the titration visits at Weeks 4, 10, and 16, only dose reductions are permitted, unless the dose has previously been reduced, in which case it can be reverted back to the previous higher dose if needed without having to wait until the next titration point. Dose increases can only be made in an urgent situation where the Investigator believes the participant is exhibiting signs of adrenal insufficiency, and in all cases, this should be discussed with the medical monitor before a dose increase is initiated (see Section 4.2 for further details).

The EOS visit will be conducted 28 weeks after randomization or at early withdrawal from the study. The total study duration is up to 40 weeks (screening period up to 4 weeks prior to screening visit, 4 weeks run-in period on IRHC up to the baseline visit, 16 weeks dose titration on randomized treatment, 12 weeks fixed dose period on randomized treatment, and follow-up phone call 4 weeks/30 days after the EOS visit). In some cases (e.g. if the participant lives a long way from the study site, or if pandemic guidelines dictate) study visits 3 and 4 may be performed as domiciliary visits and IMP shipments can be made directly to the participant's home. However, the following visits must be performed at the study site: Screening (Visit 1), Baseline (Visit 2), Week 16 (Visit 5), and EOS/early withdrawal visit (Visit 6). If necessary in some cases, IMP at Visit 5 can also be delivered to the participant's home. If a domiciliary visit is conducted the safety and endocrine blood samples must be sent to the central laboratory for analysis and the Investigator must complete the adrenal insufficiency checklist. The assessment of hirsutism and acne can be conducted via a video

call (within ±2 days of the domiciliary visit). If androgen samples are analyzed locally for safety reasons the participant must be withdrawn from treatment.

At the end of the study, participants who have completed the study will be offered the option of continuing in a long-term safety study (DIUR-015) where all participants will receive Chronocort treatment or they will be offered commercial supplies of Chronocort (the options will be dependent on territory), or the participant can return to the standard treatment they were receiving before entry into this study (see Section 6.7). For participants who agree to enter the long-term safety study DIUR-015, the EOS visit (Visit 6) will be their last assessment in this study. Participants who decide not to enter the long-term safety study or who withdrew from the study early will receive a telephone call 30 days after the last study visit to ask about any AEs that were ongoing and any new serious adverse events (SAEs) that could be related to the study medication. This telephone call will be considered the last assessment for these participants, although ongoing SAEs will be followed until resolution or stabilization, the event is otherwise explained, or the participant is lost to follow-up.

An independent DSMB will meet on a regular basis during the study to review the safety data and will operate in accordance with a pre-defined charter (see Section 9.6).

4.2. Titration Rules

The aim of titration is to establish participants on the lowest dose of glucocorticoid which will provide adequate adrenal replacement and control androgens. At each titration visit during the titration period, adrenal insufficiency symptoms will be collected using the adrenal insufficiency checklist (Appendix 5) and androgen results will be assessed at 08:00 and 13:00 hours. The adrenal insufficiency checklist should only be used to determine if symptoms of under- or over-replacement of glucocorticoids have occurred since the last visit and this questionnaire should not be used to record AEs due to other causes. The analysis of all 17-OHP and A4 levels will be conducted by a central laboratory and the results will be sent to an independent blinded physician, with the independent blinded physician being unaware of the participant's treatment allocation. The independent blinded physician will decide if the dose should be maintained or if a dose reduction is needed and the appropriate packs will be sent to the participant, either to collect from their local study site or sent directly to the participant's home. The treatment packs for each participant will always contain the same number of capsules as the previous supplies (with placebo capsules masking any changes), thus ensuring the participant is not aware of any dose changes.

If the independent blinded physician considers a dose reduction is necessary, a maximum dose reduction of 5 mg is allowed at each titration visit at Weeks 4, 10, and 16. The independent blinded physician will inform the IRT system of the recommended dose changes or that the dose does not need to be changed, which will then inform the pharmacist which IMP packs to dispense based on previous titrations according to the titration rules. The total daily dose must not exceed 30 mg and the afternoon IRHC dose must not exceed 10 mg at any point.

For all dose reductions, the results from the 08:00 hours androgen sample will be used to guide adjustment of the Chronocort night-time dose and IRHC morning dose, and the 13:00 hours androgen sample will be used to guide adjustment of the Chronocort morning dose and the IRHC afternoon dose. If 17-OHP is <300 ng/dL (the upper limit of the reference range) and A4 is <150 ng/dL for males and <200 ng/dL for females (sex-specific upper limit

of the reference range), then the dose will be adjusted down by a total of 5 mg. If one or both androgen results are above these limits, then no titration will be undertaken. Clinical symptoms of adrenal insufficiency on the adrenal insufficiency checklist should take precedence over androgen results and would inhibit titration. Only 1 of the 2 doses a participant receives (i.e. morning or afternoon/evening) should be titrated at each titration point but no dose should be reduced below 5 mg. If the androgen results indicate that both doses should be reduced, then precedence should be given to reducing the morning dose of Chronocort and the afternoon dose of IRHC. If the same situation then recurs at the next titration timepoint then the dose reduced should be alternated to avoid a mismatch of dosing. Each treatment arm will be subject to the same titration rules throughout the study, ensuring that opportunities for optimization and control of androgens are the same in both arms and thus minimizing bias in the management of participants. These androgen precursor limits have been defined based on data from previous studies in the clinical development program.

If a participant shows persistent signs of under-replacement on the randomized starting dose of 30 mg Chronocort or IRHC they will be monitored and if symptoms do not resolve the participant should be withdrawn from treatment and given alternative therapy at the Investigator's discretion. If a participant shows persistent signs of under-replacement during the titration period and the participant has received at least 1 down titration of 5 mg, a reversion to the previous dose is permitted (i.e. an increase of 5 mg) after discussion with the medical monitor. If symptoms persist, no further dose increases can be made, and the participant should be withdrawn from study treatment (such cases should be discussed with the medical monitor). If the Investigator thinks that the dose needs to be adjusted between visits, they should contact the medical monitor to discuss the case. For emergency situations, the emergency treatment pack can be used, and the medical monitor should be contacted as soon as possible.

Any dose titrations should be made within 2 to 3 weeks of the visit (dependent on the laboratory turnaround time of androgen samples, the time needed by the independent blinded physician to evaluate the data, and for new supplies to be provided to the participant). At each delivery of new supplies to the participant, all the old supplies will be collected to ensure that the participant cannot take the wrong medication. All participants will receive a telephone call 1 week after they have received the new treatment packs to enquire as to whether there have been any AEs and reinforce any other protocol requirements.

4.3. Stress Dosing Rules

All participants will be supplied with 'stress dosing rules' and an emergency treatment pack for use during intercurrent illness, as medically indicated. Participants should attend each visit only if they have been taking the study medication alone for the previous 5 days (i.e. 'stress dosing rules' have not been applied in the 5 days preceding the visit date). If 'stress dosing rules' have been applied in the previous 5 days, then the study visit should be delayed until the participant has a 5-day period of normal dosing.

4.4. Scientific Rationale for Study Design

Study Design

A previous Phase 2 study (a 2-part, single cohort, open-label, multiple dose protocol [DIUR-003]) demonstrated that Chronocort, when given as a twice daily regimen to

participants with CAH, enabled physiological replacement of cortisol that resulted in improved control of androgen precursors (17-OHP and A4) without increasing glucocorticoid exposure [Mallappa et al, 2015]. Chronocort, in contrast to IRHC, provided the physiological cortisol rise overnight thus improving the morning androgen control in CAH using an adrenal replacement dose of hydrocortisone. The designs used in study DIUR-005 (a Phase 3 study of efficacy, safety and tolerability of Chronocort compared with standard glucocorticoid replacement therapy in the treatment of CAH) and in study DIUR-006 (a Phase 3 open-label extension study for participants who were enrolled in studies DIUR-003 and DIUR-005), have also been taken into consideration in the design of this new study. The Sponsor has undertaken a prolonged period of consultation with the Food and Drug Administration (FDA) to obtain advice and this advice has also been incorporated into this protocol. [redacted]

[redacted]

[redacted]

Twice daily Chronocort will be compared to twice daily IRHC since hydrocortisone is the first line recommended glucocorticoid replacement for patients with adrenal insufficiency and CAH. Dosing times used in studies DIUR-003, DIUR-005 and DIUR-006 are continued for this present study. A double-blind technique has been used to minimize bias that may be present using an open-label design and over-encapsulation of both IMPs will be used to maintain the blinding.

Randomization to either Chronocort or IRHC will be stratified within each treatment arm based on fludrocortisone replacement status (requires fludrocortisone or does not require fludrocortisone).

Dose adjustment will be allowed at 3 titration visits to optimize control of CAH based on the participant symptoms (as documented by the Investigator in the adrenal insufficiency checklist) as well as by measurement of androgens as is currently recommended for clinical practice, with one subsequent visit to allow correction in any participant who may have been excessively down-titrated or for safety reasons. The decision whether to adjust the dose will be made by an independent blinded physician who will remain blinded to the participant's treatment assignment.

Androgens

The challenge in managing CAH is controlling the overnight and early morning rise in adrenal androgens using replacement doses of hydrocortisone [Han et al, 2014]. Daytime dosing controls adrenal androgens in CAH during the day, especially in the afternoon, but excess androgens are generated before waking. This morning peak often necessitates a higher dose of steroid to achieve control by the mid to late morning and dosing of immediate-release glucocorticoids at night when cortisol levels in healthy individuals are low. The expected benefit of Chronocort is in preventing the overnight rise in adrenal androgens before morning dosing, leading to a normalized level and profile of the androgen precursors 17-OHP and A4 which are relatively constant throughout the 24 hours with little circadian variability in individuals without CAH. The earliest practical sampling in the clinic is at 08:00 hours and therefore sampling will be undertaken at 08:00 hours before the morning dosing of Chronocort or IRHC. Timed sampling is recommended in the Endocrine Society guidelines, and although the timing of samples is not universal amongst endocrinologists, a pre-dose early morning sample is a recognized and established practice. Diurnal anticipates that this sampling practice might then inform the Chronocort label and become an established universal monitoring practice.

Although there is no consensus on when to measure androgen levels, it is recommended to measure levels both before and after treatment [Merke and Bornstein, 2005; Merke, 2008], with the optimal time to measure adrenal androgens on treatment considered to be in the early morning and during the afternoon [Debono et al, 2015]. Androgens were measured using 24-hour profiling in a tightly controlled inpatient environment in studies DIUR-003 and DIUR-005, but this study is designed to broadly reflect real-life clinical practice and so blood samples for androgen assessment will be taken at more practical times of 08:00 and 13:00 hours, as has been done in the ongoing study DIUR-006. The timing of these samples was considered to reflect the expected time of effect of administered doses of glucocorticoid and would provide a good overview of daily control of adrenal androgens. The analysis of all scheduled 17-OHP and A4 levels will be conducted by a central laboratory to ensure consistency in the results.

The decision to use both 17-OHP and A4 in the primary endpoint of biochemical responder rates is based on the fact that in CAH patients, elevated 17-OHP and A4 are considered diagnostic, are widely used in monitoring therapy, and play a central role in driving excess adrenal androgens. Only the upper limit of the optimal range for 17-OHP has been included in the study for assessing biochemical control, rather than the reference range. With current standard of care for CAH, dosing glucocorticoid therapy with the goal of controlling 17-OHP reference range risks excess glucocorticoid therapy [Speiser et al, 2018], and clinicians who manage these patients use an "optimal range" for 17-OHP to define disease control [Arlt et al, 2010; Finkielstain et al, 2012]. The upper limit for the optimal range for 17-OHP in adults (post-pubertal males or females aged >16 years) is <1200 ng/dL (36.4 nmol/L). 17-OHP levels vary little in healthy individuals during 24 hours [Ghizzoni et al, 1994], and many laboratories (e.g. The Mayo Clinic) do not quote a lower bound of the reference range. The challenge in CAH with current therapy is keeping the 17-OHP below the upper limit of the optimal range before morning dosing on an adrenal replacement dose of hydrocortisone since current therapies, even when given in reverse circadian pattern, fail to control the early morning ACTH-driven surge in adrenal androgens. In the DIUR-006 study of Chronocort, 80% of patients had a morning 17-OHP less than the upper limit of the optimal range on a median hydrocortisone dose of 20 mg and therefore the dose would not be reduced as this would risk giving inadequate adrenal replacement therapy.

Interest has been expressed by endocrinologists in using 11-keto androgens as biomarkers for monitoring disease, and there are both published [Jones et al, 2017] and unpublished data suggesting that Chronocort can control these markers more effectively than standard therapies. However, there is as yet no universally recognized and validated 11-keto-steroid biomarker and so one of these biomarkers (11-ketotestosterone) is included as an exploratory endpoint.

Endpoints

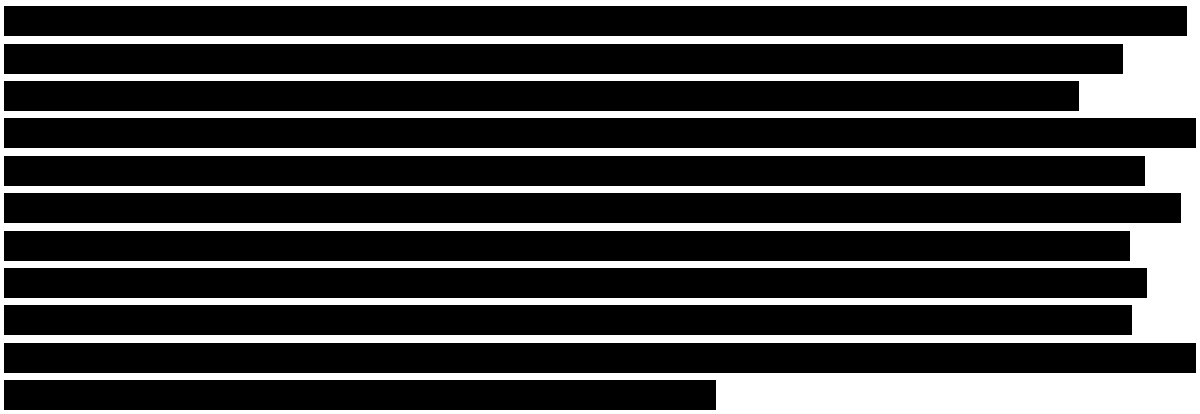
The goal of therapy in CAH is to reduce excessive androgen secretion by replacing the deficient glucocorticoid hormones [Speiser et al, 2010]. This study will achieve this goal by close monitoring of adrenal androgens (17-OHP and A4) and modifying the glucocorticoid dose in the light of biochemical control and clinical signs and symptoms of the adequacy of glucocorticoid replacement.

A participant is a dose responder if their dose after 28 weeks of randomized treatment is less than the starting dose of 30 mg/day, provided they are in biochemical control at that time. All

dose responders are biochemical responders: additionally, participants who were out of biochemical control at baseline but are in biochemical control after 28 weeks of randomized treatment are also biochemical responders, provided their dose at that time is not higher than the starting dose of 30 mg/day.

The primary efficacy analysis will be to compare Chronocort to IRHC in terms of biochemical responder rate after 28 weeks of randomized treatment. The first key secondary efficacy analysis will be to compare Chronocort to IRHC in terms of dose responder rate after 28 weeks of randomized treatment. The second key secondary efficacy analysis will be to compare Chronocort to IRHC in terms of total daily dose after 28 weeks of randomized treatment.

In addition, clinical endpoints will be assessed over the course of the study to evaluate the impact on participants' QoL and other clinical consequences of CAH.



Subject reported outcomes were used in studies DIUR-003, DIUR-005 and DIUR-006, and these have also been included in this study.

4.5. Justification for Dose

The recommended hydrocortisone dose in adults for adrenal insufficiency is 15 to 25 mg given twice daily in the morning on waking and early afternoon [Bornstein et al, 2016]. Although this is the guideline dose range for adrenal insufficiency, it is recognized that many patients with CAH require a higher dose [Speiser et al, 2018]. In the Phase 3 study DIUR-005, participants were titrated in a blinded manner to a final dose on both Chronocort and standard treatment of approximately 30 mg a day (15.8 and 17.0 mg/m^2/day, respectively) and this is a similar dose to that reported in published studies in patients with CAH of 15 to 18 mg/m^2/day [Chakhtoura et al, 2008; Arlt et al, 2010; Schnaider-Rezek et al, 2011; Finkielstain et al, 2012]. This dose then reflects real world patient care and additionally provides a dose where patients are not at risk of adrenal crisis. In addition, in the Phase 2 study DIUR-003, Chronocort patients were safely transferred from standard therapy to a dose of 30 mg hydrocortisone and then down-titrated with no ill effects [Mallappa et al, 2015].

Participants in this study will receive IRHC 30 mg a day for 4 weeks during the run-in period and will then be randomized to either stay on this therapy or switch to Chronocort 30 mg a day. If a participant shows persistent signs of under-replacement during the run-in period they must be withdrawn from the study. After 4 weeks of randomized treatment, a maximum of 3 down titrations of 5 mg will be allowed, so potentially reaching a minimum final dose of

15 mg a day, consistent with the lower range boundary of the recommended adrenal insufficiency dose. If a participant shows persistent signs of under-replacement during the titration period and has received at least 1 down titration of 5 mg, a reversion to the previous dose is permitted (i.e. an increase of 5 mg). If symptoms persist at a dose of 30 mg, no further dose increases can be made, and the participant should be withdrawn from study treatment (but will remain in the study and followed for safety assessments).

4.6. End of Study Definition

A participant is considered to have completed the study if he/she has completed all study visits up to the EOS visit (Visit 6). If the participant enters the long-term safety study DIUR-015, no further data are collected in this study. If the participant does not enter the long-term safety study (DIUR-015), a final telephone call will be made 30 days after Visit 6 to ask about any AEs that were ongoing at Visit 6 and any new SAEs that could be related to the study medication.

The end of the whole study is defined as the date of the last study visit or telephone call of the last participant (i.e. last participant last visit [LPLV]).

5. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply (note: if a participant fails to meet an inclusion criterion, re-screening is permitted if the Investigator considers that the circumstances leading to screening failure will not be relevant when the participant is re-screened at a later time):

Age

1. Participant must be aged 16 years or older at the time of signing the informed consent/assent.
2. In participants aged <18 years, height velocity must be less than 2 cm/year in the last year and puberty must be completed (Tanner stage V).

Type of Participant and Disease Characteristics

3. Participants with known classic CAH due to 21-hydroxylase deficiency diagnosed in childhood with documented (at any time) elevated 17-OHP and with or without elevated A4 and currently treated with hydrocortisone, prednisone, prednisolone or dexamethasone (or a combination of the aforementioned glucocorticoids) and on stable glucocorticoid therapy for a minimum of 3 months.
4. Participants who are receiving fludrocortisone must be on a documented stable dose for a minimum of 3 months prior to enrollment and must have stable renin levels at screening.

Sex

5. Male and female participants.
   Female participants of childbearing potential and all male participants must agree to the use of an accepted method of contraception during the study.

   A female participant is eligible to participate if she is not pregnant (Appendix 4), not breastfeeding, and at least one of the following conditions applies:

   Not a woman of childbearing potential (WOCBP) as defined in Appendix 4.

   OR

   A WOCBP with a negative pregnancy test at entry into the study.

   Note: females presenting with oligomenorrhea or amenorrhea who are aged ≤55 years should be considered potentially fertile and therefore should undergo pregnancy testing like all other female participants.

Informed Consent/Assent

6. Capable of giving signed informed consent/assent as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply (note: if a participant meets an exclusion criterion, re-screening is permitted if the Investigator considers that the circumstances leading to screening failure will not be relevant when the participant is re-screened at a later time):

Medical Conditions

1. Clinical or biochemical evidence of hepatic or renal disease e.g., creatinine >2 times the upper limit of normal (ULN) or elevated liver function tests (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] >2 times the ULN).
2. History of bilateral adrenalectomy.
3. History of malignancy (other than basal cell carcinoma successfully treated >26 weeks prior to entry into the study).
4. Participants who have type 1 diabetes, receive regular insulin, have uncontrolled diabetes, or have a screening HbA1c greater than 8%.
5. Persistent signs of adrenal insufficiency or the participant does not tolerate treatment at the end of the 4-week run-in period.
6. Participants with any other significant medical or psychiatric conditions that in the opinion of the Investigator would preclude participation in the study.

Prior/Concomitant Therapy

7. Participants on regular daily inhaled, topical, nasal or oral steroids for any indication other than CAH.
8. Co-morbid condition requiring daily administration of a medication or consumption of any material that interferes with the metabolism of glucocorticoids (examples provided at http://medicine.iupui.edu/clinpharm/ddis/clinical-table/).
9. Participants who are receiving <10 mg hydrocortisone dose at screening or the hydrocortisone dose equivalent.
10. Participants anticipating regular prophylactic use of additional steroids e.g. for strenuous exercise.

Prior/Concurrent Clinical Study Experience

11. Participation in another clinical study of an investigational or licensed drug or device within the 12 weeks prior to screening.
12. Inclusion in any natural history or translational research study that would require evaluation of androgen levels during the study period outside of this protocol's assessments.
13. Participants who have previously been exposed to Chronocort in any Diurnal study.

Other Exclusions

14. Participants who routinely work night shifts and so do not sleep during the usual night-time hours.
15. Participants, who in the opinion of the Investigator, will be unable to comply with the requirements of the protocol.
16. Participants with a known hypersensitivity to any of the components of the Chronocort capsules, the Cortef tablets, or the placebo capsules (see Section 6.1).
17. Participants with congenital galactosemia, malabsorption of glucose and galactose, or who are lactase deficient.
18. Participants with a body weight of 45 kg or less.

5.3. Lifestyle Considerations

- All participants will take study medication (or matching placebo) 3 times a day (morning, afternoon, and evening). The study medication should be taken in the morning on waking (typically between 06:00 and 08:00 hours), in the afternoon (between 15:00 and 17:00 hours), and just prior to going to bed (typically between 22:00 hours and midnight).
- When attending a clinic visit, participants should not eat any food prior to the 08:00 hour blood sampling timepoint.
- Male participants should not take multivitamins or dietary supplements containing biotin or vitamin B7 for 12 hours prior to each visit (to avoid interference with LH test results).
- Male participants should not ejaculate for 3 days prior to Visits 2 and 6 when sperm counts will be assessed (note: sperm count conducted at home only in participants who agree to this assessment).
- Participants should not take regular additional prophylactic steroids e.g. for strenuous exercise.
- Participants should not have their androgen levels assessed outside of the study visits during this study (including the use of home assessment kits).
- Participants are requested not to reveal details of the study on social media.

5.4. Screen Failures

Screen failures are defined as participants who consent/assent to participate in the clinical study but are not subsequently entered into the IRHC run-in period. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

If a participant fails to meet the screening criteria, re-screening of any inclusion/exclusion criteria is permitted if the Investigator considers that the circumstances leading to failure will not be relevant when the participant is re-screened at a later time. Re-screened participants should be assigned the same participant number as they were assigned during their initial screening visit.

6. Study Treatment

Study treatment is defined as any investigational intervention, marketed product, placebo, or medical device intended to be administered to a study participant according to the study protocol.

6.1. Study Treatments Administered

The IMPs for this study are Chronocort and IRHC (Cortef). All participants will receive 4 weeks run-in with 30 mg IRHC (20 mg in the morning on waking [typically between 06:00 and 08:00 hours] and 10 mg in the afternoon [between 15:00 and 17:00 hours]). At the end of the 4-week run-in period, participants will be randomized to either Chronocort or to continue with IRHC treatment. The last dose of study medication will be taken in the morning of the last dosing day.

Arm name:	**Chronocort**	**IRHC**	**Placebo**
Treatment name:	Chronocort	Cortef	Placebo
Type:	Drug	Drug	Placebo
Dosage formulation:	Hydrocortisone modified-release capsule	Hydrocortisone immediate-release tablet	Placebo capsule
Unit dose strengths:	5 mg and 10 mg. 5 mg presented in white opaque body/blue opaque cap size 1 hard gelatin capsules, printed with 'CHC 5 mg' on the capsule body. 10 mg presented in white opaque body/green opaque cap size 1 hard gelatin capsules, printed with 'CHC 10 mg' on the capsule body.	5 mg and 10 mg. 5 mg presented as white tablet with CORTEF 5 printed on one side. 10 mg presented as white tablet with CORTEF 10 printed on one side.	Swedish Orange capsule shells filled with inert excipient.
Dosage levels:	Starting dose of 30 mg with 3 possible 5 mg dose reductions to a minimum dose of 15 mg	Starting dose of 30 mg with 3 possible 5 mg dose reductions to a minimum dose of 15 mg	Adapted to match dose of IMP dosing
Route of Administration:	Oral	Oral	Oral
Use:	Experimental	Active comparator	Placebo
IMP:	IMP	Comparator	Placebo
Dosing instructions:	10 mg in the morning on waking (typically between 06:00 and 08:00 hours) and 20 mg at night just prior to bed (typically between 22:00 hours and midnight) then titrated as per protocol. All doses taken with a small drink of water.	20 mg in the morning on waking (typically between 06:00 and 08:00 hours) and 10 mg in the afternoon (between 15:00 hours and 17:00 hours) then titrated as per protocol. All doses taken with a small drink of water.	Adapted to match dose of Chronocort and Cortef. All doses taken with a small drink of water.
Sourcing:	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Manufacturer:	Diurnal	Pfizer	Diurnal

Packaging and Labelling:	Both dose strengths over-encapsulated with Swedish Orange capsule shells. All supplies will be labelled in accordance with local requirements.	Both dose strengths over-encapsulated with Swedish Orange capsule shells and back-filled with inert excipient. All supplies will be labelled in accordance with local requirements.	Placebo provided as Swedish Orange capsule shells filled with inert excipient. All supplies will be labelled in accordance with local requirements

IMP=investigational medical product

The active ingredients and excipients are shown below:

Chronocort	Placebo	Cortef
Active ingredient		
Active ingredient: hydrocortisone	Active ingredient: none	Active ingredient: hydrocortisone
Excipients		
Microcrystalline cellulose Povidone Methacrylic acid-methyl methacrylate copolymer (1:2) Methacrylic acid-methyl methacrylate copolymer (1:1) Talc Dibutyl sebacate	Microcrystalline cellulose	Calcium stearate Corn starch Lactose Mineral oil Sorbic acid Sucrose
Capsule	**Capsule**	**Tablet Coating**
Gelatin *5 mg:* Titanium dioxide (E171) Indigotine (E132) *10 mg:* Titanium dioxide (E171) Indigotine (E132) Yellow iron oxide (E172) *Printing ink:* Shellac Black iron oxide (E172) Propylene glycol Potassium hydroxide	Gelatin *5 mg:* Titanium dioxide (E171) Indigotine (E132) *10 mg:* Titanium dioxide (E171) Indigotine (E132) Yellow iron oxide (E172) *Printing ink:* Shellac Black iron oxide (E172) Propylene glycol Potassium hydroxide	None
Over-encapsulating Swedish Orange capsule shells		
Red Iron Oxide (E172)	Red Iron Oxide (E172)	Red Iron Oxide (E172)
Titanium Dioxide (E171)	Titanium Dioxide (E171)	Titanium Dioxide (E171)
Gelatin (Bovine)	Gelatin (Bovine)	Gelatin (Bovine)

6.1.1. Rescue Medication

Medication to be used when the 'stress dosing rules' are implemented will be supplied by the study site as part of an emergency treatment pack. The contents will typically include (according to local practice):

- A one-week supply of 10 mg oral hydrocortisone tablets (to allow rescue medication doses of up to 60 mg daily on top of the dose of IMP)
- Hydrocortisone for injection plus syringes and needles (to be given on top of the dose of IMP)

- The standard information guidance regarding ‘stress dosing rules’.

Diurnal will provide appropriate labels for the emergency treatment pack that can be used to label the drugs dispensed to participants (see Appendix 6). The participant number must be written on the emergency treatment pack label.

Participants will continue to take their usual study medication when taking emergency treatment pack medications. Any additional doses of hydrocortisone needed should only be taken from the emergency treatment pack and should not be taken from the study medication pack or any other supplies the participant may have at home. Use of the emergency treatment pack medications does not require authorization but should be recorded in the electronic participant diary that is provided to each participant.

6.2. Preparation/Handling/Storage/Accountability

The pharmacist or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatments received and any discrepancies are reported and resolved before use of the study treatments. Only participants enrolled in the study may receive study treatment and only authorized staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the pharmacy staff. The pharmacist is responsible for study treatment accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation, and final disposition records) of supplies.

At each visit, the independent blinded physician will decide if a dose adjustment is needed and the appropriate IMP packs will be sent to the participant, either to collect from their local study site or sent directly to the participant’s home (note: the changes will also include the relevant changes to the placebo capsules to maintain the blinding). At the same time, the participant’s current supplies will be collected for accountability purposes and to ensure that the participant cannot take the wrong medication. The returns pharmacy will count the number of returned capsules and enter the information in the IRT, so compliance can be calculated. Following Sponsor’s approval, all returned active and placebo capsules will either be returned to the supplier or destroyed on site.

At each visit to the study site, the participants must return the stress dosing pack and accountability must be performed at each study visit. If the emergency treatment pack has been used this must be documented and reconciled with the reported AEs for that period. If the contents of the emergency treatment pack have not been used and the products remain with sufficient expiry date then it is acceptable for it to be returned to the participant (i.e. a new emergency treatment pack does not need to be issued).

6.3. Measures to Minimize Bias: Randomization and Blinding

This is a double-blinded study with 2 treatment arms. The blinded treatment to be taken by a participant will be assigned using an IRT on a 1:1 basis (Chronocort:IRHC). Before the study is initiated, the login information and instructions for use of the IRT will be provided to each site. The randomization list will be generated by the study statistician using a computer-generated central randomization list using balanced blocks. Randomization will be balanced

within site and stratified by the participant's fludrocortisone replacement status (requires fludrocortisone or does not require fludrocortisone).

Participants will be allocated an identifying number sequentially per site at the screening visit (Visit 1) in the following format: Study No.-Site No.-Screening No. (e.g. [redacted], [redacted] etc. for site 1; [redacted] etc. for site 2). When the participant is randomized at the baseline visit (Visit 2), a separate randomization number will be allocated, which will be used internally for the purposes of treatment allocation and stratum identification. The screening number will still be used for participant identification purposes, so there may be gaps in participant ID numbers for screen failures. Randomization numbers will be assigned sequentially within each stratum as soon as participants fully satisfy all of the inclusion and none of the exclusion criteria. Screening and randomization numbers once assigned to a participant must not be re-assigned to another participant. Re-screened participants should be assigned the same participant number as they were assigned during their initial screening visit.

Potential bias in this study will be reduced by the following steps:

- Records will be kept of any participants screened, whether or not they enter the study. This will enable an assessment of the representative nature of the participants randomized.
- Both study treatments will be over-encapsulated so that they look the same, so both the participant and the Investigator will not know which treatment group the participant has been randomized to.
- The titration of each participant's dose of study treatment will be the same in both arms and will be based on the adrenal insufficiency checklist and androgen sampling thus ensuring that opportunities for optimization and control of androgens are the same in both arms.
- The dose titration decisions will be made by an independent blinded physician who will be unaware of the treatment allocation to each participant.
- The treatment packs for each participant will be pre-packed and packs issued by the IRT to ensure that each participant receives the correct number of active and placebo capsules. After each visit, new supplies will be provided to the participant that contain the same number of capsules as the previous supplies (with placebo capsules masking any changes), regardless of whether the dose was titrated or not, thus ensuring the participant is not aware of any dose changes.
- The primary endpoint is an objective biochemical measure that is not subject to bias.
- Efforts will be made to ensure that all participants remain in the study and are evaluable.
- There will be rigorous monitoring of sites to ensure compliance with all study procedures.
- The statistical analysis plan (SAP) will be completed before screening of the first participant to the study.
- Treatment will be allocated using block randomization. The block size will be determined by the statistician and will not be communicated to the study team.
- To minimize bias whilst the study is ongoing, the study team will remain blinded to aggregated and individual data prior to database lock and any data reviews will use a dummy randomization list with generic labels.

- Participants and Investigators will be requested not to reveal details of the study on social media.

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact the medical monitor prior to unblinding a participant's intervention assignment unless this could delay emergency treatment for the participant. If a participant's intervention assignment is unblinded, the Sponsor must be notified within 24 hours of this occurrence. The date and reason for the unblinding must be recorded.

6.4. Study Treatment Compliance

At each delivery of new supplies to a participant, their current supplies will be collected for accountability purposes and to ensure that the participant cannot take the wrong medication. The research team will count the number of returned capsules and enter the information in the IRT, so compliance can be calculated.

6.5. Concomitant Therapy

Previous treatments for CAH (last 26 weeks) and any other previous treatments (last 4 weeks) will be recorded at the screening visit (Visit 1) in the eCRF. Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, herbal supplements etc.) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency.

In particular, use of multivitamins or dietary supplements containing biotin or vitamin B7 in male participants should be recorded since their use is prohibited for 12 hours prior to each visit (to avoid interference with LH test results).

If a participant has received the COVID-19 vaccine then the next visit must be scheduled at least 5 days post vaccine. If the participant experiences any side effects from the COVID-19 vaccine then they should take additional stress doses in line with the "stress dosing rules" (see Appendix 6). If a stress dose is taken within 5 days of a visit (scheduled clinic visit or home assessment timepoint), then the visit should be delayed until the participant has had a 5-day period without use of any stress dose.

Participants will be instructed that no additional medication will be allowed without the prior consent of the Investigator. Any medication considered necessary for the participant's safety and well-being may be given at the discretion of the Investigator but must be recorded in the eCRF. The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy. Participants must not take part in another clinical study of an investigational or licensed drug or device within the 12 weeks prior to screening or during the course of this study.

Fludrocortisone treatment and dose adjustment will be allowed if medically indicated and will be based on blood pressure (BP) measurements and laboratory data (goal supine plasma renin activity [PRA] or plasma renin concentration [PRC] above the lower limit and <2 times ULN except in participants with known hypertension or who have a raised PRA or PRC for other reasons).

Participants receiving insulin or who are on regular daily inhaled, topical, nasal or oral steroids for any indication other than CAH at entry to the study are excluded (Section 5.2). A participant should not be given any steroids (even on an irregular basis) within 5 days of a study visit. If there is a medical need for steroid treatment within this time-frame then the visit should be postponed until a 5-day interval has elapsed.

6.5.1. Interactions With Other Medicinal Products and Other Forms of Interaction

Hydrocortisone is metabolized by cytochrome P450 3A4 (CYP3A4). Concomitant administration of medicinal products that are inhibitors or inducers of CYP3A4 may therefore lead to unwanted alterations in serum concentrations of hydrocortisone with the risk of adverse reactions, particularly adrenal crisis. The need for dose adjustment when such medicinal products are used can be anticipated and should be considered at time of inclusion of a participant in the study. Participants should be closely monitored, although it should be noted that any dose changes should be conducted in line with the titration schedule and due to the blinded nature of the study, Investigators will not be able to individually adjust participant's doses during the study.

Medicinal products inducing CYP3A4, requiring a potential increase in Chronocort dosing, include but are not limited to:

- Anticonvulsants: phenytoin, carbamazepine and oxcarbazepine
- Antibiotics: rifampicin and rifabutin
- Barbiturates including phenobarbital and primidone
- Antiretroviral medicinal products: efavirenz and nevirapine
- Herbal medicinal products such as St. John's Wort

Medicinal products/substances inhibiting CYP3A4, requiring a potential decrease in hydrocortisone dosing, include but are not limited to:

- Anti-fungals: itraconazole, posaconazole, voriconazole
- Antibiotics: erythromycin and clarithromycin
- Antiretroviral medicinal products: ritonavir
- Grapefruit juice
- Liquorice

The desired actions of hypoglycaemic medicinal products including insulin are antagonised by corticosteroids.

6.6. Dose Modification

Monitoring of the clinical response is necessary, and participants should be observed closely for signs that might require dose adjustment, including changes in clinical status resulting from remissions or exacerbations of the disease, changes in electrolytes particularly hypokalemia, individual responsiveness to the medicinal product, and the effect of stress (e.g.

surgery, infection, trauma). Concerns with an individual participant should be raised with the medical monitor as due to the blinded nature of the study, Investigators are not permitted to routinely adjust the dose during the study. As the treatment has a modified-release profile, blood tests are used to monitor clinical response by the independent blinded physician, with dose titrations being made after Visits 3, 4, and 5. Both treatment arms are subject to similar titration rules at each visit (see Section 4.2). The only dose titration permitted at the titration visits at Visits 3, 4, and 5 are a 5 mg decrease in dose, except if a participant shows persistent signs of under-replacement during the titration period and the participant has received at least 1 down titration of 5 mg, in which case a reversion to the previous dose is permitted (i.e. an increase of 5 mg). If symptoms persist, no further dose increases can be made, and the participant should be withdrawn from study treatment (such cases should be discussed with the medical monitor). If the Investigator thinks that the dose needs to be adjusted between visits, they should contact the medical monitor to discuss the case. Any other dose increases can only be made in an urgent situation where the Investigator believes the participant is exhibiting signs of adrenal insufficiency, and in all cases, this should be discussed with the medical monitor before a dose increase is initiated. For emergency situations, the emergency treatment pack can be used, and the medical monitor should be contacted as soon as possible.

6.7. Treatment after the End of the Study

All participants who have completed the study will be offered commercial supplies of Chronocort or the option to enter an open-label extension study (to be conducted under a separate protocol DIUR-015). This will be dependent on territory. Participants discontinuing from the study will not be offered the option to enter the open-label extension study.

7. Discontinuation of Study Treatment and Participant Discontinuation/Withdrawal

7.1. Discontinuation of Study Treatment

Events that will result in discontinuation of study treatment include:

- Inability to tolerate either study treatment secondary to perceived or observed side effects.
- Pregnancy (not due to safety reasons but because pregnancy may interfere with the primary endpoint)
- Any other changes to clinical signs or changes in laboratory values, physical status or AEs that could compromise the participant's status if they were to continue with the study treatment or if the Investigator feels that it is not in the best interests of the participant.

If a participant shows persistent signs of under-replacement on the starting dose of 30 mg Chronocort or IRHC they will be monitored and if symptoms do not resolve the participant should be withdrawn from study treatment. If a participant shows persistent signs of under-replacement during the titration period and has received at least 1 down titration of 5 mg, a reversion to the previous dose is permitted (i.e. an increase of 5 mg) after discussion with the medical monitor. If symptoms persist, no further dose increases can be made, and the participant should be withdrawn from study treatment (such cases should be discussed with the medical monitor).

If a participant discontinues study treatment, they should be placed onto the previous glucocorticoid treatment and dose they were receiving prior to entry into this study. They should complete as many of the assessments scheduled for Visit 6 as possible, preferably within 48 hours of stopping study treatment. In all cases except pregnancy (see Section 8.4.5 for handling of any pregnancies) the participant should be kept in the study, if the participant consents to this, and all further safety assessments conducted in line with the protocol schedule (note: no efficacy endpoints will be collected once the assessments detailed for Visit 6 [early withdrawal] are completed). The date the participant discontinues study treatment and the reason for discontinuation will be recorded on the participant's eCRF. Participants who have been randomized to study treatment and who discontinue from study treatment are not to be replaced. The handling of safety data collected after the participant has discontinued study treatment will be detailed in the SAP.

Participants who discontinue study treatment are not eligible to enter the long-term extension study (DIUR-015), except in the case of pregnancy (see Section 8.4.5).

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request without stating a reason and without prejudice to further treatment, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. Participants who become pregnant must be withdrawn from the study (see Section 8.4.5).

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent. The

participant may also request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

If at the baseline visit the participant has had persistent signs of adrenal insufficiency or they have not tolerated the 4-week run-in medication, they should be withdrawn from the study at this point before randomization.

If a participant discontinues from the study prior to the last scheduled visit, all efforts should be made to perform the EOS assessments (as per Visit 6) at the point the participant withdraws from the study (at the latest within 48 hours of the last dose of study medication). In particular, the androgen measurements should be taken if possible.

Participants who discontinue from the study are not eligible to enter the long-term extension study (DIUR-015) except in the case of pregnancy (see Section 8.4.5).

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. The following actions will be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and re-schedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study at the time of their last assessment, with a primary reason of lost to follow-up.

Discontinuation of specific sites or of the study as a whole are detailed in Appendix 1.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the Schedule of Activities (SoA) (Section 1.3). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Sponsor and the medical monitor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g. blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time-frame defined in the SoA (Section 1.3).
- At any visit, if multiple assessments are being conducted, vital signs should be conducted before any blood tests, and blood samples for androgen testing and optional saliva samples for salivary steroid profile must be conducted prior to any dosing. All other assessments should be conducted between the 08:00 and 13:00 androgen sampling points, where possible.
- If a visit has to be moved (e.g. due to use of 'stress dosing rules'), the participant should return to their usual visit schedule as soon as possible (i.e. all subsequent visits should not be moved out as well).
- In some cases (e.g. if the participant lives a long way from the study site or if pandemic guidelines dictate) study visits 3 and 4 may be performed as domiciliary visits and IMP shipments can be made directly to the participant's home. However, the following visits must be performed at the study site: Screening (Visit 1), Baseline (Visit 2), Week 16 (Visit 5), and EOS/early withdrawal visit (Visit 6). If necessary in some cases, IMP at Visit 5 can also be delivered to the participant's home. If a domiciliary visit is conducted the safety and endocrine blood samples must be sent to the central laboratory for analysis and the Investigator must complete the adrenal insufficiency checklist. The assessment of hirsutism and acne can be conducted via a video call (within ±2 days of the domiciliary visit). If androgen samples are analyzed locally for safety reasons the participant must be withdrawn from treatment.
- If a participant discontinues treatment early (see Section 7.1), the assessments scheduled for Visit 6 (end of treatment) should be conducted, if possible, preferably within 48 hours of stopping study treatment. The participant should be kept in the study, if the participant consents to this, and all further safety assessments conducted in line with the protocol schedule (note: no efficacy endpoints will be collected once the assessments detailed for Visit 6 [early withdrawal] are completed).

8.1. Study Visits

8.1.1. Visit 1 (Screening Visit - Week -4)

Four weeks prior to the baseline visit, participants will be requested to attend the study site for the screening visit (it is mandatory that this visit is conducted at the study site). Prior to the visit, the site staff should contact the participant to check that they have been receiving their usual CAH medication and 'stress dosing rules' have not been applied in the 5 days preceding the visit date. If the 'stress dosing rules' have been applied, then the visit should be postponed until the participant has been receiving their usual CAH medication for 5 days. The participant will be told to take their CAH medication at the usual times throughout the visit. The ICF should be given to the participant at least 24 hours before the screening visit, along with the Investigator's contact details, so that each participant has sufficient time to read the information and ask any questions they may have. If necessary, at Visit 1 the ICF can be reviewed again with the participant and the participant given ample opportunity to ask any questions before they are asked to sign it. The ICF must be signed at or before Visit 1 and prior to any study related procedures.

Minors will be assented, and parental consent sought in keeping with USA and EU laws and local Independent Ethics Committee (IEC) or Institutional Review Board (IRB) requirements. Minors will be re-consented on reaching the age of majority if still participating in the study at that time.

The following assessments will be carried out and recorded at this visit:

- All inclusion and exclusion criteria checked
- Demographic data
- Medical history taken (including menstrual history, menopausal status and oral contraception use in female participants)
- Details on concomitant medications taken (CAH medication will be recorded separately from other concomitant medications)
- Signs and symptoms of adrenal insufficiency using the adrenal insufficiency checklist
- Height, weight, and waist circumference will be measured
- Full physical examination
- Vital signs (BP, heart rate [HR], respiratory rate and body temperature). BP to be recorded after the participant has been semi-supine for 10 minutes.
- Urine sample for urinalysis
- Blood samples will be taken for routine biochemistry and hematology
- Sample taken for PRA or PRC, preferably after the participant has been supine for 30 minutes
- Blood sample taken for HbA1c
- Pregnancy test in WOCBP (either urine or blood as per the site's usual practice)
- Record the details of the participant's glucocorticoid doses for the previous 24 hours and throughout the visit.
- Recording of any AEs since informed consent/assent was taken.
- Blood sampling for measurement of androgen levels (17-OHP and A4)

The participants will be told not to take their morning dose of IRHC before attending for the visit (the morning dose will be taken after the 08:00 hour androgen sample). The androgen

sampling will commence at 08:00 hours, with 1 other sample taken at 13:00 hours. These blood samples are to be taken within ±30 minutes of the stated timepoints, with the exact sampling times recorded in the eCRF. Half the sample will be sent to the central laboratory for analysis, with the remaining half initially retained at the site before being sent to the central laboratory and then on to the biobank for long-term storage and possible future research. Participants will then be switched to the run-in medication, which will comprise 20 mg IRHC in the morning on waking (typically between 06:00 and 08:00 hours) and 10 mg in the afternoon (between 15:00 and 17:00 hours) for the next 4 weeks. Once the last blood sample has been taken at 13:00 hours and all other assessments have been completed, the participant will be allowed home, and instructed to take their first dose of run-in medication later that afternoon (between 15:00 and 17:00 hours). The participant will also be issued with an emergency treatment pack to be used in the event of illness and implementation of 'stress dosing rules' (Section 6.1.1). The participant will be asked to return to the clinic in 4 weeks' time for the baseline visit (Visit 2).

8.1.2. Visit 2 (Baseline Visit - Day 1: 4 Weeks After the Screening Visit)

Prior to the visit, the site staff should contact the participant to check that 'stress dosing rules' have not been applied in the 5 days preceding the visit date. If 'stress dosing rules' have been applied, then the visit should be postponed until the participant has been receiving only the run-in IRHC medication for 5 days. It is mandatory that this visit is conducted at the study site. The participant will be instructed to bring any empty packaging and any unused run-in medication and the emergency treatment pack with them to the visit for accountability purposes (note: participants take unused study medication and emergency treatment pack back home with them to use until the dose titration decision is made and new study medication dispensed). The participants will be told not to take their morning dose of IRHC before attending for the visit (the morning dose will be taken after the 08:00 hour androgen sample and optional saliva sample [where applicable]). Male participants will be asked not to take multivitamins or dietary supplements containing biotin or vitamin B7 for 12 hours prior to the visit (to avoid interference with LH test results) and also not to ejaculate for the preceding 3 days for the sperm count assessment (if the participant has consented to this assessment). If the participant has had persistent signs of adrenal insufficiency or they have not tolerated the 4-week run-in medication, they should be withdrawn from the study at this point before randomization.

The following assessments will be carried out and recorded at this visit:

- Limited check of inclusion/exclusion criteria
- Record the details of the participant's glucocorticoid doses for the previous 24 hours and throughout the visit
- Participants will be asked about any AEs and concomitant medications changes since the last visit
- Vital signs (BP, HR, respiratory rate and body temperature. BP to be recorded after the participant has been semi-supine for 10 minutes)
- Full physical examination
- Height, weight, and waist circumference will be measured
- Assessment of menstrual cycle changes in all pre-menopausal women

- Assessment of hirsutism by female participants using a VAS and by Investigators using Ferriman-Gallwey score
- Assessment of acne by female participants using a VAS and by Investigators using the GEA
- Assessment of alertness by the participant using a VAS
- Signs and symptoms of adrenal insufficiency using the adrenal insufficiency checklist
- The following questionnaires will be completed: SF-36®, MAF, and EQ-5D-5L™
- ECG
- TART measured by ultrasound in male participants (results read by central laboratory)
- Sperm count measured at home using a testing kit supplied to the male participants (only in participants who have consented to this assessment)
- Urinalysis
- Blood sample for FSH, osteocalcin, LH, 11-ketotestosterone, total testosterone, DHEA, and routine biochemistry and hematology
- Pregnancy test in WOCBP (either urine or blood as per the site's usual practice)
- Review of returned run-in medication and emergency treatment pack for compliance
- Blood sampling for measurement of androgen levels (17-OHP and A4) at 08.00 (pre-dose) and 13.00 hours
- Saliva samples collected for exploratory analysis at 08.00 (pre-dose) and 13.00 hours (optional).

The androgen blood samples are to be taken within ±30 minutes of the stated timepoints, with the exact sampling times recorded in the eCRF. Half the sample will be sent to the central laboratory for analysis, with the remaining half initially retained at the site before being sent to the central laboratory and then on to the biobank for long-term storage and possible future research. Once the participant's eligibility for the study has been confirmed, the participant will be randomized via the IRT to either Chronocort or to continue with IRHC. The IRT will take into account the participant's fludrocortisone replacement status (requires fludrocortisone or does not require fludrocortisone). Participants randomized to Chronocort will change to a dosing regimen of 10 mg in the morning on waking (typically between 06:00 and 08:00 hours) and 20 mg at night just prior to going to bed (typically between 22:00 hours and midnight) whereas participants randomized to IRHC will continue the same dosing regimen as they were receiving during the run-in period (20 mg in the morning on waking [typically between 06:00 and 08:00 hours] and 10 mg in the afternoon [between 15:00 and 17:00 hours]). Placebo capsules will also be provided to maintain the study blinding. The participant will be dispensed with the correct active and placebo study medication and an emergency treatment pack in case they need to implement 'stress dosing rules', and then they will be allowed home. Participants will be instructed to take their first dose of study medication that afternoon. Participants will be asked to record the dose, date and time they took the first dose of study medication (Chronocort or IRHC) in their electronic participant diary.

Participants will be given an electronic participant diary and will be instructed what to record in it. In particular, they will be instructed to complete the alertness VAS on a weekly basis in the morning before their morning dose of study medication. The same day of the week should

be used each week. The participant will be asked to attend the clinic for Visit 3 in 4 weeks' time.

8.1.3. Visit 3 (Titration Visit - Week 4 + 1 Week)

Four weeks after the previous visit (+ 1 week), the participant will be requested to attend the study site for testing of androgen levels (if necessary this visit can be conducted as a domiciliary visit). Prior to the visit, the site staff should contact the participant to check that 'stress dosing rules' have not been applied in the 5 days preceding the visit date. If 'stress dosing rules' have been applied, then the visit should be postponed until the participant has been receiving no stress dosing medication for 5 days. The participant will be instructed to bring any empty packaging and any unused study medication and the emergency treatment pack with them to the visit for accountability purposes (note: participants take unused study medication and emergency treatment pack back home with them to use until the dose titration decision is made and new study medication dispensed). The participants will be told not to take their morning dose of study medication before attending for the visit (the morning dose will be taken after the 08:00 hour androgen sample and optional saliva sample [where applicable]). Male participants will be asked not to take multivitamins or dietary supplements containing biotin or vitamin B7 for 12 hours prior to the visit (to avoid interference with LH test results).

The following assessments will be carried out and recorded at this visit:

- Record the details of the participant's glucocorticoid doses for the previous 24 hours and throughout the visit
- Participants will be asked about any AEs (including events considered to be of unexpected benefit) and concomitant medications changes since the last visit
- Vital signs (BP, HR, respiratory rate and body temperature. BP to be recorded after the participant has been semi-supine for 10 minutes)
- Abbreviated physical examination (if indicated by AEs)
- Height, weight, and waist circumference will be measured
- Assessment of menstrual cycle changes in all pre-menopausal women
- Assessment of hirsutism by female participants using a VAS and by Investigators using Ferriman-Gallwey score (the Investigator can assess this via a video call if a domiciliary visit is conducted for this visit [within ±2 days of the domiciliary visit])
- Assessment of acne by female participants using a VAS and by Investigators using the GEA (the Investigator can assess this via a video call if a domiciliary visit is conducted for this visit [within ±2 days of the domiciliary visit])
- Assessment of alertness by the participant using a VAS
- Signs and symptoms of adrenal insufficiency using the adrenal insufficiency checklist (the Investigator must complete the checklist even if a domiciliary visit is conducted for this visit)
- The following questionnaires will be completed: SF-36®, MAF, and EQ-5D-5L™
- Blood sample for HbA1c, FSH, osteocalcin, LH, and routine biochemistry and hematology
- Urinalysis
- Pregnancy test in WOCBP (either urine or blood as per the site's usual practice)
- Review of emergency treatment pack for compliance

- Blood sampling for measurement of androgen levels (17-OHP and A4) at 08.00 (pre-dose) and 13.00 hours
- Saliva samples collected for exploratory analysis at 08.00 (pre-dose) and 13.00 hours (optional).

The androgen blood samples are to be taken within ±30 minutes of the stated timepoints, with the exact sampling times recorded in the eCRF. Half the sample will be sent for analysis at the central laboratory, with the remaining half initially retained at the site before being sent to the central laboratory and then on to the biobank for long-term storage and possible future research.

The participant will be asked to attend the clinic for Visit 4 in 6 weeks' time. Participants will be reminded to complete the alertness VAS on a weekly basis in the morning before their morning dose of study medication. The same day of the week should be used each week. Participants will be discharged once the last androgen sample has been taken and all other assessments have been completed.

Following determination of the Visit 3 androgen levels and completion of the adrenal insufficiency checklist, a decision will be made by an independent blinded physician as to whether the participant's dose should be adjusted, and the appropriate IMP packs will be sent to the participant, either to collect from their local study site or sent directly to the participant's home (note: the changes will also include the relevant changes to the placebo capsules to maintain the blinding). The treatment packs for each participant will always contain the same number of capsules as the previous supplies (with placebo capsules masking any changes), thus ensuring the participant is not aware of any dose changes. Participants will be asked to record the dose, date and time they took the first dose of the revised study medication (if applicable) in their electronic participant diary.

Any dose titrations should be made within 2 to 3 weeks of the visit (dependent on the laboratory turnaround time of androgen samples, the time needed by the independent blinded physician to evaluate the data, and for the supplies to be sent to the participant).

8.1.4. Telephone Call T3.1 (Visit 3 + 2 to 5 Weeks)

One week after delivery of the new supplies to the participant, the study site will telephone the participant to check the supplies have been received and any old supplies returned. The participant will be asked about any AEs and changes in concomitant medications at this call and any AEs or changes in concomitant medication reported will be recorded in the eCRF.

8.1.5. Visit 4 (Titration Visit - Week 10 ± 1 Week)

Six weeks after the previous visit (± 1 week), participants will be requested to attend the study site for testing of androgen levels (if necessary this visit can be conducted as a domiciliary visit). Prior to the visit, the site staff should contact the participant to check that 'stress dosing rules' have not been applied in the 5 days preceding the visit date. If 'stress dosing rules' have been applied, then the visit should be postponed until the participant has been receiving no stress dosing medication for 5 days. The participant will be instructed to bring any empty packaging and any unused study medication and the emergency treatment pack with them to the visit for accountability purposes (note: participants take unused study medication and emergency treatment pack back home with them to use until the dose titration

decision is made and new study medication dispensed). The participants will be told not to take their morning dose of study medication before attending for the visit (the morning dose will be taken after the 08:00 androgen sample and optional saliva sample [where applicable]). Male participants will be asked not to take multivitamins or dietary supplements containing biotin or vitamin B7 for 12 hours prior to the visit (to avoid interference with LH test results).

The following assessments will be carried out and recorded at this visit:

- Record the details of the participant's glucocorticoid doses for the previous 24 hours and throughout the visit
- Participants will be asked about any AEs (including events considered to be of unexpected benefit) and concomitant medications changes since the last visit
- Vital signs (BP, HR, respiratory rate and body temperature. BP to be recorded after the participant has been semi-supine for 10 minutes)
- Abbreviated physical examination (if indicated by AEs)
- Height, weight and waist circumference will be measured
- Assessment of menstrual cycle changes in all pre-menopausal women
- Assessment of hirsutism by female participants using a VAS and by Investigators using Ferriman-Gallwey score (the Investigator can assess this via a video call if a domiciliary visit is conducted for this visit [within ±2 days of the domiciliary visit])
- Assessment of acne by female participants using a VAS and by the Investigators using the GEA (the Investigator can assess this via a video call if a domiciliary visit is conducted for this visit [within ±2 days of the domiciliary visit])
- Assessment of alertness by the participant using a VAS
- Signs and symptoms of adrenal insufficiency using the adrenal insufficiency checklist (the Investigator must complete the checklist even if a domiciliary visit is conducted for this visit)
- The following questionnaires will be completed: SF-36®, MAF, and EQ-5D-5L™
- Blood sample for HbA1c, FSH, osteocalcin, LH, and routine biochemistry and hematology
- Urinalysis
- Pregnancy test in WOCBP (either urine or blood as per the site's usual practice)
- Review of emergency treatment pack for compliance
- Blood sampling for measurement of androgen levels (17-OHP and A4) at 08.00 (pre-dose) and 13.00 hours
- Saliva samples collected for exploratory analysis at 08.00 (pre-dose) and 13.00 hours (optional).

The androgen blood samples are to be taken within ±30 minutes of the stated timepoints, with the exact sampling times recorded in the eCRF. Half the sample will be sent for analysis at the central laboratory, with the remaining half initially retained at the site before being sent to the central laboratory and then on to the biobank for long-term storage and possible future research.

The participant will be asked to attend the clinic for Visit 5 in 6 weeks' time. Participants will be reminded to complete the alertness VAS on a weekly basis in the morning before their morning dose of study medication. The same day of the week should be used each week.

Participants will be discharged once the last androgen sample has been taken and all other assessments have been completed.

Following determination of the Visit 4 androgen levels and completion of the adrenal insufficiency checklist, a decision will be made by an independent blinded physician as to whether the participant's dose should be adjusted, and the appropriate IMP packs will be sent to the participant, either to collect from their local study site or sent directly to the participant's home (note: the changes will also include the relevant changes to the placebo capsules to maintain the blinding). The treatment packs for each participant will always contain the same number of capsules as the previous supplies (with placebo capsules masking any changes), thus ensuring the participant is not aware of any dose changes. Participants will be asked to record the dose, date and time they took the first dose of the revised study medication (if applicable) in their electronic participant diary.

Any dose titrations should be made within 2 to 3 weeks of the visit (dependent on the laboratory turnaround time of androgen samples, the time needed by the independent blinded physician to evaluate the data, and for the supplies to be sent to the participant).

8.1.6. Telephone Call T4.1 (Visit 4 + 2 to 5 Weeks)

One week after delivery of the new supplies to the participant, the study site will telephone the participant to check the supplies have been received and any old supplies returned. The participant will be asked about any AEs and changes in concomitant medications at this call and any AEs or changes in concomitant medication reported will be recorded in the eCRF.

8.1.7. Visit 5 (Titration Visit - Week 16 ± 1 Week)

Six weeks after the previous visit (± 1 week), participants will be requested to attend the study site for testing of androgen levels. Prior to the visit, the site staff should contact the participant to check that 'stress dosing rules' have not been applied in the 5 days preceding the visit date. If 'stress dosing rules' have been applied, then the visit should be postponed until the participant has been receiving no stress dosing medication for 5 days. It is mandatory that this visit is conducted at the study site, although if necessary in some cases, IMP at this visit can be delivered to the participant's home. The participant will be instructed to bring any empty packaging and any unused study medication and the emergency treatment pack with them to the visit for accountability purposes (note: participants take unused study medication and emergency treatment pack back home with them to use until the dose titration decision is made and new study medication dispensed). The participants will be told not to take their morning dose of study medication before attending for the visit (the morning dose will be taken after the 08:00 hour androgen sample and optional saliva sample [where applicable]). Male participants will be asked not to take multivitamins or dietary supplements containing biotin or vitamin B7 for 12 hours prior to the visit (to avoid interference with LH test results).

The following assessments will be carried out and recorded at this visit:

- Record the details of the participant's glucocorticoid doses for the previous 24 hours and throughout the visit
- Participants will be asked about any AEs (including events considered to be of unexpected benefit) and concomitant medications changes since the last visit

- Vital signs (BP, HR, respiratory rate and body temperature. BP to be recorded after the participant has been semi-supine for 10 minutes)
- Abbreviated physical examination (if indicated by AEs)
- Height, weight and waist circumference will be measured
- Assessment of menstrual cycle changes in all pre-menopausal women
- Assessment of hirsutism by female participants using a VAS and by Investigators using Ferriman-Gallwey score
- Assessment of acne by female participants using a VAS and by Investigators using the GEA
- Assessment of alertness by the participant using a VAS
- Signs and symptoms of adrenal insufficiency using the adrenal insufficiency checklist
- The following questionnaires will be completed: SF-36®, MAF, and EQ-5D-5L™
- Blood sample for HbA1c, FSH, osteocalcin, LH, and routine biochemistry and hematology
- Urinalysis
- Pregnancy test in WOCBP (either urine or blood as per the site's usual practice)
- Review of emergency treatment pack for compliance
- Blood sampling for measurement of androgen levels (17-OHP and A4) at 08.00 (pre-dose) and 13.00 hours
- Saliva samples collected for exploratory analysis at 08.00 (pre-dose) and 13.00 hours (optional).

The androgen blood samples are to be taken within ±30 minutes of the stated timepoints, with the exact sampling times recorded in the eCRF. Half the sample will be sent for analysis at the central laboratory, with the remaining half initially retained at the site before being sent to the central laboratory and then on to the biobank for long-term storage and possible future research.

Participants will be asked to attend the clinic for Visit 6 in approximately 12 weeks' time. Participants will be reminded to complete the alertness VAS on a weekly basis in the morning before their morning dose of study medication. The same day of the week should be used each week. Participants will be discharged once the last androgen sample has been taken and all other assessments have been completed.

Following determination of the Visit 5 androgen levels and completion of the adrenal insufficiency checklist, a decision will be made by an independent blinded physician as to whether the participant's dose should be adjusted, and the appropriate IMP packs will be sent to the participant, either to collect from their local study site or sent directly to the participant's home (note: the changes will also include the relevant changes to the placebo capsules to maintain the blinding). The treatment packs for each participant will always contain the same number of capsules as the previous supplies (with placebo capsules masking any changes), thus ensuring the participant is not aware of any dose changes. Participants will be asked to record the dose, date and time they took the first dose of the revised study medication (if applicable) in their electronic participant diary.

Any dose titrations should be made within 2 to 3 weeks of the visit (dependent on the laboratory turnaround time of androgen samples, the time needed by the independent blinded physician to evaluate the data, and for the supplies to be sent to the participant).

8.1.8. Telephone Call T5.1 (Visit 5 + 2 to 5 Weeks)

One week after delivery of the new supplies to the participant, the study site will telephone the participant to check the supplies have been received and any old supplies returned. The participant will be asked about any AEs and changes in concomitant medications at this call and any AEs or changes in concomitant medication reported will be recorded in the eCRF.

8.1.9. Telephone Call T5.2 (Week 22 ± 2 Weeks)

A telephone call will be made to all participants approximately 4 weeks after the last telephone call. All participants will be asked about any AEs or any other problems plus any changes in concomitant medications since their last visit. Any AEs or changes in concomitant medications will be recorded in the eCRF.

8.1.10. Visit 6 (End of Study/Early Withdrawal Visit - 28 Weeks + 1 Week From Randomization or at Point of Discontinuing Treatment or Withdrawing From the Study)

This visit is required for all participants either 28 weeks after randomization or at the time a participant withdraws early from treatment or from the whole study. The last dose of study medication will be taken in the morning of the last dosing day after the 08:00 hour androgen sample and optional saliva sample (where applicable) are collected. It is mandatory that this visit is conducted at the study site. If a participant who was enrolled under an earlier version of the protocol (where the study was up to 52 weeks in duration) had attended Visit 5 at Week 16 and is ongoing treatment, they must continue taking the study medication and must return at 28 weeks for the EOS (Visit 6) assessments. If they have already had more than 28 weeks of treatment then they must return as soon as possible (but not within 4 weeks of previous blood sampling) for the EOS (Visit 6) assessments according to this amendment. In the case of early withdrawal from treatment or from the study, as many assessments as possible should be completed within 48 hours of the last dose of the study medication. If the participant only discontinues study treatment, they should remain in the study where possible and be followed for safety assessments until the scheduled EOS visit (note: no efficacy endpoints will be collected once the assessments detailed for Visit 6 [early withdrawal] are completed).

Prior to the visit, the site staff should contact the participant to check that ‘stress dosing rules’ have not been applied in the 5 days preceding the visit date. If ‘stress dosing rules’ have been applied, then the visit should be postponed until the participant has been receiving no stress dosing medication for 5 days. The participant will be instructed to bring any empty packaging and any unused study medication and the emergency treatment pack with them to the visit for accountability purposes. The participants will be told not to take their morning dose of study medication before attending for the visit (the morning dose will be taken after the 08:00 hour androgen sample and optional saliva sample [where applicable]). Male participants will be asked not to take multivitamins or dietary supplements containing biotin or vitamin B7 for 12 hours prior to the visit (to avoid interference with LH test results) and also not to ejaculate for the preceding 3 days for the sperm count assessment (if the participant has consented to this assessment).

The following assessments will be carried out and recorded at this visit:

- Record the details of the participant's glucocorticoid doses for the previous 24 hours and throughout the visit
- Participants will be asked about any AEs and concomitant medications changes since the last visit
- Vital signs (BP, HR, respiratory rate and body temperature. BP to be recorded after the participant has been semi-supine for 10 minutes)
- Full physical examination
- Height, weight, and waist circumference will be measured
- Assessment of menstrual cycle changes in all pre-menopausal women
- Assessment of hirsutism by female participants using a VAS and by Investigators using Ferriman-Gallwey score
- Assessment of acne by female participants using a VAS and by the Investigators using the GEA
- Assessment of alertness by the participant using a VAS
- Assessment of treatment preference (randomized treatment compared to their usual medication) using a VAS
- Signs and symptoms of adrenal insufficiency using the adrenal insufficiency checklist
- The following questionnaires will be completed: SF-36®, MAF, and EQ-5D-5L™
- ECG
- TART measured by ultrasound in male participants (results read by central laboratory)
- Sperm count measured at home using a testing kit supplied to the male participants (only in participants who have consented to this assessment)
- Urinalysis
- Sample taken for PRA or PRC, preferably after the participant has been supine for 30 minutes
- Blood sample for HbA1c, FSH, osteocalcin, LH, 11-ketotestosterone, total testosterone, DHEA, and routine biochemistry and hematology
- Pregnancy test in WOCBP (either urine or blood as per the site's usual practice)
- Review of emergency treatment pack for compliance
- Blood sampling for measurement of androgen levels (17-OHP and A4) at 08.00 (pre-dose) and 13.00 hours
- Saliva samples collected for exploratory analysis at 08.00 (pre-dose) and 13.00 hours (optional).

The androgen blood samples are to be taken within ±30 minutes of the stated timepoints, with the exact sampling times recorded in the eCRF. All samples taken at the EOS visit will be shipped to the central laboratory in the same shipment. Half of the samples will be analyzed and half will be sent on to the biobank for long-term storage and possible future research. Once the last blood sample has been taken at 13:00 hours and all other assessments have been completed, the participant will be discharged from the clinic. At this point the participants can either return to the CAH medication they were taking prior to the study or if they have completed the study with up to 28 weeks of randomized treatment, they can enter an open-label extension study and receive Chronocort (to be conducted under a separate protocol

DIUR-015) or they will be offered commercial supplies of Chronocort. The options will be dependent on territory.

8.1.11. Telephone Call T6.1 (Visit 6 + 30 Days ± 1 Week)

Participants who do not enter the open-label extension study will be contacted by telephone by the local site staff approximately 30 days after Visit 6 to ask about any AEs that were ongoing at Visit 6 and any new SAEs that could be related to the study medication. Any AEs or SAEs reported will be recorded in the eCRF and any SAEs will be reported to the pharmacovigilance group using the paper SAE form.

8.1.12. Unscheduled Visits or Telephone Calls

If an unscheduled visit or telephone call is required, e.g. to follow up on an AE, then the details should be recorded in the eCRF, along with the results of any tests carried out. If laboratory results are needed urgently these can be processed at the local laboratory. Additional telephone calls may also be required in between visits to maintain contact with the participant and to ensure AEs and use of any 'stress dosing rules' are being noted. Any additional data obtained in such calls must be recorded in the eCRF, where relevant.

8.1.13. COVID-19 Procedures

If necessary, appropriate measures will be put in place to enable the study to continue during COVID-19 restrictions. These may include domiciliary visits being performed and IMP shipments being made directly to the participant's home. If a domiciliary visit is conducted the safety and endocrine blood samples must be sent to the central laboratory for analysis and the Investigator must complete the adrenal insufficiency checklist. The assessment of hirsutism and acne can be conducted via a video call (within ±2 days of the domiciliary visit). If androgen samples are analyzed locally this will unblind the participant and so the participant will then be withdrawn from treatment. If local laboratories are used, then normal ranges and certification of the local laboratories will be required. Such procedures would be agreed between the investigator and Sponsor before implementation.

8.2. Efficacy Assessments

The timing of each efficacy assessment is shown in the SoA (Section 1.3) and detailed in Section 8.1. Wherever possible, all efficacy assessments for a participant should be conducted by the same individual.

8.2.1. Efficacy Blood Samples

The date and time of collection of all blood samples will be recorded in the eCRF. Blood samples for the following tests will be taken by suitably qualified study personnel and sent to a central laboratory for analysis:

- Androgen testing (17-OHP and A4) at 08:00 and 13:00 hours for all participants at Visits 1, 2, 3, 4, 5, and 6. A draw window of ±30 minutes is permitted, but exact times of sampling must be recorded in the eCRF. Half of each sample will be sent to the central laboratory for analysis, with the remaining half initially retained at the site before being sent to the central laboratory and then on to the biobank for long-term storage and possible future research (note: samples taken at the EOS visit will all be

shipped to the central laboratory at the same time and the central laboratory will send half the samples to the biobank for long-term storage). The central laboratory will analyze 17-OHP and A4 using liquid chromatography tandem mass spectrometry (LC-MS-MS) methods, with full details of the assay methods provided in a separate manual.

- Blood samples for HbA1c will be taken at screening and then at each visit after Visit-2.
- Blood samples for FSH, LH, and osteocalcin will be taken at each visit after Visit 1.
- Serum samples for 11-ketotestosterone and DHEA will be taken at Visits 2 and 6.
- Serum samples for total testosterone will be taken at Visits 2 and 6.

Participants are required to fast before the collection of the 08:00 androgen sample, but there is no requirement to fast for any of the other laboratory tests.

The maximum amount of blood collected from each participant over the course of the study will not exceed approximately 200 mL. Repeat or unscheduled samples may be taken in addition for safety reasons or for technical issues with the samples.

8.2.2. Adrenal Insufficiency Checklist

The adrenal insufficiency checklist (Appendix 5) is completed by the Investigator for all participants at Visits 1, 2, 3, 4, 5, and 6. The adrenal insufficiency checklist should only be used to determine if symptoms of under- or over-replacement of glucocorticoids have occurred since the last visit and this questionnaire should not be used to record AEs due to other causes.

8.2.3. Saliva Samples

Optional saliva samples for exploratory analyses will be taken at 08:00 hours (pre-dose) and 13:00 hours in the clinic at each study visit after Visit 1 in participants who have consented to this procedure. The samples will be collected using a passive drooling method and then split into 2 samples and frozen. The samples will then be sent to the central laboratory and then on to the biobank for long-term storage and possible future research. The analyses to be conducted will be determined at a later date but are likely to include steroid profiling and androgens. Samples may be stored for up to 10 years.

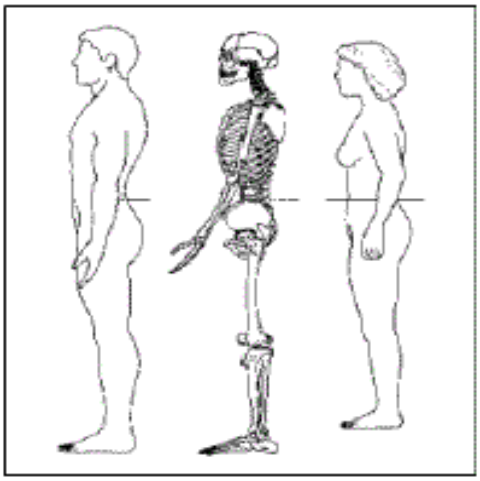
8.2.4. Body Weight

Body weight will be recorded at each visit and the results recorded in the eCRF. Weight will be measured with outer clothing and shoes removed.

8.2.5. Waist Circumference

Waist circumference will be recorded at each visit and the results recorded in the eCRF. Waist circumference will be measured midway between the uppermost border of the iliac crest and the lower border of the costal margin (rib cage). The tape should be placed around the abdomen at the level of this midway point and a reading taken when the tape is snug but does not compress the skin (Figure 1). It may be difficult for very overweight participants to accurately palpate the bony landmarks, in which case placing the tape at the level of the belly button is recommended.

Figure 1: Measuring Tape Position for Waist Circumference



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8.2.6. Fertility

Menstrual irregularities including oligomenorrhea (fewer than 9 menstrual cycles per year or cycle length >35 days) and secondary amenorrhea (absent menses for ≥3 months) are common in females with classic CAH. An electronic participant diary will be used to record menstrual cycle details for all pre-menopausal women, but only those who have not had a hysterectomy and are not using hormonal contraception will be included in the statistical analysis. Restoration of menses in a woman with secondary amenorrhea or normal menstrual regularity with cycles occurring every 21 to 35 days, will be captured and documented in the electronic patient reported outcomes (ePRO) device. The details in the diary will be reviewed at each visit after Visit 1.

Fertility in men will be assessed at each visit after Visit 1 by measurement of LH (see efficacy blood samples Section 8.2.1), and at Visits 2 and 6 by ultrasound for detection of TART and sperm count (measured at home using a testing kit supplied to male participants who have consented to this assessment) will be assessed. All ultrasounds conducted for TART will be assessed by a central reviewer.

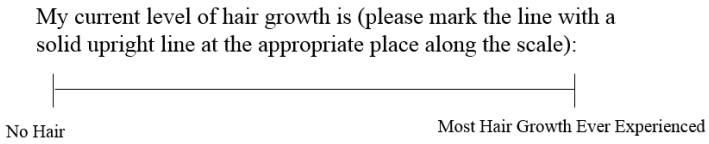
8.2.7. Quality of Life Questionnaires

QoL questionnaires (SF-36®, MAF, and EQ-5D-5L™) will be completed by the participants at each visit after Visit 1 using the electronic participant diary and the results will be transferred electronically into the database. At the first visit the questionnaires are completed (Visit 2), the Investigator or designee will instruct the participant how to complete each questionnaire. However, completion of the QoL questionnaires will not be supervised and no review or follow-up of responses will be conducted by the site staff. All QoL questionnaires will be administered on the study visit days between the first and second blood samplings and they will be completed in a quiet environment. The QoL questionnaires will be administered in the following order: SF-36®, MAF, and EQ-5D-5L™.

8.2.8. Hirsutism

Hirsutism will be assessed in female participants at each visit after Visit 1 using a 10 cm VAS ranging from 'No Hair' to 'Most Hair Growth Ever Experienced' which will be completed by the participant.

Example VAS for Hirsutism:



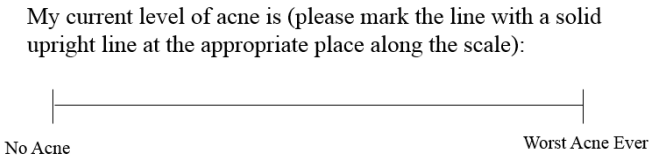
This assessment will be conducted on the study visit days between the first and second blood samplings. The VAS will be completed using the electronic participant diary and the results will be transferred electronically into the database. A change of ≥1 cm in the VAS will be considered clinically relevant.

Assessment of hirsutism in female participants will also be assessed by the Investigators at each visit after Visit 1 using the Ferriman-Gallwey score [Hatch, 1981], with the score being entered into the eCRF.

8.2.9. Acne

Acne will be assessed in women only at each visit after Visit 1 using 2 methods. The Investigator will assess the acne objectively using the GEA scale [Dreno, 2011], with the score being entered into the eCRF, and the participants will assess their acne subjectively using a 10 cm VAS ranging from 'No Acne' to 'Worst Acne Ever'.

Example VAS for Acne:

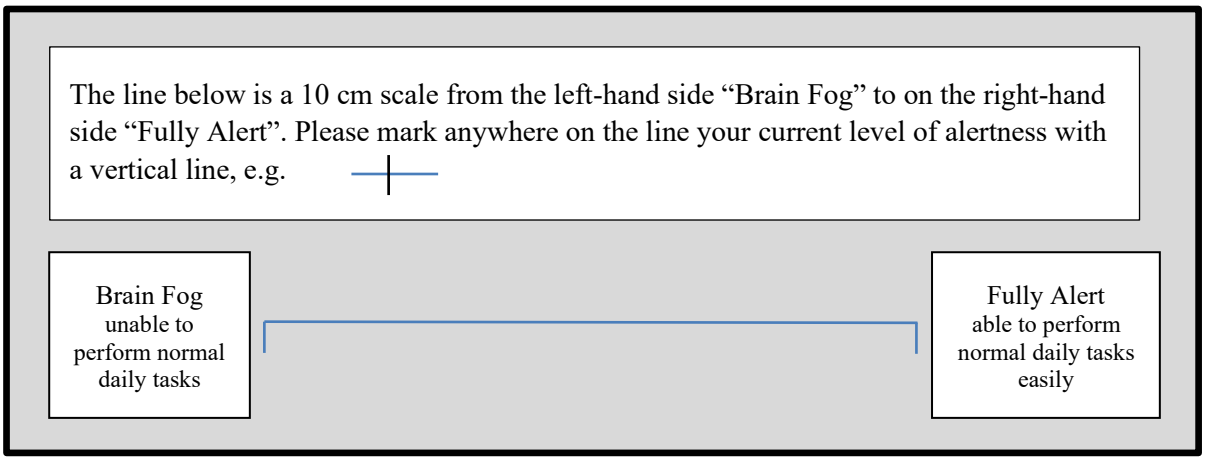


Both assessments will be conducted on the study visit days between the first and second blood samplings. The VAS will be completed using the electronic participant diary and the results will be transferred electronically into the database. A change of ≥1 cm in the VAS will be considered clinically relevant.

8.2.10. Alertness

Alertness will be assessed on a weekly basis in the morning before the participant takes their morning dose of study medication. The same day of the week should be used each week. When the alertness VAS is conducted at the study visits, it will be completed between the first and second blood samplings.

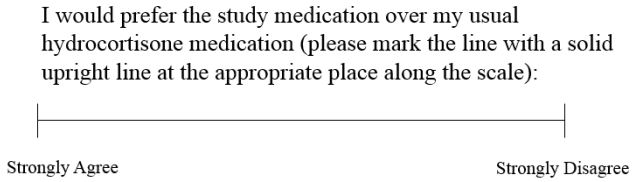
Alertness will be assessed using the VAS below. The VAS will be completed using the electronic participant diary and the results will be transferred electronically into the database. A change of ≥1 cm in the VAS will be considered clinically relevant.



8.2.11. Preference for Treatment

At the EOS visit (Visit 6), an assessment of the preference of the randomized treatment to the participant's usual medication (i.e. prior to the run-in period) will be made.

Example VAS for Treatment Preference:



The assessment will be conducted on the study visit day between the first and second blood samplings. The VAS will be completed using the electronic participant diary and the results will be transferred electronically into the database. A change of ≥1 cm in the VAS will be considered clinically relevant.

8.3. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (Section 1.3).

8.3.1. Physical Examinations

A full physical examination to assess the participant's general appearance and overall health will be carried out at Visits 1, 2, and 6. This physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal and neurological systems. Investigators should pay special attention to clinical signs related to previous serious illnesses. Significant findings that are present **prior to randomization** must be included in the relevant medical history/current medical status section of the eCRF. Significant findings made **after randomization** which meet the definition of an AE must be recorded as AEs in the eCRF. At Visits 3, 4, and 5, an abbreviated physical examination will be conducted if indicated by AEs, noting any changes from the baseline assessment. Any abnormal findings will be recorded on the eCRF.

Standing height will be measured at each visit and will be measured with the participant's shoes removed. Weight and waist circumference are recorded as efficacy parameters (see Section 8.2). Body mass index (BMI) will be calculated within the eCRF.

8.3.2. Vital Signs

BP, HR, respiratory rate and body temperature will be measured at Visits 1, 2, 3, 4, 5, and 6. Vital signs should be recorded before any blood samples have been taken or at least 1 hour after any blood sampling. BP and HR measurements should be preceded by 10 minutes of rest (semi-supine position) in a quiet setting without distractions (e.g. television, cell phones). BP should be measured in the non-dominant arm. Three measurements for BP, HR and respiratory rate will be taken and recorded in the eCRF (3 consecutive readings will be recorded at intervals of at least 1 minute), with the average then being calculated within the eCRF. The mean arterial BP will also be calculated within the eCRF.

8.3.3. Electrocardiograms

A single 12-lead ECG will be recorded at Visits 2 and 6 using an ECG machine that automatically calculates the HR and measures PR, QRS, QT, and QTc intervals. The same ECG machine and operator should be used throughout the study for each participant if possible. ECGs should be recorded at least 1 hour after any blood samples have been taken. ECG measurements should be preceded by 10 minutes of rest (semi-supine position) in a quiet setting without distractions (e.g. television, cell phones). The ECGs will be read locally, and any abnormal findings recorded on the eCRF as an AE. The original ECG printouts will be stored in the participant's source notes.

8.3.4. Clinical Safety Laboratory Assessments

- See Appendix 2 for the list of clinical safety laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency. Participants are required to fast before the collection of the 08:00 androgen sample, but there is no requirement to fast for any of the other laboratory tests. Note: the blood sample for PRA or PRC will be collected at screening and at the EOS visit according to local practice but if possible, should be taken after the participant has been supine for 30 minutes. All laboratory samples will be analyzed by a central laboratory.
- The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or the Sponsor's medical monitor.
    - If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified.
    - All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).
    - If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant

management or are considered clinically significant by the Investigator (e.g. SAE or AE), then the results must be recorded in the eCRF.

- Pregnancy tests in WOCBP are conducted at each visit and can be either urine or blood as per the site's usual practice.

8.3.5. Stress Dosing Rules

All participants will be educated regarding 'stress dosing rules'. 'Stress dosing rules', a written guideline detailing what to do during any illness, will be given to all participants (as is done for all CAH patients) (Appendix 6). Use of 'stress dosing rules' will be recorded in the electronic participant diary, including duration, dose of steroid and use of injection, as applicable.

8.4. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 3 (Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting). All participants will be questioned about the occurrence of any AEs at all study visits and in all telephone calls. Any AEs reported by the participant will be recorded in the eCRF and any SAEs will be reported to the pharmacovigilance group using the paper SAE form by the Investigator or designee. The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or study procedures, or that caused the participant to discontinue from receiving study treatment or from the whole study (see Section 7 [Discontinuation of Study Treatment and Participant Discontinuation/Withdrawal]). Note that signs and symptoms of adrenal insufficiency recorded on the adrenal insufficiency checklist do not need to be reported as AEs unless they are considered unrelated to the participant's CAH (i.e. they are due to another reason) or they meet the criteria for reporting as an SAE.

8.4.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected for all participants from the time of signing the ICF up to the EOS visit (Visit 6) in participants who are entering the open-label extension study or early withdrawal visit (if applicable), or to the final telephone call T6.1 (approximately 30 days following the last visit) in participants who are not entering the open-label extension study. AEs must be reported equally for both study treatments, regardless of whether the Investigator thinks the AEs are related to the study treatment. Any AEs or SAEs still ongoing at the final visit will be followed until resolution or stabilization if resolution is not expected.

Medical occurrences that begin before the start of study treatment but after the ICF is signed will be recorded on the Medical History/Current Medical Conditions section of the eCRF, not the AE section.

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix 3. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

After the final visit or telephone call, Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she

considers the event to be reasonably related to the study treatment or study participation, the Investigator must promptly notify the Sponsor.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

8.4.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to enquire about AE occurrences.

8.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and non-serious AEs of special interest (as defined in Section 8.4.8), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up. Further information on follow-up procedures is given in Appendix 3.

8.4.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IECs/IRBs, and Investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators, as necessary.
- An Investigator who receives a safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IEC/IRB, if appropriate according to local requirements.

8.4.5. Pregnancy

Female subjects who are pregnant or lactating will not be allowed to enter the study and all female participants of childbearing potential and all male participants must agree to the use of an accepted method of contraception during the study (Appendix 4). If a participant becomes pregnant during the study, they should be withdrawn from the study - not due to safety reasons but because pregnancy may interfere with the study endpoints. However, participants who withdraw from the study due to pregnancy may be eligible to enter the long-term extension study (DIUR-015) at the discretion of the Investigator providing that at least 6 weeks has lapsed after the pregnancy is complete (i.e. at least 6 weeks post-partum

regardless of outcome or at least 6 weeks after abortion or termination) or at least 6 weeks after they have finished lactating and are no longer breast feeding (whichever is longer).

As soon as the pregnancy is confirmed, the Investigator will conduct as many of the evaluations included in the EOS visit (Visit 6) as possible and the participant will be asked to sign a pregnancy consent form to enable information on the course of the pregnancy to be collected. The Investigator will transition the participant onto the appropriate standard of care therapy. AEs will be collected for 30 days after the EOS visit and a follow-up telephone call will be conducted at 30 days. No other data will be collected while the participant is off study due to the pregnancy unless the Investigator considers any AEs are related to study treatment, in which case every reasonable attempt will be made to follow up until resolution of the event.

The outcome of the pregnancy will be collected via a Pregnancy Report Form that must be sent to Pharmalex: diurnalclinicalsafety@pharmalex.com.

Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and should be reported as such.

8.4.6. Cardiovascular and Death Events

Cardiovascular events will be reported in the same manner as other AEs/SAEs. All deaths will be reported as SAEs in this study, regardless of the cause.

8.4.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

None in this study.

8.4.8. Adverse Events of Special Interest

Some of the AEs likely to occur in participants with CAH are of special interest (adverse events of special interest [AESI]). These AESIs will be recorded in the eCRF and will also be reported to the Sponsor using the SAE/AESI form (see Appendix 3 for further details). These events will include, but not be limited to:

- any events causing implementation of ‘stress dosing rules’
- Addisonian crisis, with Addisonian or adrenal crisis being defined as follows (based on Allolio, 2015):

  (A): Major impairment of general health with at least 2 of the following signs/symptoms:

  Hypotension (systolic blood pressure <100 mmHg)

  Nausea or vomiting

  Severe fatigue

  Fever

  Somnolence

  Hyponatremia (<132 mmol/L) or hyperkalemia (as judged by characteristic ECG changes)

Hypoglycemia

AND

(B): Parenteral glucocorticoid (hydrocortisone) administration followed by clinical improvement including:

Outpatient care only

Hospital care (general ward)

Admission to intensive care unit

OR

Death from adrenal crisis (with or without parenteral glucocorticoid administration)

- any other event that is considered to be an unexpected benefit (note: events recorded as efficacy assessments e.g. change in menses, acne and hirsutism, should not be recorded as AESIs to avoid duplication)

8.5. Treatment of Overdose

For this study, any dose of Chronocort or IRHC greater than 60 mg within a 24-hour time period will be considered an overdose. In the event of an overdose, the participant should immediately contact the Investigator or Study Nurse for advice. There is no antidote available for Chronocort or IRHC, however, it should be noted that the active ingredient is hydrocortisone intended for replacement therapy in cortisol deficient patients. The Investigator should then:

1. Contact the Sponsor's medical monitor immediately.
2. Closely monitor the participant for any AEs/SAEs or laboratory abnormalities.
3. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Sponsor's medical monitor based on the clinical evaluation of the participant.

8.6. Pharmacokinetics

PK parameters are not evaluated in this study.

8.7. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.8. Genetics

Genetics evaluations are not being conducted in this study. However, if retrospective genetic information to confirm the diagnosis of CAH is available, this should be recorded in the eCRF.

8.9. Biomarkers

17-OHP and A4 are used as biomarkers of disease control and are evaluated as efficacy endpoints in this study (see Section 8.2.1 for full details).

8.10. Immunogenicity Assessments

Immunogenicity assessments are not evaluated in this study.

8.11. Health Economics

Health economics parameters are not evaluated in this study.

9. Statistical Considerations

9.1. Statistical Hypotheses

9.1.1. Primary Analysis

A participant is a biochemical responder if:

i) they are in biochemical control at 08:00 hours after 28 weeks of randomized treatment (Visit 6)

where 'biochemical control' is defined as a 17-OHP concentration equal to or less than the upper limit of optimal control and a A4 concentration equal to or less than the upper limit of the reference range - if either or both these conditions are not met the participant is not in biochemical control.

and

ii) their total daily dose after 28 weeks of randomized treatment is 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)

The primary null hypothesis is that the response rate in the Chronocort arm is worse than or equal to the response rate in the IRHC arm minus 15 percentage points.

The primary alternate hypothesis is that the response rate in the Chronocort arm is better than the response rate in the IRHC arm minus 15 percentage points.

Biochemical non-inferiority of Chronocort to IRHC will be declared if the 95% CI for the difference in response rates between the 2 treatment arms (Chronocort minus IRHC) is wholly above minus 15 percentage points.

9.1.2. First Key Secondary Analysis

A participant is a dose responder if:

i) their total daily dose after 28 weeks of randomized treatment is not more than 25 mg

and

ii) they are in biochemical control at 08:00 hours after 28 weeks of randomized treatment (Visit 6)

where 'biochemical control' is defined as a 17-OHP concentration equal to or less than the upper limit of optimal control and a A4 concentration equal to or less than the upper limit of the reference range - if either or both these conditions are not met the participant is not in biochemical control.

The first key secondary null hypothesis is that the response rate in the Chronocort arm is worse than or equal to the response rate in the IRHC arm.

The first key secondary alternate hypothesis is that the response rate in the Chronocort arm is better than the response rate in the IRHC arm.

Dose superiority of Chronocort to IRHC will be declared if the 95% CI for the difference in response rates between the 2 treatment arms (Chronocort minus IRHC) is wholly above zero, provided that biochemical non-inferiority of Chronocort to IRHC has been declared under the primary efficacy objective.

9.1.3. Second Key Secondary Analysis

The second key secondary null hypothesis is that the mean total daily dose after 28 weeks of randomized treatment in the Chronocort arm is higher than or equal to the mean total daily dose after 28 weeks of randomized treatment in the IRHC arm.

The second key secondary alternate hypothesis is that the mean total daily dose after 28 weeks of randomized treatment in the Chronocort arm is lower than the mean total daily dose after 28 weeks of randomized treatment in the IRHC arm.

Superiority of Chronocort to IRHC with respect to the total daily dose after 28 weeks of randomized treatment will be declared if the 95% CI for the difference in means between the 2 treatment arms (Chronocort minus IRHC) is wholly below zero, provided that dose superiority of Chronocort to IRHC has been declared under the first key secondary efficacy objective.

9.2. Sample Size Determination

Sufficient participants will be screened and enrolled into the run-in period to achieve approximately 50 participants randomly assigned to either Chronocort or IRHC at Visit 2 (25 participants per treatment arm, regardless of baseline strata), or until a cut-off date of 30 April 2023, whichever is reached first. Individual study sites should not randomize more than 8 participants without first consulting the Sponsor. A sample size of 25 participants per treatment arm will provide at least 80% power to demonstrate non-inferiority of Chronocort to IRHC when the biochemical response rate in the IRHC arm is 40%, the non-inferiority margin is 15%, and the biochemical response rate in the Chronocort arm is 68% using a 1-sided continuity corrected z-test with unpooled variance and a 1-sided alpha of 2.5%.

Note: "Enrolled" means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified.

Note: Basing the sample size calculation on a continuity corrected z-test provides a conservative estimate of sample size relative to the test, based on a logistic model adjusted for stratification factors, which will actually be used.

Note: The anticipated response rates in the treatment arms are based on the corresponding results in Study DIUR-005.

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Screened Set	All participants who sign the ICF.
Safety Analysis Set (SAF)	All participants who received, either as part of the run-in or post-randomization periods, at least 1 dose of Chronocort or IRHC. Participants will be analyzed according to the treatment they actually received. The SAF is a subset of the Screened Set.
Full Analysis Set (FAS)	All participants with CAH who were randomized into the study and who received at least 1 dose of post-randomization study treatment (Chronocort or IRHC). Participants in the FAS will be analyzed according to randomized treatment. The FAS is a subset of the SAF.
Efficacy Evaluable Set (EES)	All participants in the FAS who had Visit 2 and Visit 6 (EOS), 17-OHP and A4 measurements taken at 08:00 hours, and who have no critical protocol deviations that affect the assessment of efficacy. The EES is a subset of the FAS.

9.4. Statistical Analyses

The SAP will be developed and finalized before screening of the first participant to the study. It will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints. Minor changes to the analyses specified in this section need not trigger a protocol amendment but must be documented in the CSR.

9.4.1. General Considerations

All baseline, disposition, protocol compliance, exposure, efficacy and safety variables will be listed and summarized by treatment arm. The standard summary statistics for continuous baseline and outcome variables are: N, mean, standard deviation (SD), median, quartiles, minimum and maximum.

The standard summary statistics for categorical baseline and outcome variables are count and proportion (expressed as percentage).

9.4.2. Efficacy Analyses

Standard methodology for comparisons: Unless otherwise stated, continuous outcome variables will be compared between treatment arms using analysis of variance (ANOVA) adjusting for the standard explanatory variables. If a non-normal distribution is anticipated or observed, then consideration will be given to using a logarithmic transformation or a non-parametric analysis. Analyses of change from baseline will always include the baseline value as a covariate.

Unless otherwise stated, binary outcome variables will be compared between treatment arms using logistic regression adjusted for the standard explanatory variables.

Standard explanatory variables: The standard explanatory variables are (i) whether or not the participant was in biochemical control at baseline, (ii) whether or not the participant was receiving fludrocortisone at baseline and (iii) their interaction. Randomization of participants to treatment arm is stratified by fludrocortisone treatment and the analyses will include the stratification of biochemical control.

Analyses will be stratified or adjusted, as appropriate, on the basis of (i) the participant's fludrocortisone replacement status at baseline (requires fludrocortisone or does not require fludrocortisone) and (ii) whether they are in biochemical control at baseline or not (based on the androgen results from the baseline visit [Visit 2]). Participants with 17-OHP equal to or below the upper limit for optimal control at 08:00 hours and A4 equal to or below the upper limit of the reference range will be classified as 'in biochemical control'. Participants with 17-OHP above the upper limit for optimal control and/or A4 above the upper limit of the reference range will be classified as 'not in biochemical control'.

Analysis	Statistical Analysis Methods
Primary analysis	Non-inferiority: a 95% CI will be calculated for the difference (Chronocort minus IRHC) in biochemical responder rates. Biochemical non-inferiority will be declared if the 95% CI lies wholly above minus 15%. The primary analysis will be conducted using the FAS.
First key secondary analysis	Superiority analysis: a 95% CI will be calculated for the difference (Chronocort minus IRHC) in dose responder rates. Dose superiority will be declared if the 95% CI lies wholly above zero, provided that biochemical non-inferiority of Chronocort to IRHC has been declared under the primary efficacy objective. The first key secondary analysis will be conducted using the FAS.
Second key secondary analysis	Superiority analysis: a 95% CI will be calculated for the difference (Chronocort minus IRHC) in mean total daily dose after 28 weeks of randomized treatment. Superiority with respect to total daily dose after 28 weeks of randomized treatment will be declared if the 95% CI lies wholly below zero, provided that dose superiority of Chronocort to IRHC has been declared under the first key secondary objective. The second key secondary analysis will be conducted using the FAS.
Other analyses of the primary outcome variable and of the key secondary outcome variables (classed as secondary outcome analyses)	Analyses of the primary outcome variable other than the primary analysis and analyses of the key secondary outcome variables other than the key secondary analyses, such as: • analysis at other timepoints • assessment of the effect of baseline and disease characterizing variables, including stratification variables • analysis using the EES and subgroups are deemed to be supplementary analyses and will be performed using the same statistical methodology as will be used for the primary analysis and key secondary analyses. Calculated p-values will be indicative rather than substantive.
Other secondary outcome variables and exploratory	Analysis of any other secondary outcome variables and of exploratory outcome variables will be performed using the standard statistical methodology. Calculated p-values will be indicative rather than substantive.

outcome variables	

9.4.2.1. Primary Efficacy Analysis

Assessment	17-OHP and A4 plasma concentration obtained from the 08:00 hours blood sample at Visit 6 (EOS) and daily dose of hydrocortisone.
Estimand	The difference (Chronocort arm minus IRHC arm) in the proportion of participants who are biochemical responders at 08:00 hours at Visit 6 (EOS).
Population	The FAS, being representative of the target CAH population.
Outcome Variable	The primary efficacy outcome variable is whether or not the participant is a biochemical responder after 28 weeks of randomized treatment. A biochemical responder is a participant who: i) is in biochemical control at the 08:00 hour assessment after 28 weeks of randomized treatment (where in biochemical control is defined as both a 17-OHP concentration equal to or below the upper limit for optimal control and an A4 concentration equal to or below the upper limit of the reference range) and ii) is receiving after 28 weeks of randomized treatment 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).
Intercurrent Events	(1) participants who withdraw from treatment before Visit 6 (EOS) or who do not meet the criteria for being a biochemical responder are deemed not to be a biochemical responder. (2) participants receiving rescue medication (under 'stress dosing rules') will continue in the study with unchanged procedures, except that Visit 6 (EOS) will be delayed if necessary, to 5 days after the use of rescue medication.
Summary Statistic	The proportion of participants in each treatment arm who are biochemical responders at 08:00 hours at Visit 6 (EOS).
Analysis	The difference (Chronocort arm minus IRHC arm) in the proportion of participants who are biochemical responders is estimated using logistic regression [Ge, 2011], and fludrocortisone use at baseline, biochemical control at baseline, and their interaction as explanatory variables.
Interpretation	Biochemical non-inferiority of Chronocort to IRHC will be declared if the 95% CI for the difference in proportions lies wholly above minus 15 percentage points.

[redacted]

Sensitivity Analysis: The main statistical analysis assumes that the treatment effect is constant over the standard explanatory variables. Sensitivity analyses will investigate whether the treatment effect varies with the explanatory variables.

Other Analyses: Any other analyses of 17-OHP and A4 concentrations, not otherwise specified as a secondary analysis, are supplementary analyses.

9.4.2.2. First Key Secondary Analysis

Assessment	17-OHP and A4 plasma concentration obtained from the 08:00 hours blood sample at Visit 6 (EOS) and daily dose of hydrocortisone.
Estimand	The difference (Chronocort arm minus IRHC arm) in the proportion of participants who are dose responders at 08:00 hours at Visit 6 (EOS).
Population	The FAS, being representative of the target CAH population.
Outcome Variable	The primary efficacy outcome variable is whether or not the participant is a dose responder after 28 weeks of randomized treatment. A dose responder is a participant who: i) is receiving after 28 weeks of randomized treatment a total daily dose of hydrocortisone of not more than 25 mg and ii) is in biochemical control at the 08:00 hour assessment after 28 weeks of randomized treatment (where in biochemical control is defined as both a 17-OHP concentration equal to or below the upper limit for optimal control and an A4 concentration equal to or below the upper limit of the reference range).
Intercurrent Events	(1) participants who withdraw from treatment before Visit 6 (EOS) or who do not meet the criteria for being a dose responder are deemed not to be a dose responder. (2) participants receiving rescue medication (under 'stress dosing rules') will continue in the study with unchanged procedures, except that Visit 6 (EOS) will be delayed if necessary, to 5 days after the use of rescue medication.
Summary Statistic	The proportion of participants in each treatment arm who are dose responders at 08:00 hours at Visit 6 (EOS).
Analysis	The difference (Chronocort arm minus IRHC arm) in the proportion of participants who are dose responders is estimated using logistic regression [Ge, 2011], and fludrocortisone use at baseline, biochemical control at baseline, and their interaction as explanatory variables.
Interpretation	Dose superiority of Chronocort to IRHC will be declared if the 95% CI for the difference in proportions lies wholly above zero, provided that biochemical non-inferiority of Chronocort to IRHC has been declared.

Sensitivity Analysis: The main statistical analysis assumes that the treatment effect is constant over the standard explanatory variables. Sensitivity analyses will investigate whether the treatment effect varies with the explanatory variables.

Other Analyses: Any other analyses of dose response, not otherwise specified as a secondary analysis, are supplementary analyses.

9.4.2.3. Second Key Secondary Analysis

Assessment	Total daily dose of hydrocortisone at Visit 6 (EOS).
Estimand	The difference (Chronocort arm minus IRHC arm) in the mean total daily dose at Visit 6 (EOS).
Population	The FAS, being representative of the target CAH population.
Outcome Variable	Total daily dose of hydrocortisone at Visit 6 (EOS).
Intercurrent Events	(1) participants who die or withdraw from treatment before Visit 6 (EOS) will have their Visit 6 (EOS) dose imputed within a repeated measures model. (2) participants receiving rescue medication (under 'stress dosing rules') will continue in the study with unchanged procedures, except that Visit 6 (EOS) will be delayed if necessary, to 5 days after the use of rescue medication.
Summary Statistic	The mean total daily dose in each treatment arm at Visit 6 (EOS).
Analysis	The mean difference (Chronocort arm minus IRHC arm) in total daily dose after 28 weeks of randomized treatment is estimated using a repeated measures model with timepoints 10, 16, and 28 weeks after randomization using fludrocortisone use at baseline, biochemical control at baseline, and their interaction as explanatory variables.
Interpretation	Superiority of Chronocort to IRHC with respect to total daily dose after 28 weeks of randomized treatment will be declared if the 95% CI for the difference in means lies wholly below zero, provided that dose superiority of Chronocort to IRHC has been declared.

Sensitivity Analysis: The main statistical analysis assumes that the treatment effect is constant over the standard explanatory variables. Sensitivity analyses will investigate whether the treatment effect varies with the explanatory variables.

Other Analyses: Any other analyses of total daily dose, not otherwise specified as a secondary analysis, are supplementary analyses.

9.4.2.4. Other Secondary Efficacy Analyses

Outcome Variables	**Outline Analyses**
Whether or not the participant is a biochemical responder at 4, 10, and 16 weeks after randomization.	The same analysis will be used as for the primary outcome variable (except that at 4 weeks there has been no opportunity for a dose titration so the condition on dose is not used).
Whether or not the participant is a dose responder at 10 and 16 weeks after randomization.	The same analysis will be used as for the first key secondary outcome variable.
Total daily dose at 10 and 16 weeks after randomization.	The same analysis will be used as for the second key secondary outcome variable.
Whether or not the participant is in biochemical control (provided total daily dose is not greater than 30 mg) at 4, 10, 16, and 28 weeks after randomization.	The same analysis will be used as for the primary outcome variable.
The difference in range as calculated as the difference between the 08:00 and 13:00 17-OHP	Standard methodology for comparisons.

levels at 4, 10, 16, and 28 weeks after randomization.	
The difference in range as calculated as the difference between the 08:00 and 13:00 A4 levels at 4, 10, 16, and 28 weeks after randomization.	Standard methodology for comparisons.
The mean of the 08:00 and 13:00 levels for each androgen at 4, 10, 16, and 28 weeks after randomization.	Standard methodology for comparisons.
The total daily glucocorticoid dose at 4, 10, 16, and 28 weeks after randomization.	Standard methodology for comparisons. Additionally, the mean total daily dose by treatment will be calculated for participants in and not in biochemical control at the EOS visit.
The change from baseline to 4, 10, 16, and 28 weeks of randomized treatment in menstrual regularity	Standard methodology for comparisons (only in pre-menopausal women without hysterectomy and not using hormonal contraception)
The change from baseline to 4, 10, 16, and 28 weeks of randomized treatment in LH levels	Standard methodology for comparisons (men only)
The change from baseline to 28 weeks of randomized treatment in size of TART	Standard methodology for comparisons (men only)
The change from baseline to 28 weeks of randomized treatment in sperm count	Standard methodology for comparisons (men only)
The change from baseline to 4, 10, 16, and 28 weeks of randomized treatment in objective hirsutism using the Ferriman-Gallwey score	Standard methodology for comparisons (women only)
The change from baseline to 4, 10, 16, and 28 weeks of randomized treatment in objective acne using the Global Evaluation Acne (GEA) scale	Standard methodology for comparisons (women only)
The change from screening to 4, 10, 16, and 28 weeks of randomized treatment in HbA1c levels	Standard methodology for comparisons
The change from baseline to 4, 10, 16, and 28 weeks of randomized treatment in waist circumference	Standard methodology for comparisons
The change from baseline to 4, 10, 16, and 28 weeks of randomized treatment in body weight	Standard methodology for comparisons
The change from baseline to 4, 10, 16, and 28 weeks of randomized treatment in QoL using the self-completed SF-36® total score and the sub-domain of vitality	Standard methodology for comparisons
The change from baseline to 4, 10, 16, and 28 weeks of randomized treatment in QoL using the MAF	Standard methodology for comparisons
The change from baseline to 4, 10, 16, and 28 weeks in subjective hirsutism and acne using a participant-reported VAS.	Standard methodology for comparisons (women only).
The change from baseline to 4, 10, 16, and 28 weeks in QoL using the EQ-5D-5L™.	Standard methodology for comparisons.

[redacted]

9.4.2.6. Safety Analyses

All safety analyses will be performed on the SAF.

Endpoint	Statistical Analysis Methods
AEs	AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 or later and summarized descriptively. Only TEAEs will be included in the main safety analysis. A TEAE is defined as any AE that has an onset on or after the first dose of study treatment and before the last dose of study treatment + 30 days or is any pre-existing AE that has worsened in severity on or after the first dose of study treatment and before the last dose of study treatment + 30 days. The incidence, nature, severity, relatedness, duration, outcome, seriousness and expectedness of TEAEs will be tabulated. AEs of special interest will be additionally separately tabulated.
Need for additional glucocorticoid doses	Use of hydrocortisone from the stress dosing packs or use of any additional glucocorticoid treatment during the study will be summarized descriptively.
Other safety assessments	For laboratory parameters, vital signs, and ECGs, change from baseline will be calculated at each scheduled post-baseline visit and summary statistics will be presented both for absolute values (at baseline and each scheduled post-baseline visit) and changes from baseline by treatment arm, and visit. Shift tables of baseline to minimum and maximum on-treatment will be produced for the appropriate parameters displaying the number and percentage of participants in each of the categories (High, Low and Normal) relative to the category of their baseline assessment. Results considered clinically significant by the Investigator will be summarized at each visit. Physical examination results, and their change from baseline, will be summarized at each visit.

9.4.2.7. Compliance

Percentage treatment compliance between visits and overall will be listed and summarized by treatment arm.

9.4.2.8. Study Conduct

Protocol deviations will be classified as ‘major’ or ‘minor’ and will be listed and summarized by treatment arm.

9.4.2.9. Other Analyses

None.

9.5. Interim Analyses

No formal interim analysis is planned. However, safety data will be generated at regular intervals for review by the independent DSMB (see Section 9.6). Details of these DSMB outputs will be specified in the DSMB Organizational Meeting Presentation and Minutes and DSMB Charter. Any outputs provided to the DSMB will be unblinded, but outputs provided to other team members will use a dummy randomization list with generic labels.

9.6. Data Safety Management Board

An independent DSMB will meet on a regular basis during the study to review safety data. The DSMB will operate in accordance with a charter, which is a separate controlled document. During the course of the study, if unblinded analyses indicate that AEs are occurring more frequently than anticipated, the DSMB will notify the Sponsor, who will notify regulatory authorities expeditiously as appropriate.

10. Supporting Documentation and Operational Considerations

Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
  - Applicable ICH GCP Guidelines.
  - Applicable laws and regulations.
- The protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (e.g. advertisements) must be submitted to an IEC/IRB by the Investigator and reviewed and approved by the IEC/IRB before the study is initiated.
- Any substantial amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IECs/IRBs annually or more frequently in accordance with the requirements, policies, and procedures established by the IEC/IRB.
  - Notifying the IEC/IRB of SAEs or other significant safety findings as required by IEC/IRB procedures.
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IEC/IRB, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Minors will be assented and parental consent sought in keeping with local laws and local IEC/IRB requirements. Minors will be re-consented on reaching the age of majority if still participating in the study at that time.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative (as defined in the relevant country) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act

(HIPAA) requirements, where applicable, and the IEC/IRB or study site.
- The medical record must include a statement that written informed consent/assent was obtained before the participant was entered in the study and underwent any study-specific assessments, and the date the written consent/assent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must generally be re-consented to the most current version of the ICF(s) during their participation in the study (i.e. if the change affects procedures or adds new safety information) but re-consent may not be required for minor administrative changes.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

A participant who is re-screened is not required to sign another ICF if the re-screening occurs within 30 days from the previous ICF signature date.

Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IEC/IRB members, and by inspectors from regulatory authorities.

Committees Structure

Data Safety Management Board

This study will include a DSMB which is constituted to safeguard the interests of study participants, assist and advise the Sponsor, assess the safety of the study treatments, monitor the overall conduct of the clinical study, and uphold data integrity. A separate charter will be created to outline the roles and responsibilities of the DSMB, including the timing of meetings, methods of providing information to and from the DSMB, frequency and format of meetings, recommendations on safety and statistical issues, and relationships with the Sponsor and study project team.

Data Review Meeting

The Sponsor will convene a Data Review Meeting after the data has been cleaned and the database soft-locked but before final database lock and analysis has commenced. The review will be performed within the framework of the requirements of the ICH Guideline E9. The terms of reference for the Data Review Meeting will include, but will not be limited to:

- the determination of whether protocol deviations are 'major' or 'minor', or not a protocol deviation at all
- the allocation of participants to analysis sets
- a review of missing data and of outliers
- a review of whether additional covariates need to be included in the analyses

- revisions to SAP in light of any Data Review Meeting findings

All persons taking part in the Data Review Meeting must only have access to datasets masked to treatment allocation. Treatment arm allocations will be scrambled using a dummy randomization list and presented using generic treatment labels (for example, “Group A” and “Group B”).

Dissemination of Clinical Study Data

The Sponsor will comply with regulatory requirements on disclosure and dissemination of clinical study data in line with its SOPs.

Data Quality Assurance

- All participant data relating to the study will be recorded on eCRFs unless transmitted directly to the Sponsor or designee electronically (e.g. laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IEC/IRB review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g. risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (e.g. Contract Research Organizations).
- Study monitors will perform ongoing source data verification (SDV) to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator after study completion for as long as local regulations or institutional policies require. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Remote Monitoring Visits

If remote monitoring is being conducted, SDV against the source documents will be conducted using remote access to the participants electronic medical records or using scanned documents, if either are permitted. All participant identifiers must be redacted prior to scanning (further details are provided in the Clinical Monitoring Plan). However, it should be noted that sending copies of medical records, even pseudonymized, is not authorized in France, in accordance with the national recommendations published on the ANSM website

(https://www.ansm.sante.fr/Activites/Essais-cliniques/COVID-19-Ongoing-clinical-trials/(offset)/1).

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- The information in original documents and records (e.g. patient files, laboratory results, etc.) are defined as source data and will be reviewed by the monitor for SDV. SDV ensures accuracy and credibility of the data obtained. During monitoring visits, reported data are reviewed with regard to being accurate, complete and verifiable from source documents.

Study and Site Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The Sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination. Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the Investigator.
- Discontinuation of further study treatment development.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organizations used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participants and should assure appropriate therapy and follow-up.

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multi-site studies only in their entirety and not as individual site data. In this case, a Coordinating Investigator will be designated by mutual agreement.

- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

The Sponsor will also publish the study results in an appropriate public registry that complies with the regulations and rules applicable to the study.

Appendix 2: Clinical Laboratory Tests

The tests detailed in the table below will be performed by the central laboratory. The results will either be entered into the eCRF by the site staff or transferred electronically by the central laboratory. The Investigator must document their review of each laboratory safety report. Participants are required to fast before the collection of the 08:00 androgen sample, but there is no requirement for the participant to be fasting for any of the other laboratory tests.

Protocol-Required Safety and Efficacy Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet count		RBC Indices: Mean corpuscular volume (MCV) Mean cell hemoglobin (MCH) Mean cell hemoglobin concentration (MCHC) Red cell distribution width (RDW)	White blood cell (WBC) count with differential (absolute and %): Neutrophils Lymphocytes Monocytes Eosinophils Basophils
	Red blood cell (RBC) count			
	Hemoglobin			
	Hematocrit			
	HbA1c			
Clinical Chemistry	Blood urea nitrogen (BUN)	Potassium	AST/serum glutamic-oxaloacetic transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	ALT/serum glutamic-pyruvic transaminase (SGPT)	Total protein
	Inorganic phosphorus	Calcium	Alkaline phosphatase	Lactate dehydrogenase (LDH)
	Chloride	Total carbon dioxide (CO_2)	Albumin	Total creatine kinase (CK)
	Total magnesium	FSH	LH	Uric acid
	Osteocalcin	DHEA	11-ketotestosterone	Total testosterone
	Androgens (17-OHP and A4)			
	Plasma renin activity (PRA) or plasma renin concentration (PRC) after the participant has been supine for 30 minutes if possible			
Routine Urinalysis	• Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, and urobilinogen. • Microscopic examination (if blood or protein is abnormal).			
Other Screening Tests	• Urine or blood human chorionic gonadotropin (hCG) pregnancy test (as needed for WOCBP).			
NOTES: *All events of ALT ≥3 × ULN and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN at any time may indicate severe liver injury (possible Hy's Law) and must be reported as an SAE.*				

Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g. ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e. not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • 'Lack of efficacy' or 'failure of expected pharmacological action' *per se* will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g. endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital or hospitalization for elective surgery). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g. hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Medically Important Events

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g. hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the eCRF and any SAEs will be reported to the pharmacovigilance group using the SAE/AESI Report Form.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor or designee.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- All AEs will be assigned one of the following assessments of causality (note: both Chronocort and IRHC and the stress dosing medication are considered study treatments in this context):
    - Definitely related to the study treatment
    - Probably related to the study treatment
    - Possibly related to the study treatment

- Unlikely to be related to the study treatment
- Not related to the study treatment

- All AEs judged by either the Investigator or the Sponsor as having a reasonable suspected causal relationship to a study treatment or are due to an interaction with a study treatment, qualify as adverse drug reactions (ADRs).

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF and the SAE/AESI Report Form.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

Reporting of SAEs and AESIs

SAE and AESI Reporting via Paper Form

The SAE or AESI information should be reported by email using the SAE/AESI Report Form to the Sponsor's Medical Monitor and to the pharmacovigilance contact below:

Pharmalex
Email: diurnalclinicalsafety@pharmalex.com

The medical monitor will be allocated by the Contract Research Organization and the contact details provided to each site.

Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Female participants presenting with oligomenorrhea or amenorrhea who are aged ≤55 years should be considered potentially fertile and therefore should undergo pregnancy testing like all other female participants.

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP

1. Pre-menopausal female with 1 of the following:
   - documented hysterectomy
   - documented bilateral salpingectomy
   - documented bilateral oophorectomy.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

2. Post-menopausal female
   - A post-menopausal state is defined as a woman over 55 years who has not had menses for 12 months without an alternative medical cause. A high FSH level in the post-menopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status before study enrollment.

Contraception Guidance

Couples should agree not to try to become pregnant during this study. It should be noted that Chronocort treatment may result in improved fertility and so appropriate precautions against pregnancy should be taken.

Male participants

- Male participants with female partners of childbearing potential are eligible to participate if they agree to ONE of the following:
  - Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.
  - Agree to use a male condom when having penile-vaginal intercourse with a WOCBP who is not currently pregnant.

Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration

for the duration of the study. Men must also refrain from donating sperm for the duration of the study and for 7 days after the last dose of study treatment.

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in the table below. The methods of contraception must remain the same throughout the study in both nature and dose. The type of contraception should have been ongoing for ≥90 days prior to the study and at least 7 days after the final dose. If <90 days prior to the study, additional use of a double barrier method until 90 days is reached is required.

Contraceptive Methods

Highly Effective Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[b] • oral • intra-vaginal • trans-dermal.
Progestogen only hormonal contraception associated with inhibition of ovulation • oral • injectable.
Highly Effective Methods That Are User Independent [a]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation[b] • intra-uterine device • intra-uterine hormone-releasing system. • Bilateral tubal occlusion.
Vasectomized partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

Barrier methods of contraception Condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository. The following should be noted: Failure rates indicate that, when used alone, the diaphragm and condom are not highly effective forms of contraception. Therefore, the use of additional spermicides does confer additional theoretical contraceptive protection. However, spermicides alone are inefficient at preventing pregnancy when the whole ejaculate is spilled. Therefore, spermicides are not a barrier method of contraception and should not be used alone.
NOTES: a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. b) Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. In this case, 2 highly effective methods of contraception should be utilized during the treatment period and for 7 days after the last dose of study treatment.

Pregnancy testing

- WOCBP should only be included after a confirmed negative highly sensitive urine pregnancy test (or blood test if required according to usual site practices) taken at the screening visit (Visit 1).
- Additional pregnancy testing should be performed at every clinic visit from Visit 2 onwards.
- Pregnancy testing will be performed if pregnancy is suspected.

Collection of Pregnancy Information

Male participants with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy to Pharmalex (diurnalclinicalsafety@pharmalex.com). The female partner will also be followed up to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Participants who become pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy to Pharmalex (diurnalclinicalsafety@pharmalex.com). The participant will be followed up to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any

termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy-related SAE considered reasonably related to the study treatment by the Investigator will be reported to the Sponsor as described in Section 8.4.1. While the Investigator is not obligated to actively seek this information in former study participants, he/she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study treatment and will be followed up as detailed above (with consent of the participant). However, participants who withdraw from the study due to pregnancy may be eligible to enter the long-term extension study (DIUR-015) at the discretion of the Investigator providing that at least 6 weeks has lapsed after the pregnancy is complete (i.e. at least 6 weeks post-partum regardless of outcome or at least 6 weeks after abortion or termination) or at least 6 weeks after they have finished lactating and are no longer breast feeding (whichever is longer).

Appendix 5: Adrenal Insufficiency Checklist

*This questionnaire should be used to determine if symptoms of **under- or over-replacement of glucocorticoids** have occurred in the preceding 4 weeks. Symptoms unrelated to CAH, but due to other causes, e.g. nausea with migraine, should be recorded on the eCRF AE page.*

Date of assessment (mm/dd/yyyy):				
Please ask subject:	Have you experienced any of the following symptoms more than once per week in the last 4 weeks?			
Symptoms	**Yes**	**If Yes, do you believe this to be related to under or over replacement of glucocorticoid? Please state over/under.**	**No**	**Any clinically significant findings? Y/N**
Sudden weight loss				
Sudden weight gain				
Lack of appetite				
Increased appetite				
Nausea				
Vomiting				
Headache				
Blurred vision				
Fatigue				
Weakness				
Dizziness				
Lightheadedness				
Syncope (sudden loss of consciousness)				
Sleeping difficulties				
Increased acne				
Other				
If yes to Other please specify:				

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Appendix 6: Stress Dosing Rules

Each site should follow their own stress dosing rules, or if these are not available then the following rules should be used:

ADRENAL INSUFFICIENCY

Your body does not make adequate cortisol or aldosterone. Cortisol is a hormone which has many purposes in the body including maintaining blood pressure. Normally cortisol is secreted in the body in small amounts every day by the adrenal glands. In addition to the usual production of cortisol, the body normally has the ability to increase cortisol production in response to various stressors such as infection or trauma. Aldosterone is a hormone which is important in regulating salt and water balance. Sufficient aldosterone is necessary to prevent dehydration. These two hormones are being replaced in your body by medications.

Extra hydrocortisone must be given during times of **extreme physical stress** such as illness with fever and significant trauma.

For illnesses which result in:

Fever greater than or equal to 100°F (37.7°C)/ minor illnesses: take 10 mg **hydrocortisone** three times a day in addition to the usual daily dose of study medication.

Fever greater than or equal to 101°F (38.3°C)/ more severe illness: take 20 mg **hydrocortisone** three times a day in addition to the usual daily dose of study medication.

Vomiting: If you vomit, wait one half-hour and then take 20 mg of hydrocortisone for stress dosing rules from your packet provided. If you vomit the study medication dose do not take another dose of study medication until the next dose is due. Call the study team to let us know you are sick. If you are vomiting and cannot keep the medication down (vomit less than 1 hour after the dose), you need to administer injectable hydrocortisone. **Do not delay giving injectable hydrocortisone.** Drink **SMALL** amounts of clear liquids frequently, as tolerated. Call your doctor or go to an emergency room if your symptoms worsen or you do not improve within one hour.

Watch for signs of acute cortisol deficiency: headache, nausea, abdominal pain, dehydration, confusion, weakness, fatigue.

An injectable form of hydrocortisone must be kept in an easily accessible location for emergencies (i.e., purse, briefcase, desk at work). It may be kept for several years in the unmixed form at room temperature. It should not be exposed to extreme hot or cold (i.e., do not store in the glove compartment of a car). Check the expiration date routinely and obtain a prescription refill when needed. Also make sure you have the needle necessary to inject the medication.

Your dose of hydrocortisone for injection is 100 mg – 2 mL by intramuscular injection to the thigh.

Other points to remember:

- When you are sick, drink sugar and salt containing liquids (e.g., non-diet soda, Gatorade, Lucozade, soup).

- If you need to have surgery, extensive dental work, or you have been in an accident, extra doses of hydrocortisone will be needed, usually by intramuscular injection or intravenous administration. Notify any physician or dentist that you have ADRENAL INSUFFICIENCY, so proper amounts of hydrocortisone can be given prior to a procedure.

- It is essential that you wear a medical identification bracelet or necklace to alert people in times of emergency that you have adrenal insufficiency and are taking medication. It is also a good idea to have a wallet card or something on your driver's licence identifying you as having ADRENAL INSUFFICIENCY.

- Call your doctor for:
  Fever for more than three days
  Changes in behavior, such as acting confused

- If you are living with someone, let them know to seek medical help on your behalf if you are unresponsive or difficult to arouse.

  Ensure that you have a list of important phone numbers:
  Nurse:
  Doctor:
  Pharmacy:

Appendix 7: Abbreviations

Abbreviation	Definition
17-OHP	17-hydroxyprogesterone
A4	Androstenedione
ACTH	Adrenocorticotropic hormone
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration versus time curve
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
CAH	Congenital adrenal hyperplasia
CFR	Code of Federal Regulations
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	Creatine kinase
CO_2	Carbon dioxide
CONSORT	Consolidated Standards of Reporting Trials
CSR	Clinical Study Report
CYP3A4	Cytochrome P450 3A4
DHEA	Dehydroepiandrosterone
DSMB	Data Safety Management Board
ECG	Electrocardiogram
eCRF	Electronic case report form
EES	Efficacy Evaluable Set
EOS	End of study
ePRO	Electronic patient reported outcome
EQ-5D-5L™	5-level Standardized Health Questionnaire
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GEA	Global Evaluation Acne
HbA1c	Glycated hemoglobin
hCG	Human chorionic gonadotropin
HIPAA	Health Insurance Portability and Accountability Act
HR	Heart rate
HRT	Hormone replacement therapy
ICF	Informed consent form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IMP	Investigational medicinal product

IRB	Institutional Review Board
IRHC	Immediate-release hydrocortisone
IRT	Interactive response technology
LC-MS-MS	Liquid chromatography tandem mass spectrometry
LDH	Lactate dehydrogenase
LH	Luteinizing hormone
LPLV	Last participant last visit
MAF	Multidimensional Assessment of Fatigue
MCH	Mean cell hemoglobin
MCHC	Mean cell hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
NDA	New Drug Application
PK	Pharmacokinetic(s)
PRA	Plasma renin activity
PRC	Plasma renin concentration
QoL	Quality of life
RBC	Red blood cell
RDW	Red cell distribution width
SAE	Serious adverse event
SAF	Safety Analysis Set
SAP	Statistical analysis plan
SD	Standard deviation
SDV	Source data verification
SF-36®	Medical Outcome Study 36-Item Short Form Health Survey
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
SoA	Schedule of Activities
SOP	Standard Operating Procedure
SUSAR	Suspected unexpected serious adverse reactions
TART	Testicular adrenal rest tumors
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
VAS	Visual analog scale
WBC	White blood cell
WOCBP	Woman of childbearing potential

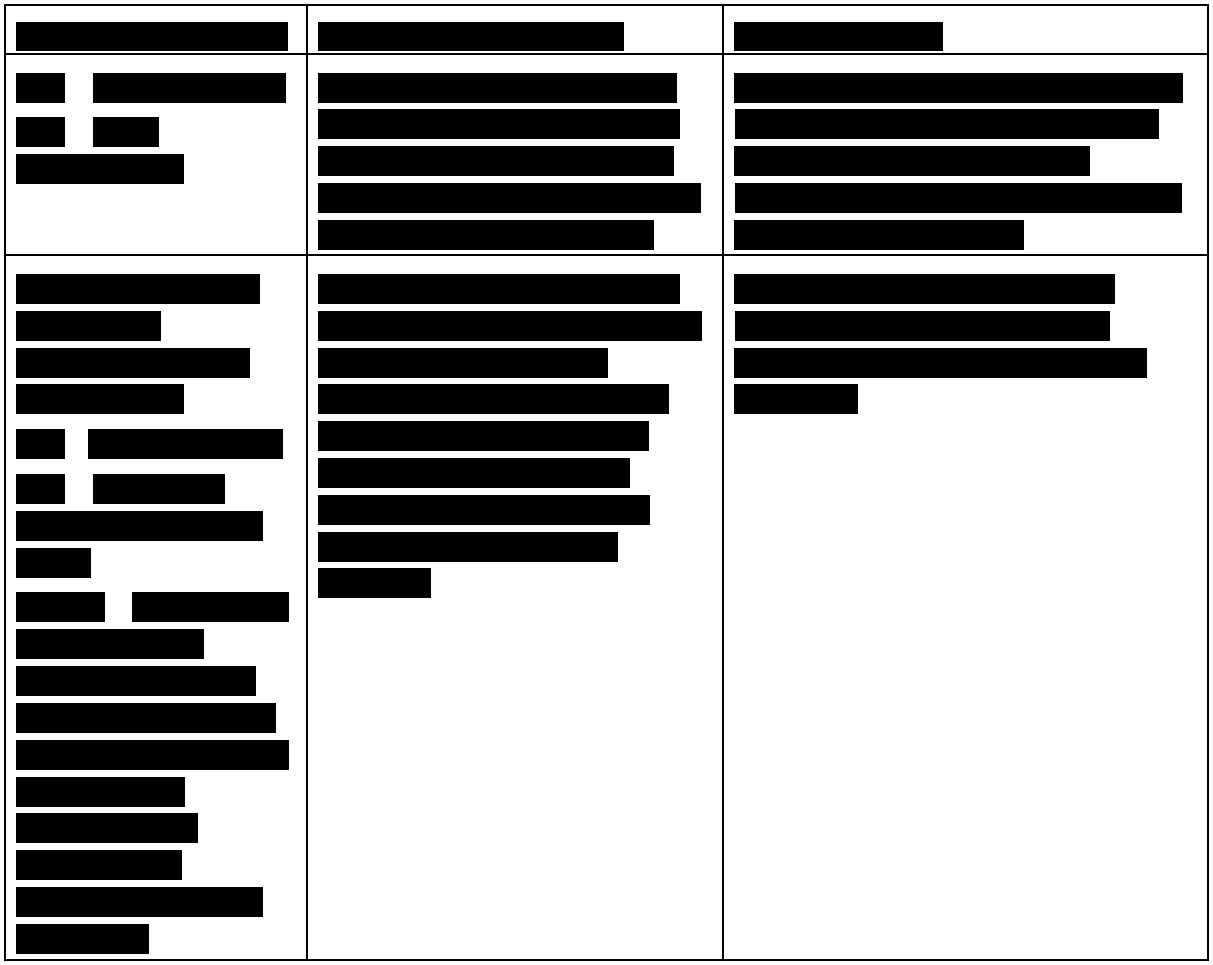
Note: A participant in this clinical study is an individual subject who agrees to participate in the study as either as recipient of an investigational medicinal product or as a control.

Appendix 8: Protocol Amendment History

Amendment 1 (04-May-2021)

Overall Rationale for the Amendment:

In developing the detailed titration guidelines for the investigator, it was determined that there was the potential for unblinding by allowing the investigators to know the androgen levels (17-OHP and A4) so this was amended so only the central independent blinded physician has access to the androgen results. In addition, the choices for participants at the end of the study was amended to allow access to commercial Chronocort, depending on the territory.



Amendment 2 (27-Jan-2022)

Overall Rationale for the Amendment:

Following review by the FDA and the French Regulatory Authority (ANSM) several changes have been made to the protocol. In addition, a few other changes have been made to amend errors or to reflect how the study will be run. All these changes are detailed below:

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Amendment 3 (04-Mar-2022)

Overall Rationale for the Amendment:

Following a second review by the French Regulatory Authority (ANSM) an additional change has been made to the protocol. In addition, a few other changes have been added that have arisen during the study start-up process. All these changes are detailed below:

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Amendment 4 (23-Mar-2022)

Overall Rationale for the Amendment:

The schedule of assessments was incorrect, so this plus a few other minor changes have been implemented. All these changes are detailed below:

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Amendment 5 (09-Feb-2023)

Overall Rationale for the Amendment:

Following a change in the Sponsor's regulatory strategy, the 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). In addition, the visit windows for the telephone calls have been widened for practical reasons. Elsewhere other clarifications have been added. All the changes are marked in the tracked changes version of the protocol, with the key changes summarized below:

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

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