CLINICAL STUDY PROTOCOL PLUS AMENDMENT 19
(applicable for USA and France only)

A Phase III extension study of efficacy, safety and tolerability of Chronocort® in the treatment of congenital adrenal hyperplasia

IND No.: **76485**
Protocol No.: **DIUR-006**
EUDRACT No.: **2015-005448-32**
Version No.: **20.0**
Date of Protocol: **16 June 2022**

STUDY SPONSOR:
Diurnal Ltd
Cardiff Medicentre
Heath Park
Cardiff
CF14 4UJ, UK

Sponsor Signature: [redacted]

Confidentiality Statement:

This study will be conducted in compliance with Good Clinical Practice (GCP), the Declaration of Helsinki (with amendments) and in accordance with local legal and regulatory requirements.

PRINCIPAL COORDINATING INVESTIGATOR SIGNATURE PAGE

Principal Coordinating Investigator	[redacted]
Address:	[redacted]
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Fax:	[redacted]
Email:	[redacted]

I, the undersigned, have reviewed this protocol, plus amendment 19, and including appendices, and I will conduct the clinical study as described and will adhere to GCP/ICH and all the ethical and regulatory considerations stated. I have read and understood the contents of the Investigator's Brochure.

Signature: [redacted]

SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

[NOTE: THIS PAGE MUST BE CUSTOMISED TO EACH STUDY SITE]

Principal Investigator Address:	*To be customised as appropriate for each site*
Tel: Fax: Email:	

I, the undersigned, have reviewed this protocol, plus amendment 19, and including appendices, and I will conduct the clinical study as described and will adhere to GCP/ICH and all the ethical and regulatory considerations stated. I have read and understood the contents of the Investigator's Brochure.

Signature: _____ Date: _____

Dr ..... *[full name to be added]*
Principal Investigator

STATISTICIAN SIGNATURE PAGE

Statistician:	[redacted]
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I, the undersigned, have reviewed this protocol, plus amendment 19, and including appendices, and I will conduct my role in the clinical study as described and will adhere to GCP/ICH and all the ethical and regulatory considerations stated. I have read and understood the contents of the Investigator's Brochure.

Signature [redacted]

1. Protocol Synopsis

PROTOCOL TITLE:	A Phase III extension study of efficacy, safety and tolerability of Chronocort® in the treatment of congenital adrenal hyperplasia
PROTOCOL No:	DIUR-006
PRINCIPAL COORDINATING INVESTIGATOR	[redacted]
SPONSOR:	Diurnal Limited Cardiff Medicentre Heath Park Cardiff, CF14 4UJ UK
INVESTIGATIONAL PRODUCT:	Chronocort® (Hydrocortisone Modified Release Capsule)
PHASE OF DEVELOPMENT:	Phase III
STUDY DESIGN	Open label extension study
STUDY CENTRES	Approved centres who participated in Chronocort® studies DIUR-003 and DIUR-005
INCLUSION CRITERIA 1. Subjects with congenital adrenal hyperplasia (CAH) who have successfully completed the DIUR-003 or DIUR-005 clinical trials with the current formulation of Chronocort® 2. Provision of signed written informed consent.	
EXCLUSION CRITERIA 1. Co-morbid condition requiring daily administration of a medication (or use of any medications/supplements) that interferes with the metabolism of glucocorticoids. 2. Clinical or biochemical evidence of hepatic or renal disease. Creatinine over twice the upper limit of normal (ULN) or elevated liver function tests (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] >2 times ULN]). 3. Females who are pregnant or lactating. 4. Subjects on regular daily inhaled, topical, nasal or oral steroids for any indication other than CAH. 5. History of malignancy (other than basal cell carcinoma successfully treated >6 months prior to entry into the study). 6. Subjects with a history of bilateral adrenalectomy. 7. Participation in another clinical trial of an investigational or licensed drug or device within the 3 months prior to inclusion in this study, except for another clinical trial with the current formulation of Chronocort®. 8. Subjects unable to comply with the requirements of the protocol. 9. Subjects who routinely work night shifts and so do not sleep during the usual nighttime hours.	
STUDY DURATION: The length of the study will be approximately 5.5 years from the date of the first subject entering the study, so subjects will be treated for a maximum of 5.5 years (i.e. from August 2016 to February 2022). All subjects must be enrolled by 31 October 2018, with no subjects allowed to enter the study after this date.	
NUMBER OF SUBJECTS: All eligible subjects from study DIUR-003 (16 subjects) and DIUR-005 (122 subjects) may enter this study, giving a maximum of 138 subjects.	
TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION:	Chronocort® will be provided as 5 mg, 10 mg and 20 mg capsules for oral administration.
REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION:	None.

OBJECTIVES:

Primary Objective: Safety and tolerability of Chronocort® over time, as assessed by signs and symptoms of adrenal insufficiency or over-treatment, use of sick day rules, adrenal crisis, adverse events (AEs), laboratory measures and clinical observation.

Secondary Objectives:

The long-term efficacy of Chronocort® will be assessed over time by the measurement of:

1. Total daily dose of Chronocort® in mg/day of hydrocortisone and by body surface area (BSA) during the study and the incidence of dose titrations
2. 17-hydroxyprogesterone (17-OHP) and androstenedione (A4), measured at two time points (at 09:00 and 13:00 hours) for:
    a. Disease control at each visit as assessed by both 17-OHP and A4 levels in the optimal and normal range, respectively, at both time points and by the proportion of dose given at night
    b. 17-OHP and A4 standard deviation scores (SDS)
    c. Change in absolute values compared to pre-Chronocort® baseline values
3. Changes compared to pre-Chronocort® baseline in:
    a. Bone turnover markers - serum C-terminal cross-linked telopeptide (CTX), osteocalcin
    b. Testosterone (total)
    c. Fasting insulin and blood glucose levels, and glycated haemoglobin (HbA1c)
    d. High sensitivity c-reactive protein (hsCRP) and plasma renin activity (PRA)
    e. Body composition (dual energy X-ray absorptiometry [DEXA]) (fat mass, lean mass and total bone density) (except in Germany)
    f. Quality of life – SF-36®, Multidimensional Assessment of Fatigue (MAF), EQ-5D™

Note: Pre-Chronocort® baseline means prior to the first dose of continuous Chronocort® which is:

- *The reassessed baseline under DIUR-006 for subjects entering from study DIUR-003 and those subjects from DIUR-005 who had a gap between completing study DIUR-005 and starting study DIUR-006,*
- *Visit 4 (Week 24) from the feeder study for subjects who received standard glucocorticoid replacement therapy in study DIUR-005 and immediately entered DIUR-006,*
- *Prior to the first Chronocort® dose in study DIUR-005 for subjects who received Chronocort® in study DIUR-005 (i.e. DIUR-005 baseline visit) and immediately entered DIUR-006.*

METHODOLOGY:

Subjects completing study DIUR-005 and those who have already completed study DIUR-003 will be offered the opportunity either to continue Chronocort® therapy or to switch from their current glucocorticoid therapy to Chronocort® in this open-label study.

All subjects will have a screening visit prior to the baseline assessment to allow DIUR-006 procedures to be fully explained and informed consent to be given by the subject. For subjects from DIUR-003 and any subjects from DIUR-005 who had a gap between completing study DIUR-005 and starting study DIUR-006 during which they received standard glucocorticoid therapy, this screening visit will include safety blood tests. Any subjects not meeting the inclusion/exclusion criteria following these blood tests will be not be entered into the study.

All subjects will then return for the baseline visit. For subjects entering from study DIUR-003 and any subjects from DIUR-005 who had a gap between completing study DIUR-005 and starting study DIUR-006 during which they received standard glucocorticoid therapy, the full set of baseline assessments will be completed, including 2 blood samples (one at 09:00 and one at 13:00 hours) for 17-OHP and A4 (note: baseline DEXA scan only needed for subjects entering from study DIUR-003). For subjects entering immediately from study DIUR-005, test results from their last visit in the feeder study (V4) will be used for this baseline assessment, with the 09:00 and 13:00 hour results taken from the 24-hour hormone profiles conducted at the visit. Any subjects not meeting the inclusion/exclusion criteria following these blood tests will be withdrawn from this study.

Once the baseline assessments are completed, the subjects will be given sufficient Chronocort® to use until the next visit at Week 4. Subjects entering immediately from study DIUR-005 who were previously on Chronocort® will continue on the same dose of Chronocort® that they were receiving at the end of the feeder study. Subjects from study DIUR-005 on standard therapy, subjects from DIUR-005 who had a gap between completing study DIUR-005 and starting study DIUR-006 during which they received standard glucocorticoid therapy, and subjects from study DIUR-003 will have their initial dose of Chronocort® determined using the hydrocortisone equivalent of their previous treatment (immediately prior to the baseline visit).

All subjects will return to the study centre at 4, 12 and 24 weeks after starting study DIUR-006 for additional blood tests and dose titration, if necessary. Visits thereafter will take place at 6-monthly intervals. If there is a change of dose, an interim dose titration visit or telephone call will be needed in between the 6-monthly visits.

All subjects will receive welfare telephone calls at 3 monthly intervals, and unscheduled visits will be arranged if necessary. Subjects will be provided with Chronocort® supplies from the study pharmacy at either 3-or 6-monthly intervals.

All subjects have the following assessments conducted during the study:

At all visits:

- AEs recorded, with particular note taken of use of sick day rules and adrenal crises.
- Dose of Chronocort® given, along with compliance assessment.
- Concomitant medications recorded.
- Measurement of 17-OHP and A4 at two time points (the first at 09:00 and the second at 13:00 hours).
- Urine pregnancy test for women of childbearing potential (note: females presenting with oligomenorrhoea or amenorrhoea who are aged ≤55 years of age should be considered potentially fertile and should therefore undergo pregnancy testing like all other female subjects).

At baseline, at each 6-monthly visit and at the final visit:

- Physical examination, vital signs, weight, body mass index (BMI) and waist circumference.
- Safety blood tests, serum CTX, osteocalcin, PRA, hsCRP, HbA1c, testosterone, fasting insulin and blood glucose levels.
- Quality of life – SF-36®, MAF, EQ-5D™

At yearly intervals (except Germany):

- body composition (DEXA) (fat mass, lean mass and total bone density) (to be taken at baseline for subjects entering from study DIUR-003).

At the end of the study subjects will have the option to enter a second long-term study (DIUR-015) to enable them to continue to receive open-label Chronocort® until it is commercially available in their region or it is decided to stop Chronocort® treatment. Subjects who decide to enter the DIUR-015 study immediately following this DIUR-006 study do not require a telephone call 30 days after the end of this study. If there is a gap between finishing this DIUR-006 study and entering the DIUR-015 study of greater than 30 days, then the 30-day telephone call is required.

Dose Titration Algorithm

The intention of dose adjustment is to optimise control of CAH according to current standard of care based on subject symptoms and the measurement of androgens. As this study is open and uncontrolled, titration will be performed by the investigating physician. Dose adjustment will be based on clinical symptoms using the "signs and symptoms of adrenal insufficiency questionnaire" and the measurement of 17-OHP and A4. The 17-OHP and A4 sample taken at 09:00 will reflect the Chronocort® dose taken at 23:00 hours and the sample taken at 13:00 will reflect the 07:00 hour Chronocort® dose. Dose adjustments will be considered if the samples show out of range values for 17-OHP or A4. If 17-OHP and A4 show inconsistent trends, the A4 parameter will take precedence in directing dose adjustment. Confirmation of the dose following the hormone results will be made by telephone within two weeks of the visit and will be followed up in writing whether dose titration is needed or not. If a dose titration is needed, an interim dose titration visit or telephone call (at the investigator's discretion) will be required to take place approximately 4 weeks after the decision has been communicated to the participant.

The rationale for any dose adjustment will be recorded in the electronic case report form (eCRF). No dose adjustments outside of the protocol-defined dose adjustments should be conducted, unless clinical signs and symptoms indicate an immediate need. In such cases the Sponsor's medical monitor must be contacted (preferably before any dose changes are implemented). Any such unscheduled dose adjustments should be based on clinical symptoms only, with repeated androgen testing discouraged and must be pre-approved by the Sponsor's medical monitor. Stress doses of hydrocortisone will be given for inter-current illnesses as medically indicated according to "sick day rules". Fludrocortisone dose adjustment will be made if medically indicated and will be based on blood pressure measurements and laboratory data (goal supine PRA < 1.5 x ULN).

In subjects who have undetectable androgens at baseline on their regular medication, caution will be taken with dose reductions if there is suspicion of the subject having a suppressed hypothalamic-pituitary-adrenal axis.

STATISTICAL METHODS:

A detailed and comprehensive Statistical Analysis Plan (SAP) will be prepared and signed-off before the first subject has given informed consent for this extension study. Interim data analyses are expected to be required for regulatory review as part of any marketing authorisation applications. No changes to the overall study conduct and no changes to the planned formal statistical analyses are anticipated as a result.

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). Geometric mean and coefficient of variation will also be presented for variables which will subsequently be log-transformed during the analysis.

For all analyses using change from baseline, baseline values for this DIUR-006 study will be used for subjects entering from study DIUR-003 and for subjects receiving standard therapy in study DIUR-005 or who had a gap between completing study DIUR-005 and starting study DIUR-006 during which they received standard glucocorticoid therapy. For subjects who received Chronocort® in study DIUR-005 and went straight into this DIUR-006 extensions study without a gap, baseline will be the baseline in the DIUR-005 study (i.e. before the start of any Chronocort® treatment).

All efficacy endpoints, including change from baseline, will be summarised at each visit by previous treatment, and by study. Exposure to Chronocort® and the incidence of dose titrations will be summarised as efficacy variables. All efficacy endpoints will be summarised over time. Disease control will be based on whether 17-OHP levels are in the optimal range and also whether the A4 levels are in the normal range (both analysed separately). A subject will be considered a responder (i.e. disease controlled) if their results are in the optimal or normal range, respectively.

AEs will be coded using the latest version of the MedDRA drug dictionary. Data will be summarised using preferred term (PT) and primary system organ class (SOC). Only treatment-emergent AEs, i.e. AEs with an onset at or after the first administration of Chronocort® in this study, will be presented in summary tables. Where changes in severity are recorded in the eCRF, the most severe incidence of the AE will be reported in the tables. Rates will be calculated as the proportion of subjects with at least one AE related to the number of subjects treated in each treatment group. Frequency tables will be provided concerning severity and drug relationship.

Summary vital signs changes from baseline will be presented in tabular form using standard summary statistics.

Absolute and change from baseline in safety laboratory variables will be summarised over time using standard summary statistics at each time point. Shift tables from baseline to the maximum and minimum on-treatment values will be presented. The 3 x 3 cross tabulations (from low, normal and high to low, normal and high) will be presented. Values outside the normal ranges (provided with the laboratory report), will be flagged in the subject data listings.

2. List of Abbreviations

17-OHP	17-hydroxyprogesterone
A4	Androstenedione
ACTH	Adrenocorticotropic hormone
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
AUC	Area under the curve
BMI	Body mass index
BSA	Body surface area
BUN	Blood urea nitrogen
CAH	Congenital adrenal hyperplasia
CBC	Complete blood count
CK	Creatine kinase
C_{max}	Maximum concentration
COVID-19	severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
CRA	Clinical Research Associate
CRADA	Cooperative Research and Development Agreement
CRH	Corticotropin-releasing hormone
CRO	Contract Research Organisation
CTX	C-terminal cross-linked telopeptide
CYP	Cytochrome P
DEXA	Dual energy X-ray absorptiometry
dL	Decilitre
DSMB	Data Safety Management Board
ECG	Electrocardiogram
eCRF	Electronic case report form
EQ-5D™	EQ-5D™ Standardised Health Questionnaire (5-level)
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
Hb	Haemoglobin
HbA1c	Glycated haemoglobin
Hct	Haematocrit
HDL	High density lipoprotein
HDPE	High density polyethylene
hsCRP	High sensitivity c-reactive protein
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IMP	Investigational medicinal product

IPI	Identifiable private information
IRB	Institutional Review Board
IRHC	Immediate release hydrocortisone
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
MAF	Multidimensional Assessment of Fatigue
MCH	Mean cell haemoglobin
MCHC	Mean cell haemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
NF	National Formulary
NIH	National Institutes of Health
PK	Pharmacokinetics
PP	Polypropylene
PRA	Plasma renin activity
PT	Preferred term
PV	Pharmacovigilance
QoL	Quality of life
RBC	Red blood cell count
RDW	Red cell distribution width
RSI	Reference Safety Information
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SDS	Standard deviation score
SDV	Source data verification
SF-36®	Medical Outcome Short Form Health Survey Form 36 (Subject Questionnaire)
SmPC	Summary of Product Characteristics
SOC	System organ class
SUSAR	Suspected Unexpected Serious Adverse Reaction
T_{max}	Time taken to reach C_{max}
TMF	Trial Master File
ULN	Upper limit of normal
WBC	White blood cell

The term ‘feeder study’ refers to the study the subject was in prior to entering this extension study: the feeder studies are DIUR-003 and DIUR-005.

3. Table of Contents

4. Investigators and Administrative Structure

Co-ordinating Principal Investigator

[redacted]

Medical Expert (Sponsor)

[redacted]

Project Manager (Sponsor)

[redacted]

Statistical Consultants

[redacted]

Contract Research Organisation/ Monitors

[redacted]

Central Laboratory

[redacted]

[redacted]

[redacted]

Safety Reporting

[redacted]

[redacted]

5. Introduction

5.1 Overview

Congenital adrenal hyperplasia (CAH), generally due to 21-hydroxylase deficiency, is a disease of the adrenal cortex characterised by cortisol deficiency with or without aldosterone deficiency, and androgen excess. The severe or classic form occurs in 1 in 15,000 births worldwide (Merke 2005; Pang 1993; Therrell 2001), while the mild non-classic form is a common cause of hyperandrogenism (New 2006). The discovery of glucocorticoid therapy as a treatment for CAH occurred in the 1950s resulting in subjects with classic CAH surviving. However, existing glucocorticoid treatment remains suboptimal and many unresolved clinical problems exist (Han 2014).

The glucocorticoid therapies currently used often fail to normalise the growth and development of children with CAH. Also adults may experience iatrogenic Cushing's syndrome, hyperandrogenism, infertility or the development of metabolic syndrome (Arlt 2010). Chronocort®, a newly-developed modified release oral formulation of hydrocortisone, is designed to mimic the normal serum levels of the endogenous cortisol circadian rhythm, offering the prospect of an improved treatment outcome. Phase II and III studies have been carried out to evaluate whether a twice a day dosing regimen of Chronocort® given at night and in the morning (which can more closely normalise cortisol levels) will improve control of adrenal androgen production (as measured by 17-hydroxyprogesterone [17-OHP] and androstenedione [A4]). This study is a long-term extension study for subjects who were included in studies DIUR-003 and DIUR-005 to obtain long-term safety data and to continue to monitor long-term efficacy.

5.2 Overview of Congenital Adrenal Hyperplasia

The adrenal cortex secretes the stress hormone cortisol, a glucocorticoid steroid that regulates energy balance and many intracellular processes. Cortisol synthesis is stimulated by adrenocorticotrophic hormone (ACTH), which increases the synthesis of the cytochrome P (CYP) enzymes that are involved in the synthesis of cortisol. ACTH secretion by the pituitary, in turn, is increased by hypothalamic secretion of corticotropin-releasing hormone (CRH), which is partly regulated by the central 'zeitgeber', or clock. Both ACTH and CRH secretion are inhibited by hypercortisolism. The adrenal cortex also secretes aldosterone, a mineralocorticoid steroid hormone that regulates sodium, potassium and water balance.

The pathophysiology of 21-hydroxylase deficiency-related adrenal hyperplasia is closely linked to the degree of enzyme deficiency. In the most severe form, concomitant aldosterone deficiency leads to salt loss and dehydration. In CAH, the defect in cortisol biosynthesis leads to a compensatory increase in ACTH and hypothalamic CRH due to a lack of the usual negative feedback by cortisol. Conventional glucocorticoid and mineralocorticoid replacement doses fail to replicate the close temporal relationship between CRH, ACTH and subsequent cortisol pulses (Krieger 1971; Ross 2005). Supraphysiologic doses of glucocorticoid are often necessary to adequately suppress excess adrenal androgen and oestrogen production (Cutler 1990; Merke 2001). Thus subjects with treated CAH are often poorly controlled on current standard therapy.

Conventional medical treatment of CAH is often a difficult balancing act between the undesirable states of hypercortisolism and hyperandrogenism (Han 2014). Subjects with CAH are at risk of developing a number of clinical manifestations, such as obesity in children

(Cornean 1998), insulin resistance (Azziz 1994; Moran 2000; New 1993; Speiser 1985), and polycystic ovaries, which may contribute to infertility in women with CAH. Oligomenorrhoea or amenorrhoea may be present in adolescence (Barnes 1994; Deneux 2001). The development of ectopic adrenal tissue or adrenal rest tissue is also associated with CAH.

5.3 Overview of Chronocort®

The active ingredient of Chronocort® is hydrocortisone. The safety profile of hydrocortisone is well characterised in humans and there is extensive clinical experience with the use of hydrocortisone in subjects with CAH. The excipients (inactive ingredients) used in the Chronocort® formulation under investigation are also well-characterised and are approved for use in humans at the proposed levels. The Chronocort® formulation has been manufactured and is supplied in accordance with current Good Manufacturing Practice (GMP).

Chronocort® is a patented oral modified release formulation of hydrocortisone which is intended to mimic, or closely match, the serum levels of endogenous cortisol, thereby improving the treatment of subjects with CAH. The rationale for Chronocort® is based on the belief that the delivery of a physiological cortisol profile will offer significant clinical benefits over current treatment. Formulations of immediate release hydrocortisone (IRHC) and other glucocorticoids used in the treatment of CAH are recognised to be unsatisfactory due to issues with:

- suboptimal disease control
- risk of glucocorticoid over-treatment
- inconvenient dosing regimens
- complex and inconsistent protocols for monitoring therapy
- poor subject compliance

Mimicry of the physiological cortisol profile is achieved by a delayed release and sustained absorption profile, such that when the dosage form is administered at night time (approximately 23:00 hours) there is a period of absence of drug release followed by a period of sustained absorption, to yield an elevation in serum cortisol concentration according to the normal circadian profile, with peak concentration occurring in the morning (approximately 06:00-08:00 hours) (Whitaker 2014; Mallappa 2015).

5.4 Rationale for the use of Chronocort® in the treatment of CAH

Subjects with classic CAH receive replacement glucocorticoid and mineralocorticoid. Many different regimens of glucocorticoid are advocated. Hormone levels are monitored prior to morning dose of medication, aiming for mildly elevated morning 17-OHP levels and normal renin levels (Joint LWPES/ESPE CAH Working Group 2002; Merke 2005; Speiser 2003). Physical features and clinical symptoms are monitored for evidence of excessive (e.g. obesity, striae, and decreased linear growth in children) or insufficient (e.g. hirsutism, amenorrhoea or virilisation in women, fatigue, and increased linear growth, early puberty, advanced bone maturation in children) treatment. It is often quite difficult to reduce excess androgen without giving excess glucocorticoid because current therapies cannot replace the normal circadian rhythm of cortisol.

Chronocort® is a newly-developed formulation of hydrocortisone that allows for slow absorption after oral administration when given at 23:00 hours (20 mg) and 07:00 hours (10 mg), so that cortisol levels peak in the early morning (Whitaker 2014). The compound has

the unique potential to provide the best possible physiologic replacement of cortisol and promises to ameliorate many of the unresolved medical issues surrounding the management of subjects with CAH (Mallappa 2015).

5.5 Overview of Chronocort® clinical studies

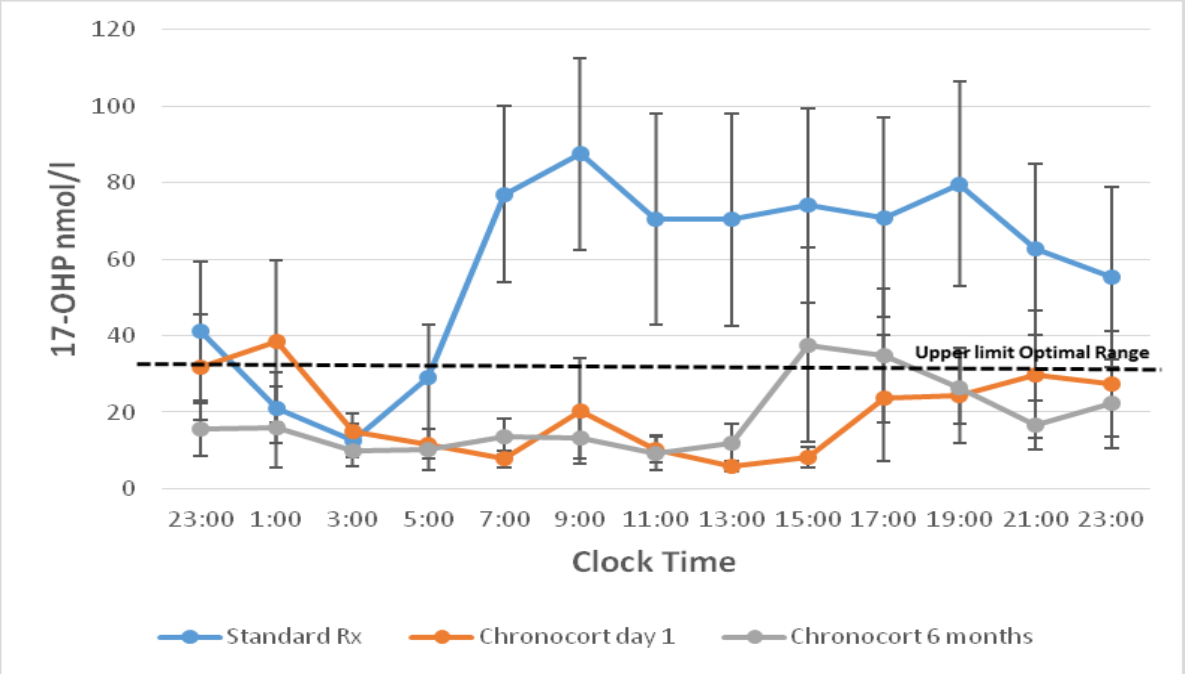
One Phase I study has been completed to assess the pharmacokinetics (PK) of Chronocort® (study DIUR-002) (Whitaker 2014). Study DIUR-002 fully characterised the PK performance and dose proportionality of Chronocort®. The target PK criteria, commensurate with the endogenous circadian profile for cortisol, were as follows: mean maximum concentration (C_{max}) >300 nmol/L (>10.8 mcg/dL) for the 20 mg dose, time taken to reach C_{max} (T_{max}) approximately 6-8 hours post-dosing to prime waking, mean cortisol level >100 nmol/L (>3.6 mcg/dL) up to 16:00 hours, mean cortisol level <100 nmol/L (>3.6 mcg/dL) after 22:00 hours, and relative bioavailability >80%. In study DIUR-002, all assessment criteria were met.

Study DIUR-003 (Phase II pilot study) was conducted in 16 subjects at a single site, the [redacted] (Mallappa 2015). DIUR-003 evaluated the PK profile of cortisol following short-term twice-daily administration of Chronocort® (20 mg at night and 10 mg in morning) in subjects with CAH and this was compared with data from healthy volunteers in the Phase I study. It also examined the effects of both short-term and long-term treatment with Chronocort® on key disease-related biochemical markers and other indices of efficacy/PK. The study evaluated 16 subjects with CAH over a 6-month period. All subjects started the study on 30 mg daily (given as 10 mg at 07:00 and 20 mg at 23:00), with dose titration then taking place within 2 weeks, following investigator review of biochemical and clinical parameters.

The PK profile of Chronocort® after 20 mg at 23:00 and 10 mg at 07:00 in subjects with CAH was similar to that seen in the Phase I clinical study (DIUR-002). The PK profile was characterised by an overnight rise in cortisol levels reaching a maximal concentration approximately 8 hours post-dosing, consistent with the physiological endogenous profile of cortisol reported in normal individuals. The variation in C_{max} and area under the curve (AUC) was similar to that seen in physiological cortisol levels in healthy volunteers.

This physiological replacement of cortisol with Chronocort® improved the control of disease-related biomarker androgens in subjects (control compared to baseline standard therapy). This was achieved with a similar dose of glucocorticoid; the mean hydrocortisone dose equivalent on standard therapy was 28 mg and on Chronocort® was 26 mg. On standard therapy at baseline, the majority of subjects had uncontrolled androgen levels, with most having high levels of 17-OHP and A4. Following 6-months titration with Chronocort®, the majority of subjects had 17-OHP and A4 levels in the normal or optimal range (see Figure 1).

Figure 1: ***17-OHP levels (mean ± standard error of the mean) during standard therapy at baseline and after the first administration of Chronocort® (Day 1) and following 6 months of continued Chronocort® treatment***



There were no safety issues reported in DIUR-002. There were no serious adverse events (SAEs) and no events leading to withdrawal from study DIUR-003. Two groups of adverse events (AEs) were considered sufficiently remarkable to warrant examination at the time: 5 subjects had treatment-emergent anaemia and 3 subjects had median nerve entrapment (carpal tunnel) syndrome. The anaemia cases were all consistent with acute low level red cell reduction attributable to blood loss secondary to the blood draws related to the study. The aetiology of the carpal tunnel syndrome was not clear, although thought most likely to be due to increased fluid retention. All events were mild and their relationship to the investigational medicinal product (IMP) was uncertain. All subjects recovered and the findings were not considered to alter the risk/benefit analysis or to raise cause for concern.

Study DIUR-004 was an open-label, randomised, single dose, 3-period, crossover study in 18 healthy male volunteers that was designed to assess the impact of food on the PK of Chronocort®. The study also evaluated the relative bioavailability of Chronocort® and immediate release hydrocortisone in the fasted state to support dosing in clinical practice. The results of this study showed that whilst extent of absorption of Chronocort® is unaffected, T_{max} is delayed by approximately 2 hours, and C_{max} is reduced by approximately 20% after food. Thus it is recommended that the morning dose of Chronocort® is taken on an empty stomach at least 1 hour before a meal and the evening dose should be taken at least 2 hours after the last meal of the day. From a safety perspective, one subject had mild AEs of epigastric pain and shortness of breath that were considered not related to the study drug (both were considered related to dexamethasone administration). Both events commenced together more than 4 days after dosing and lasted 11 days. The subject was withdrawn from the study as a result of these events. A second subject reported an AE of headache, but this occurred 14 days pre-dose and lasted 1.5 hours and there was no causal relationship with the study drug.

Study DIUR-005 was an open-label, randomised, parallel arm, Phase III study that was designed to evaluate the efficacy, safety and tolerability of Chronocort® compared with standard glucocorticoid replacement therapy in the treatment of subjects with CAH. This study has just completed and the results have been reported. The primary endpoint of the study (change from baseline to Week 24 of the natural logarithm of the mean of the 24-hour standard deviation score [SDS] profile for the natural logarithm of 17-OHP) was not met. However, secondary and post-hoc analyses were consistent in showing improved control of 17-OHP with Chronocort® treatment. In addition, a reduced incidence of adrenal crises, fewer occurrences of the use of sick day rules for AEs, and an increased incidence of therapeutic benefits (fatigue reduction, improvement of hirsutes, menstrual benefits) were reported following Chronocort® treatment.

5.6 Proposed study

The proposed study aims to build on the results of studies DIUR-003 and DIUR-005 and evaluate the long-term safety of Chronocort® and also its long-term efficacy in improving control of serum androgen levels (using 17-OHP and A4 as markers).

5.7 Benefit/Risk Assessment

The subjects in this study have classic CAH. As such, they have an absolute requirement for lifelong glucocorticoid replacement therapy. It is proposed that the formulation of hydrocortisone being evaluated in this study, Chronocort®, has characteristics that may improve the outcome in patients with CAH.

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 mimic the physiological circadian profile of cortisol. It is hypothesised that this will provide improved CAH disease control. Results of clinical trials using Chronocort® have demonstrated that cortisol levels on Chronocort® approximated physiologic cortisol rhythm over 24 hours, and improved control of androgens in subjects with CAH when compared to baseline conventional glucocorticoid therapy.

The risks associated with this study include those associated with blood sampling and general involvement with clinical trials. The investigators in this trial are all highly experienced both in clinical trials and in the management of patients with CAH, and so these risks are therefore negligible. In addition, to minimise the risk of anaemia associated with the withdrawal of multiple blood samples for laboratory testing (as seen in a previous study), the planned blood volume to be drawn at each visit has been limited to a maximum of 49 mL. The other risks then relate to the potential under- or over-treatment of subjects with glucocorticoids as seen in day-to-day clinical practice. These risks apply to both conventional treatment and Chronocort®. The patients will be informed of the potential for under-treatment (as occurs when there is an intercurrent illness) and are taught to manage this with supplemental steroids (emergency pack for sick day rules) and to seek medical assistance. It is also possible that the new formulation of Chronocort® might fail to release properly in the gut with resultant low levels of cortisol. If this were to occur once, the associated risk would be low, as a subsequent dose would be given either 8 or 16 hours later with little consequence. It would be hazardous if this occurred repeatedly. However, the formulation technology used is commonly used for other pharmaceuticals, and the studies so far in healthy subjects and subjects with CAH do not suggest that this happens. If this were to occur, then sick day rules would come into force as the subjects would become unwell. Such episodes would also be identified as AEs, which

would come to the notice of the independent Data Safety Management Board (DSMB). The DSMB will meet on a regular basis during the study to review the safety data and will operate in accordance with a predefined charter.

Over-treatment with hydrocortisone is unfortunately common in this condition as physicians try to control the androgen levels. Regular assessment of the subjects (both biochemically and clinically) in the study will identify over-treatment and correct it through a reduction in dose.

Thus the potential risks of the study are minimised and mitigated through investigator oversight, use of sick day rules by the individual patients when needed, and specific study activities (titration of dose, and identification of AEs). All subjects will be given the relevant information about the the risks and potential benefits of the study and all subjects have to sign a consent form prior to inclusion in the study that meets all the requirements of GCP and national regulations.

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 subject will have received at entry into the Chronocort® studies. However, the delivery of hydrocortisone with Chronocort® has been demonstrated to produce a cortisol profile more similar to the endogenous cortisol profile than current immediate-release hydrocortisone formulations and this is expected to result in improved disease control in patients with CAH. For subjects in the study, the potential benefits exceed the potential risks.

6. Study Objectives

6.1 Primary Objective

To evaluate the safety and tolerability of Chronocort® over time, as assessed by signs and symptoms of adrenal insufficiency or over-treatment, use of sick day rules, adrenal crisis, AEs, laboratory measures and clinical observation.

6.2 Secondary Objectives

The long-term efficacy of Chronocort® will be assessed over time by the measurement of:

1. Total daily dose of Chronocort® in mg/day of hydrocortisone and by body surface area (BSA) during the study and the incidence of dose titrations
2. 17-OHP and A4, measured at two time points (at 09:00 and 13:00 hours) for:
    a. Disease control at each visit as assessed by both 17-OHP and A4 levels in the optimal and normal range, respectively, at both time points and by the proportion of dose given at night.
    b. 17-OHP and A4 SDS
    c. Change in absolute values compared to pre-Chronocort® baseline values
3. Changes compared to pre-Chronocort® baseline in:
    a. Bone turnover markers - serum C-terminal cross-linked telopeptide (CTX), osteocalcin
    b. Testosterone (total)
    c. Fasting insulin and blood glucose levels, and glycated haemoglobin (HbA1c)
    d. High sensitivity c-reactive protein (hsCRP) and plasma renin activity (PRA)
    e. Body composition (dual energy X-ray absorptiometry [DEXA])(fat mass,

lean mass and total bone density) (except in Germany)

f. Quality of life – SF-36®, Multidimensional Assessment of Fatigue (MAF), EQ-5D™

7. Study Endpoints

7.1 Primary Endpoint

The primary endpoint is the safety of Chronocort® over time, assessed using but not limited to the following endpoints:

1. Signs and symptoms of adrenal insufficiency or over-treatment throughout the study.
2. Use of sick day rules throughout the study.
3. Occurrence of adrenal crises throughout the study.
4. Occurrence of AEs throughout the study.
5. Change from pre-Chronocort® baseline in safety laboratory assessments at each visit throughout the study.
6. Change from pre-Chronocort® baseline in vital signs, weight, body mass index (BMI), and waist circumference at each visit throughout the study.

7.2 Secondary Endpoints

To assess the long-term efficacy of Chronocort®, the following secondary endpoints will be assessed:

1. Total daily dose of Chronocort® in mg/day of hydrocortisone and by BSA
2. Disease control throughout the study as assessed by both 17-OHP and A4 levels in the optimal and normal range, respectively, at 09:00 and at 13:00, and by the proportion of dose given at night
3. Change from pre-Chronocort® baseline at each visit in SDS of 17-OHP and A4 at 09:00, 13:00 and the mean of the two timepoints. Pre-Chronocort® baseline means prior to the first dose of continuous Chronocort® which is:
   - The reassessed baseline under DIUR-006 for subjects entering from study DIUR-003 and those subjects from DIUR-005 who had a gap between completing study DIUR-005 and starting study DIUR-006,
   - Visit 4 (Week 24) from the feeder study for subjects who received standard glucocorticoid replacement therapy in study DIUR-005 and immediately entered DIUR-006,
   - Prior to the first Chronocort® dose in study DIUR-005 for subjects who received Chronocort® in study DIUR-005 (i.e. DIUR-005 baseline visit) and immediately entered DIUR-006.
4. Change from pre-Chronocort® baseline at each visit in the absolute values of 17-OHP and A4 at 09:00 and 13:00
5. Change from pre-Chronocort® baseline at each visit in:
   a. Bone turnover markers - CTX, osteocalcin
   b. Testosterone (total)
   c. Fasting insulin and blood glucose levels, and HbA1c
   d. hsCRP and PRA

e. Body composition (DEXA)(fat mass, lean mass and total bone density) (except in Germany)
f. Quality of life – SF-36®, MAF, EQ-5D™

6. Incidence of dose titrations

8. Study Design

Subjects completing study DIUR-005 and those who have already completed study DIUR-003 will be offered the opportunity either to continue Chronocort® therapy or to switch from their current glucocorticoid therapy to Chronocort® in this open-label study.

The intention is that subjects will transition straight from study DIUR-005 into DIUR-006 without a gap. However, during the conduct of the study, logistical issues arose precluding this for some subjects and so the protocol has been amended to allow these subjects who have been unable to transition immediately into DIUR-006 to be able to participate in the study (incorporated into Protocol version 7.0). However, all subjects must be enrolled by 31 October 2018, with no subjects allowed to enter the study after this date. In general, subjects who complete study DIUR-005 should **not** have an interruption in treatment; if this does occur prior approval should be sought from the Sponsor before entering them into study DIUR-006.

All subjects will have a screening visit prior to the baseline assessment to allow DIUR-006 procedures to be fully explained and informed consent to be given by the subject. For subjects from DIUR-003 and any subjects from DIUR-005 who had a gap between completing study DIUR-005 and starting study DIUR-006 during which they received standard glucocorticoid therapy, this screening visit will include safety blood tests. Any subjects not meeting the inclusion/exclusion criteria following these blood tests will be not be entered into the study.

All subjects will then return for the baseline visit. For subjects entering from study DIUR-003 and any subjects from DIUR-005 who had a gap between completing study DIUR-005 and starting study DIUR-006 during which they received standard glucocorticoid therapy, the full set of baseline assessments will be completed, including 2 blood samples (one at 09:00 and one at 13:00 hours) for 17-OHP and A4 (note: baseline DEXA scan only needed for subjects entering from study DIUR-003). For subjects entering immediately from study DIUR-005, test results from their last visit in the feeder study (V4) will be used for this baseline assessment, with the 09:00 and 13:00 hour results taken from the 24-hour hormone profiles conducted at the visit. Any subjects not meeting the inclusion/exclusion criteria following these blood tests will be withdrawn from this study.

Once the baseline assessments are completed, the subjects will be given sufficient Chronocort® to use until the next visit at Week 4. Subjects entering immediately from study DIUR-005 who were previously on Chronocort® will continue on the same dose of Chronocort® as they were receiving at the end of the feeder study. Subjects from study DIUR-005 on standard therapy, subjects from DIUR-005 who had a gap between completing study DIUR-005 and starting study DIUR-006 during which they received standard glucocorticoid therapy, and subjects from study DIUR-003 will have their initial dose of Chronocort® determined using the hydrocortisone equivalent of their previous treatment (immediately prior to the baseline visit).

All subjects will return to the study centre at 4, 12 and 24 weeks after starting study DIUR-006 for additional blood tests and dose titration, if necessary. Visits thereafter will take place at 6-monthly intervals. If there is a change of dose, a dose titration interim visit or telephone call will be needed in between the 6-monthly visits.

All subjects will receive welfare telephone calls at 3 monthly intervals, and unscheduled visits will be arranged if necessary. Subjects will be provided with Chronocort® supplies from the study pharmacy at either 3- or 6-monthly intervals.

At the end of the study subjects will have the option to enter a second long-term study (DIUR-015) to enable them to continue to receive open-label Chronocort® until it is commercially available in their region or it is decided to stop Chronocort® treatment. Subjects who decide to enter the DIUR-015 study immediately following this DIUR-006 study do not require a telephone call 30 days after the end of this study. If there is a gap between finishing this DIUR-006 study and entering the DIUR-015 study of greater than 30 days, then the 30-day telephone call is required.

All subjects have the following assessments conducted during the study (see Table 1):

At all visits:

- AEs recorded, with particular note taken of use of sick day rules and adrenal crises.
- Dose of Chronocort® given, along with compliance assessment.
- Concomitant medications recorded.
- Measurement of 17-OHP and A4 at two time points (the first at 09:00 and the second at 13:00 hours).
- Urine pregnancy test for women of childbearing potential (note: females presenting with oligomenorrhoea or amenorrhoea who are aged ≤55 years of age should be considered potentially fertile and should therefore undergo pregnancy testing like all other female subjects).

At baseline, at each 6-monthly visit and at the final visit:

- Physical examination, vital signs, weight, BMI and waist circumference.
- Safety blood tests, serum CTX, osteocalcin, PRA, hsCRP, HbA1c, testosterone, fasting insulin and blood glucose levels.
- Quality of life – SF-36®, MAF, EQ-5D™

At yearly intervals (except Germany):

- Body composition (DEXA) (fat mass, lean mass and total bone density) (also taken at baseline for subjects entering from study DIUR-003) (note: subjects with a gap between completing study DIUR-005 and starting study DIUR-006 do not require an additional DEXA scan at the time they enter study DIUR-006).

8.1 Dose Titration Algorithm

The intention of dose adjustment is to optimise control of CAH according to current standard of care based on subject symptoms and the measurement of androgens. As this study is open and uncontrolled, titration will be performed by the investigating physician. Dose adjustment will be based on clinical symptoms using the "signs and symptoms of adrenal insufficiency questionnaire" and the measurement of 17-OHP and A4. The 17-OHP and A4 sample taken at 09:00 will reflect the Chronocort® dose taken at 23:00 hours and the sample taken at 13:00 will reflect the 07:00 hour Chronocort® dose. Dose adjustments will be considered if the samples show out of range values for 17-OHP or A4. If 17-OHP and A4 show inconsistent trends, the A4 parameter will take precedence in directing dose adjustment. Confirmation of the dose following the hormone results will be made by telephone within two weeks of the visit and will be followed up in writing whether dose titration is needed or not. If a dose titration is needed, an interim dose titration visit or telephone call (at the investigator's discretion) will be required

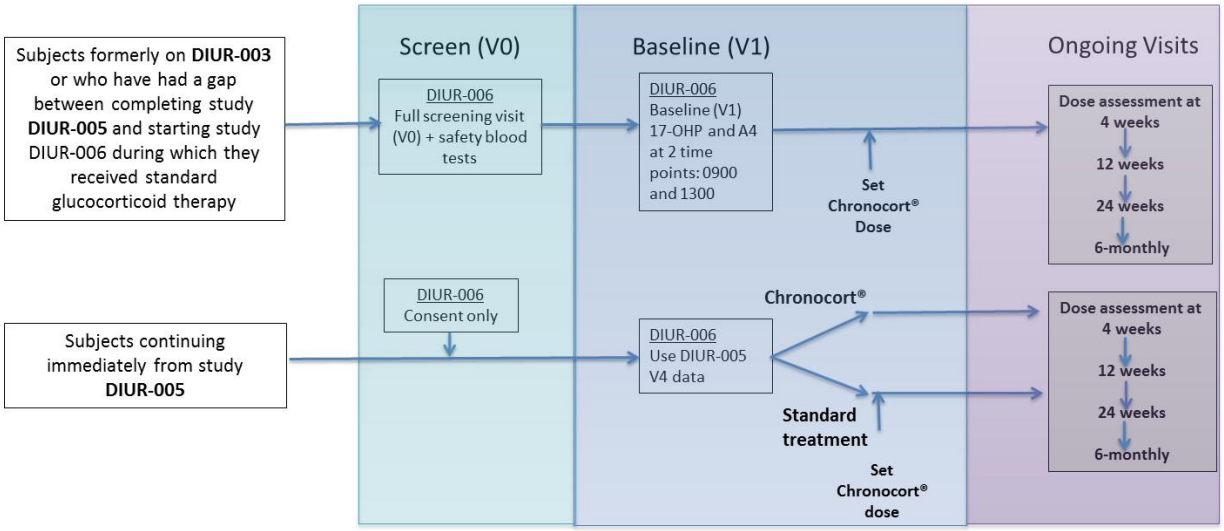
to take place approximately 4 weeks after the decision has been communicated to the participant.

The rationale for any dose adjustment will be recorded in the electronic case report form (eCRF). No dose adjustments outside of the protocol-defined dose adjustments should be conducted, unless clinical signs and symptoms indicate an immediate need. In such cases the Sponsor's medical monitor must be contacted (preferably before any dose changes are implemented). Any such unscheduled dose adjustments should be based on clinical symptoms only, with repeated androgen testing discouraged and must be pre-approved by the Sponsor's medical monitor. Stress doses of hydrocortisone will be given for inter-current illnesses as medically indicated according to "sick day rules". Fludrocortisone dose adjustment will be made if medically indicated and will be based on blood pressure measurements and laboratory data (goal supine PRA < 1.5 x upper limit of normal [ULN]).

In subjects who have undetectable androgens at baseline on their regular medication, caution will be taken with dose reductions if there is suspicion of the subject having a suppressed hypothalamic-pituitary-adrenal axis.

The study design is shown graphically in Figure 2.

Figure 2: Overview of DIUR-006 Study Schema



Note: any subject who has a dose titration during the study will have an interim dose titration visit or telephone call 4 weeks later
Note: subjects with a gap between finishing study DIUR-005 and starting study DIUR-006 do not require an additional DEXA scan at the time they enter study DIUR-006

9. Subject Population

9.1 Number of Subjects and Subject Selection

All eligible subjects from study DIUR-003 (16 subjects) and DIUR-005 (122 subjects) may enter this study, giving a maximum of 138 subjects. The study centres in this study will be the same centres that recruited the subject into the initial study.

9.2 Inclusion Criteria

1. Subjects with CAH who have successfully completed the DIUR-003 or DIUR-005 clinical trials with the current formulation of Chronocort®.

2. Provision of signed written informed consent.

9.3 Exclusion Criteria

1. Co-morbid condition requiring daily administration of a medication (or use of any medications/supplements) that interferes with the metabolism of glucocorticoids.
2. Clinical or biochemical evidence of hepatic or renal disease. Creatinine over twice the ULN or elevated liver function tests (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] >2 times ULN]).
3. Females who are pregnant or lactating.
4. Subjects on regular daily inhaled, topical, nasal or oral steroids for any indication other than CAH.
5. History of malignancy (other than basal cell carcinoma successfully treated >6 months prior to entry into the study).
6. Subjects with a history of bilateral adrenalectomy.
7. Participation in another clinical trial of an investigational or licensed drug or device within the 3 months prior to inclusion in this study, except for another clinical trial with the current formulation of Chronocort®.
8. Subjects unable to comply with the requirements of the protocol.
9. Subjects who routinely work night shifts and so do not sleep during the usual nighttime hours.

10. Study Medication and Administration

10.1 Randomisation and Blinding

This is an open-label, non-comparative study so no randomisation or blinding will occur. Subjects will retain the three-digit site number and the three-digit subject number used in the feeder study (i.e., the number used for that subject in DIUR-003 and DIUR-005), but 600 will be added to the study number. Thus subject D005/001/001 in study DIUR-005 will become D605/001/001 in study DIUR-006 and subject D003/001/001 in study DIUR-003 will become D603/001/001 in study DIUR-006.

10.2 Description and Handling of IMPs

The IMP for this study is Chronocort® (Hydrocortisone Modified Release Capsule). In this study Chronocort® will be supplied in three unit dose strengths of 5 mg, 10 mg and 20 mg per capsule.

Diurnal will supply the study sites with adequate bulk study medication of Chronocort® in batches over the study period.

10.2.1 Chronocort® Formulation

Chronocort® is a modified-release formulation of hydrocortisone for oral administration. Chronocort® is available for this study in dose strengths of 5 mg, 10 mg and 20 mg hydrocortisone. The 5 mg formulation will be presented in white opaque body/blue opaque cap size 1 hard gelatin capsules, printed with either 'CHRONOCORT 5mg' or 'CHC 5mg' on the capsule body. The 10 mg formulation will be presented in white opaque body/green opaque cap size 1 hard gelatin capsules, printed with either 'CHRONOCORT 10mg' or 'CHC 10mg' on the capsule body. The 20mg formulation will be presented in white opaque body/orange opaque

cap size 0 hard gelatin capsules, printed with either 'CHRONOCORT 20mg' or 'CHC 20mg' on the capsule body.

All excipients used in Chronocort® modified release capsules are standard materials normally used in pharmaceutical drug products, are the subject of United States Pharmacopeia/National Formulary (NF) and/or European Pharmacopeia Monographs, and have been used in pharmaceutical products worldwide over many years.

10.2.2 Packaging and Labelling

Chronocort® capsules are contained within either a PVC/PE/PVdC blister pack sealed with aluminium lidding foil or a high-density polyethylene (HDPE) bottle sealed with a polypropylene (PP) lid. Each blister pack contains 10 capsules of the same dose strength. Each bottle contains 50 capsules of the same dose strength. The Sponsor will supply Chronocort® to the pharmacy at the study site as clinical packs containing 100 capsules of each dose strength, i.e. 10 x 10-count blisters (100-count pack) or 2 x 50-count bottles.

A treatment pack for each subject will be assembled by the pharmacy using the required number of clinical packs according to the individual subject prescription. Subjects will receive treatment packs at baseline, Week 4, Week 12, Week 18 and then either 3- or 6-monthly thereafter. At each visit the subjects will return the used packs and any unused medication to the pharmacy for compliance accountability. At baseline and Week 4, two weeks extra medication will be included in each treatment pack to allow for dose adjustments and overage. If the subject collects their medication at 3-monthly intervals, a total of 100 days of Chronocort® will be supplied to each subject or if a 6-monthly supply schedule is used, a total of 200 days of Chronocort® will be supplied to each subject. The three dose strengths will be identifiable by the unique colour hard gelatin capsule and product/dose identifier printed on the capsule.

Chronocort® will be labelled as shown in Appendix 8.

10.2.3 Storage

Chronocort® will be securely stored in the study site pharmacy at a temperature not exceeding 25°C. Subjects dispensed with Chronocort® will be advised to store it securely in a cool (room temperature) and dry place out of the reach of children.

10.2.4 Accountability and Compliance

The study team or pharmacist will review the returned packs and count the number of used and unused capsules at each visit. This information will be entered in the eCRF so compliance can be calculated against the treatment prescriptions. All used and unused packs will be stored in a secure location and made available for review by the Clinical Research Associate (CRA) as outlined in Section 14.8. Following the Sponsor's approval, all remaining Chronocort® will either be returned to the supplier or destroyed on site unless otherwise instructed.

Accountability must also be performed at each visit for the safety pack (see Section 10.5), which should be used in conjunction with the site's "sick day rules". Any use of the medications in the safety pack should be recorded in the eCRF, along with the reason for use. If the safety pack is unused then it should be given back to the subject intact. If the safety pack has been used then the medication used will be replaced and the pack re-sealed and prescribed to the subject for the next study period.

10.3 Dosage and Administration

For subjects entering from DIUR-003, subjects receiving standard therapy in study DIUR-005, and subjects from DIUR-005 who had a gap between completing study DIUR-005 and starting study DIUR-006 during which they received standard glucocorticoid therapy, the initial dose of Chronocort® will be determined using the hydrocortisone equivalent of the subject's previous treatment (immediately prior to the baseline visit). Subjects from study DIUR-005 who are on Chronocort® at the end of DIUR-005 and enter study DIUR-006 immediately will start study DIUR-006 on the same dose as they completed study DIUR-005.

Approximately 2/3rds of the daily dose will be given in the evening, with the remainder given in the morning. All morning doses of Chronocort® in this study should be taken at approximately 07:00 hours on an empty stomach at least 1 hour before a meal and all the evening doses should be taken at approximately 23:00 hours at least 2 hours after the last meal of the day. Subjects will be asked to self-administer the dose of Chronocort® with a small drink of water.

10.4 Dose Adjustments

The intention of dose adjustment is to optimise control of CAH according to current standard of care based on subject symptoms and the measurement of androgen levels. Stress doses of hydrocortisone will be given for intercurrent illnesses as medically indicated according to "sick day rules" (see Appendix 3 for an example). All dose adjustments must be recorded in the subject notes and the eCRF.

- Dose adjustment will be based on clinical symptoms using the "signs and symptoms of adrenal insufficiency questionnaire" (Appendix 4) and the measurement of the 17-OHP and A4 levels at two time points at 09:00 and 13:00 hours. The adrenal insufficiency questionnaire should only be used to determine if symptoms of under or over replacement of glucocorticoids have occurred over the last 4 weeks – it should not be used to record AEs due to other causes.
- Dose adjustments will be made by the investigator according to the instructions provided in Section 8 under the heading "Dose Titration Algorithm"
- Dose adjustment will be made within 2 weeks after the visits at which 17-OHP and A4 levels are assessed. Subjects will be contacted by telephone to tell them of the outcome of the dose adjustment process – either to tell them of the new dose, or of no change in dose. This will be followed in writing (whether there is a change in dose or not) repeating the instruction of the phone call. If a dose titration is needed, an interim dose titration visit or telephone call (at the investigator's discretion) will be required to take place approximately 4 weeks after the decision has been communicated to the participant.
- No dose adjustments outside of the protocol-defined dose adjustments should be conducted, unless clinical signs and symptoms indicate an immediate need. In such cases the Sponsor's medical monitor must be contacted (preferably before any dose changes are implemented). Any such unscheduled dose adjustments should be based on clinical symptoms only, with repeated androgen testing discouraged and must be pre-approved by the Sponsor's medical monitor. Any such dose changes must be recorded in the eCRF.

Fludrocortisone dose adjustment will be made if medically indicated and will be based on blood pressure measurements and laboratory data (goal supine PRA < 1.5 x ULN).

In subjects who have undetectable androgens at baseline on their regular medication, caution will be taken with dose reductions if there is suspicion of the subject having a suppressed hypothalamic-pituitary-adrenal axis.

10.5 Other Study Medications (Non-Investigational Medicinal Products)

Stress doses to be used when the "sick day rules" are implemented will be supplied by the study site as part of a safety pack, which will typically include (according to local practice):

- A supply of oral hydrocortisone that would allow dosage of up to 20 mg three times daily
- 2 vials of hydrocortisone for injection plus syringes and needles
- The site's standard information guidance regarding "sick day rules" (routinely given to any subject receiving hydrocortisone replacement therapy)

Any use of the safety pack medication must be recorded in the eCRF, along with the reason for use.

Diurnal will also provide appropriate labels for the safety pack that can be used to label the drugs dispensed to subjects (See Appendix 8).

Subjects will continue to take Chronocort® twice daily when taking stress doses. **Any additional doses of hydrocortisone needed should only be taken from the safety pack and should not be taken from the study medication packs**. Further safety pack supplies can be obtained from the study site if required.

10.6 Permitted Concomitant Medications/Treatments

The subjects must be instructed that no additional medication is allowed without the prior consent of the investigator. Any medication considered necessary for the subject's safety and well-being may be given at the discretion of the investigator. Medication for sick days does not require authorisation but any use of the safety pack medication must be recorded in the eCRF. All concomitant medications and treatments will be recorded in the subject's eCRF.

If a participant has received the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2/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 "sick day rules" (see Appendix 3 - Sick Day Rules). If a stress dose is taken within 5 days of a scheduled visit, then the visit should be delayed until the participant has had a 5-day period without use of any stress doses.

11 Study Procedures

The study procedures to be conducted for each subject enrolled in the study are summarised in Table 1. Written informed consent must be taken prior to any study related procedures.

Table 1: Schedule of Study Assessments

	Screening Visit (V0) -14 days	Baseline Visit (V1) Day 0[17]	Week 4 (V2) ±3 days[17]	Week 12 (V3) ±3 days	Week 18 ±3 days then every 3 months ±2 weeks	Week 24 (V4) then every 6 months[1] ±2 weeks	Final Visit[18]	Follow-up telephone call[19]
Informed consent form[2]	X							
Inclusion/exclusion criteria	X	X						
Demography/medical history/current medical status[3]		X						
Previous/concomitant medication[4]		X[5]	X	X		X	X	
Physical examination		X[5]				X	X	
Weight, BMI, waist circumference		X[5]				X	X	
Vital signs (blood pressure, heart rate, respiratory rate, body temperature)		X[5]				X	X	
Blood samples for 17-OHP and A4 testing[6]		X[7]	X	X		X	X	
Glucocorticoid/Chronocort dose recorded (mg/day)		X[8]	X	X		X	X	
Dose titration			X[9]	X[9]		X[9]		
Study medication dispensed		X	X	X	X[16]	X		
Compliance assessment			X	X		X	X	
Serum CTX, osteocalcin, hsCRP, HbA1c, testosterone		X[5]				X	X	
Fasting insulin and glucose		X[5]				X	X	
PRA[10]		X[5]				X	X	
DEXA[11]		X[5]				X[11]		
QoL (MAF, SF-36®, EQ-5D™)		X[5]				X	X	
AEs and SAEs[12]	X	X	X	X	X	X	X	X
Signs and symptoms of adrenal insufficiency, incidence of adrenal crisis and implementation of sick day rules			X	X		X	X	
Safety blood tests	X[13]	X[5]				X	X	
Urine pregnancy test (females)[14]	X[13]	X[5]	X	X		X	X	
Genotyping	X[15]							
Interim telephone calls			X	X	X	X		

[1] After the initial visits at 4, 12 and 24 weeks, subjects will have a visit every 6 months. If the Chronocort® dose is changed at any point after the Week 24 visit, the subject should have an interim dose titration visit (which will include the assessments noted for Week 4) or an interim dose titration telephone call to check on the well-being of the subject (the telephone call includes all Week 4 assessments apart from blood sampling for 17-OHP and A4, and the urine pregnancy test). The subject will then continue with visits every 6 months.

[2] The informed consent form must be given to the subject at least 24 hours prior to the screening visit so they have sufficient time to review before being asked to sign.

[3] For subjects from study DIUR-005 only, demography and medical history can be obtained from the start of the DIUR-005 feeder study, with any changes that occurred during or after the feeder study and prior to entry into this DIUR-006 study being noted.

[4] Previous medication recorded in the 4 weeks prior to entry into DIUR-006.

[5] New information collected in subjects entering from study DIUR-003 and in subjects who have a gap between completing study DIUR-005 and starting study DIUR-006 during which they received standard glucocorticoid therapy (with the exception of DEXA scan - see Note 11). In subjects entering immediately from study DIUR-005 this information can be taken from the last visit of the feeder study.

[6] Two samples taken: the first at 09:00 and the second at 13:00 hours.

[7] In study DIUR-005 the results from the last endocrine profile can be used (V4) if the subject has entered study DIUR-006 immediately following completing study DIUR-005. If there is a gap between DIUR-005 and DIUR-006 then new samples must be taken at this baseline visit.

[8] At baseline, details of the last glucocorticoid dose taken prior to attending the visit will be recorded, including details of the drug(s), dose and time of administration. The initial dose of Chronocort will then be determined as follows: in DIUR-003 it will be determined using the hydrocortisone equivalent of the subject's previous treatment (immediately prior to the baseline visit); for subjects on Chronocort® in DIUR-005 the same dose of

Chronocort® will be used; and for subjects on standard therapy in DIUR-005 and for subjects who have a gap between completing study DIUR-005 and starting study DIUR-006 during which they received standard glucocorticoid therapy, the initial dose will be determined using the hydrocortisone equivalent of their previous treatment (immediately prior to the baseline visit).

[9] Dose adjusted based on 17-OHP and A4 measurements taken at each visit and clinical symptoms assessed using the signs and symptoms of adrenal insufficiency questionnaire. Where 17-OHP and A4 show inconsistent trends, the A4 parameter will take precedence in directing dose adjustment. The subject will be notified whether a dose adjustment is needed or not by telephone within two weeks of the visit and this will be followed up in writing.

[10] Blood sample taken for PRA after the subject has been supine for 30 minutes.

[11] To be conducted at baseline only for subjects entering from study DIUR-003 and then annually in all subjects (except in Germany) (note: subjects with a gap between completing study DIUR-005 and starting study DIUR-006 do not require an additional DEXA scan at the time they enter study DIUR-006).

[12] AEs and SAEs will be recorded from the time of informed consent in this study until 30 days after the last dose of Chronocort® or until the subject starts receiving Chronocort® in the second long-term extension study (DIUR-015) if this is less than 30 days after the end of dosing in this DIUR-006 study. Any AEs or SAEs experienced after this 30-day period should only be reported if the Investigator suspects a causal relationship to Chronocort® and treatment with Chronocort® has stopped.

[13] Only in subjects from study DIUR-003 and any subjects from DIUR-005 who had a gap between completing study DIUR-005 and starting study DIUR-006 during which they received standard glucocorticoid therapy.

[14] Females presenting with oligomenorrhoea or amenorrhoea who are aged ≤55 years of age should be considered potentially fertile and should therefore undergo pregnancy testing like all other female subjects.

[15] A blood sample for genotyping will be obtained, if necessary, from subjects entering from study DIUR-003, but if previous genotyping has been performed the patient will be asked for their permission for this information to be taken from their medical records and recorded in the eCRF and recorded in the eCRF.

[16] 3-monthly drug supplies can be issued at this visit if necessary, or the site can issue 6 months' supply at the 6-monthly site visits.

[17] Baseline and Week 4 visits are repeated for subjects who re-enter the study post-pregnancy (see Section 11.7 for details).

[18] If the end of study visit is within 3 months after a scheduled 6-monthly visit then only minimal safety assessments (AE and SAE collection only) will be performed.

[19] At the end of the study subjects will have the option to enter a second long-term study (DIUR-015). Subjects who decide to enter the DIUR-015 study immediately following this DIUR-006 study do not require this telephone call. If there is a gap between finishing this DIUR-006 study and entering the DIUR-015 study of greater than 30 days, then this 30-day telephone call is required.

11.1 Visit Schedule

A window of +/- 3 days is allowed around each visit up to and including the Week 18 visit. After Week 18, a visit window of +/- 2 weeks is allowed around each visit. If a visit is delayed e.g. due to sick day rules, the visit schedule will continue as scheduled i.e. the original timings will not be adjusted based on the delayed visit date.

If a participant has received the COVID-19 vaccine then the next visit must be scheduled at least 5 days post-vaccine.

11.1.1 Screening Visit (Visit 0)

- At least 24 hours prior to the screening visit subjects must be given the informed consent document to review (this can be sent to subjects by email). At this screening visit any questions they have about the study will be answered and the subject will then be asked to sign the consent form.
- All inclusion and exclusion criteria will be checked.
- For subjects entering from study DIUR-003 and any subjects from DIUR-005 who had a gap between completing study DIUR-005 and starting study DIUR-006 during which they received standard glucocorticoid therapy, safety blood tests and a urine pregnancy test will be done to confirm eligibility criteria. A blood sample for genotyping will also be obtained, if necessary, from subjects entering from study DIUR-003, but if previous genotyping has been performed the patient will be asked for their permission for this information to be taken from their medical records and recorded in the eCRF.

The subject will then be asked to attend Visit 1 in a maximum of 2 weeks' time (for subjects in study DIUR-005 who are entering immediately into this extension study this can be Day 2 of Visit 4 of the DIUR-005 study). During the time between the screening visit and Visit 1, the subject will continue to take the medication they are currently receiving i.e. standard treatment for subjects in study DIUR-003 and for those subjects in DIUR-005 who have had a gap between completing study DIUR-005 and entering this extension study, and study medication for subjects in study DIUR-005 who are entering study the extension study immediately.

11.1.2 Baseline Visit (Visit 1) – Day 0

If the subject has been receiving their normal glucocorticoid medication for the previous 5 days (i.e. sick days rules have not been applied in the preceding 5 days) they will attend the clinic on the morning of Visit 1 (this will also be Visit 4 of the DIUR-005 study for subjects who are entering study the extension study immediately, so some test results will be included in both studies). If sick day rules have been applied in the previous 5 days then this visit should be postponed until the subject has been receiving their normal medication for 5 days. Subjects from study DIUR-003 and subjects in DIUR-005 who have had a gap between completing study DIUR-005 and entering this extension study must attend this visit after fasting from 21:00 hours the previous evening. Subjects entering immediately from study DIUR-005 will be admitted for Visit 4 of the DIUR-005 study and so will be fasting overnight as part of this Visit 4.

The following assessments will be conducted at this visit:

- Check of inclusion/exclusion criteria.

- Demographic data, medical history and any current medical conditions will be recorded in the eCRF. For subjects from study DIUR-005 only, demography and medical history can be obtained from the start of the DIUR-005 feeder study, with any changes that occurred during or after the feeder study and prior to entry into this DIUR-006 study being noted.

For subjects entering immediately from study DIUR-005, the following test results can be obtained from the data collected at Visit 4. However, if these are not available or the subject enters from study DIUR-003 or has a gap between completing study DIUR-005 and starting study DIUR-006 during which they received standard glucocorticoid therapy, the following assessments must be completed:

- Previous medications taken within the last 4 weeks and any current concomitant medications will be recorded. CAH medication will be recorded separately from other concomitant medications.
- Record the last glucocorticoid dose taken prior to attending for this visit, with details of the drug(s), dose and time of administration being recorded in the eCRF.
- A physical examination will be conducted and weight, BMI, and waist circumference recorded.
- Vital signs (blood pressure, heart rate, respiratory rate and body temperature) will be recorded.
- Blood samples will be taken for PRA after the subject has been supine for 30 minutes.
- Blood samples taken for serum CTX, osteocalcin, hsCRP, HbA1c, testosterone, fasting insulin and glucose, and safety laboratory tests.
- Blood sample taken for 17-OHP and A4 at 09:00 and 13:00 hours.
- Urine sample will be taken for a urine pregnancy test in females of childbearing potential (note: females presenting with oligomenorrhoea or amenorrhoea who are aged ≤55 years of age should be considered potentially fertile and should therefore undergo pregnancy testing like all other female subjects).
- DEXA scan to be taken at baseline for subjects entering from study DIUR-003 (except in Germany) (note: subjects with a gap between completing study DIUR-005 and starting study DIUR-006 do not require an additional DEXA scan at the time they enter study DIUR-006).
- Completion of the following questionnaires: MAF, SF-36® and EQ-5D™
- Chronocort® supplies issued, with the starting dose for subjects currently on Chronocort® in study DIUR-005 being based on the dose being taken at the end of the feeder study. For subjects from study DIUR-003 and for subjects receiving standard therapy in study DIUR-005, the Chronocort® starting dose will be based on the hydrocortisone dose equivalent, with the hydrocortisone dose calculated as prednisone and prednisolone dose multiplied by 5 and dexamethasone dose multiplied by 80 (up to a maximum starting dose of Chronocort® 30mg, split as 20mg at night and 10mg in the morning).

Once all the above assessments have been completed, the subject will be allowed home.

11.1.3 Week 4 (Visit 2) (± 3 Days)

If the subject has been receiving their Chronocort® medication for the previous 5 days (i.e. sick days rules have not been applied in the preceding 5 days) they will attend the clinic on the morning of Visit 2. If sick day rules have been applied in the previous 5 days then Visit 2 should be postponed until the subject has been receiving their normal medication for 5 days.

The subject will be asked to return all packs of study medication, including any unused medication, and the number of capsules used and unused will be counted and recorded in the eCRF so compliance can be calculated. The safety pack should also be returned and checked, with any rescue medication use being recorded. Subjects will then be dispensed with new study medication for the next treatment period. If the safety pack has been used then the medication used will be recorded for drug accountability purposes, replaced, and the pack re-sealed and prescribed to the subject for the next study period.

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

- Subjects will be asked about any AEs and concomitant medications changes since the last visit.
- Signs and symptoms of adrenal insufficiency (see checklist in Appendix 4) and any occurrences of adrenal crises or implementation of sick day rules.
- Record the time and dose of the last Chronocort® dose taken prior to attending this visit (this should be the 07:00 hours dose on the morning of this visit).
- Blood samples will be taken at 09:00 and 13:00 hours for testing of 17-OHP and A4 level.
- Urine sample will be taken for a urine pregnancy test in females of childbearing potential (note: females presenting with oligomenorrhoea or amenorrhoea who are aged ≤55 years of age should be considered potentially fertile and should therefore undergo pregnancy testing like all other female subjects).

Once all the above assessments have been completed, the subject will be allowed home. Subjects will be asked to attend the clinic in 8 weeks' time.

11.1.4 Telephone call (within 2 weeks of Visit 2)

Following the assessment of the 17-OHP and A4 levels and the clinical evaluation using the adrenal insufficiency checklist conducted at the previous visit, a decision will be made by the investigator whether to adjust the dose for the subject. This assessment must be made within 2 weeks of the visit. All subjects will be contacted by telephone, whether or not a dose adjustment is needed. The subject will receive clear written instructions of the dose they will be taking until the next study visit (even if there is no adjustment to be made) following the telephone call. Subjects will be asked about any AEs at this call and any AEs reported will be recorded in the eCRF.

If a dose titration is needed, an interim dose titration visit or telephone call (at the investigator's discretion) will be required to take place approximately 4 weeks after the decision has been communicated to the participant. The same assessments as noted for the Week 4 visit will be performed at the interim dose titration visit. If an interim dose titration telephone call is used instead, blood sampling for 17-OHP and A4 and the urine pregnancy test will not be performed but all other Week 4 assessments will be performed.

11.1.5 Week 12 (Visit 3) (± 3 Days)

If the subject has been receiving their Chronocort® medication for the previous 5 days (i.e. sick days rules have not been applied in the preceding 5 days) they will attend the clinic on the morning of Visit 3. If sick day rules have been applied in the previous 5 days then Visit 3 should be postponed until the subject has been receiving their normal medication for 5 days.

The subject will be asked to return all packs of study medication, including any unused medication, and the number of capsules used and unused will be counted and recorded in the eCRF so compliance can be calculated. The safety pack should also be returned and checked, with any rescue medication use being recorded. Subjects will then be dispensed with new study medication for the next treatment period. If the safety pack has been used then the medication used will be recorded for drug accountability purposes, replaced, and the pack re-sealed and prescribed to the subject for the next study period.

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

- Subjects will be asked about any AEs and concomitant medications changes since the last visit.
- Signs and symptoms of adrenal insufficiency (see checklist in Appendix 4) and any occurrences of adrenal crises or implementation of sick day rules.
- Record the time and dose of the last Chronocort® dose taken prior to attending this visit (this should be the 07:00 hours dose on the morning of this visit).
- Blood samples will be taken at 09:00 and 13:00 hours for testing of 17-OHP and A4 level.
- Urine sample will be taken for a urine pregnancy test in females of childbearing potential (note: females presenting with oligomenorrhoea or amenorrhoea who are aged ≤55 years of age should be considered potentially fertile and should therefore undergo pregnancy testing like all other female subjects).

Once all the above assessments have been completed, the subject will be allowed home. Subjects will be asked to attend the clinic in 12 weeks' time.

11.1.6 Telephone call (within 2 weeks of Visit 3)

Following the assessment of the 17-OHP and A4 levels and the clinical evaluation using the adrenal insufficiency checklist conducted at the previous visit, a decision will be made by the investigator whether to adjust the dose for the subject. This assessment must be made within 2 weeks of the visit. All subjects will be contacted by telephone, whether or not a dose adjustment is needed. The subject will receive clear written instructions of the dose they will be taking until the next study visit (even if there is no adjustment to be made) following the telephone call. Subjects will be asked about any AEs at this call and any AEs reported will be recorded in the eCRF.

If a dose titration is needed, an interim dose titration visit or telephone call (at the investigator's discretion) will be required to take place approximately 4 weeks after the decision has been communicated to the participant. The same assessments as noted for the Week 4 visit will be performed at the interim dose titration visit. If an interim dose titration telephone call is used instead, blood sampling for 17-OHP and A4 and the urine pregnancy test will not be performed but all other Week 4 assessments will be performed.

11.1.7 Week 24 and then every 6-months (± 2 Weeks)

Subjects will have a visit at 24 weeks and then every 6 months afterwards until the final visit or early withdrawal from the study, as long as their Chronocort® dose remains stable. Interim welfare telephone calls and supply of medication (if necessary) will be conducted on a 3-monthly basis (see Section 11.1.8). At Week 24 and then at each 6-monthly visit, the assessments listed below will be conducted. However, if the investigator thinks that the Chronocort® dose needs to be changed at any point after the Week 24 visit, then the subject should undergo an interim dose titration visit or telephone call approximately 4 weeks after the dose has been changed to check on the well-being of the subject. The same assessments as noted for the Week 4 visit will be performed at the interim dose titration visit. If an interim dose titration telephone call is used instead, blood sampling for 17-OHP and A4 and the urine pregnancy test will not be performed but all other Week 4 assessments will be performed.

The subject should then continue with the 6-monthly visit schedule as determined before this visit (i.e. the original timings will be maintained with this extra interim dose itration visit or telephone call added in between).

If the subject has been receiving their Chronocort® medication for the previous 5 days (i.e. sick days rules have not been applied in the preceding 5 days) they will attend the clinic on the morning of the visit. If sick day rules have been applied in the previous 5 days then the visit should be postponed until the subject has been receiving their normal medication for 5 days. Subjects must attend this visit after fasting from 21:00 hours the previous evening.

At each visit, the subject will be asked to return all packs of study medication, including any unused medication, and the number of capsules used and unused will be counted and recorded in the eCRF so compliance can be calculated. The safety pack should also be returned and checked, with any rescue medication use being recorded. Subjects will then be dispensed with new study medication for the next treatment period. If the safety pack has been used then the medication used will be recorded for drug accountability purposes, replaced, and the pack re-sealed and prescribed to the subject for the next study period.

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

- Subjects will be asked about any AEs and concomitant medications changes since the last visit.
- Signs and symptoms of adrenal insufficiency (see checklist in Appendix 4) and any occurrences of adrenal crises or implementation of sick day rules.
- Urine sample will be taken for a urine pregnancy test in females of childbearing potential (note: females presenting with oligomenorrhoea or amenorrhoea who are aged ≤55 years of age should be considered potentially fertile and should therefore undergo pregnancy testing like all other female subjects).
- A physical examination will be conducted and weight, BMI, and waist circumference recorded.
- Vital signs (blood pressure, heart rate, respiratory rate and body temperature) will be recorded.
- Record the time and dose of the last dose of Chronocort® taken prior to attending for this visit.
- Blood samples taken for serum CTX, osteocalcin, hsCRP, HbA1c, testosterone, fasting

insulin and glucose, and safety laboratory tests.
- Blood sample taken for PRA after the subject has been supine for 30 minutes.
- Blood samples will be taken at 09:00 and 13:00 hours for testing of 17-OHP and A4 level.
- DEXA scan conducted annually (except in Germany).
- Completion of the following questionnaires: MAF, SF-36® and EQ-5D™.

Once all the above assessments have been completed, the subject will be allowed home.

11.1.8 Telephone call (within 2 weeks of previous visit)

Following the assessment of the 17-OHP and A4 levels and the clinical evaluation using the adrenal insufficiency checklist conducted at the previous visit, a decision will be made by the investigator whether to adjust the dose for the subject. This assessment must be made within 2 weeks of the visit. All subjects will be contacted by telephone, whether or not a dose adjustment is needed. The subject will receive clear written instructions of the dose they will be taking until the next study visit (even if there is no adjustment to be made) following the telephone call. Subjects will be asked about any AEs at this call and any AEs reported will be recorded in the eCRF.

If a dose titration is needed, an interim dose titration visit or telephone call (at the investigator's discretion) will be required to take place approximately 4 weeks after the decision has been communicated to the participant. The same assessments as noted for the Week 4 visit will be performed at the interim dose titration visit. If an interim dose titration telephone call is used instead, blood sampling for 17-OHP and A4 and the urine pregnancy test will not be performed but all other Week 4 assessments will be performed.

11.1.9 Week 18 (± 3 Days) and then 3-monthly between the 6-monthly visits (± 2 Weeks)

In between the 6-monthly visits, telephone calls only (i.e. not a formal study visit) will be made at approximately 3 months to check on the welfare of the subjects. Any Aes spontaneously reported by the subjects at these calls will be recorded in the eCRF. Subjects may either return to the site pharmacy every 3 months between the 6-monthly site visits to collect new supplies of Chronocort® or the site may issue 6 month's supply of Chronocort® at each 6-monthly site visit. Subjects will be asked to return all packs of study medication, including any unused medication, at these visits for drug accountability purposes. The safety pack should also be returned and checked, with any rescue medication use being recorded. Subjects will then be dispensed with new study medication for the next treatment period. If the safety pack has been used then the medication used will be recorded for drug accountability purposes, replaced, and the pack re-sealed and prescribed to the subject for the next study period.

11.1.10 Final visit or early withdrawal visit

If the subject has been receiving their Chronocort® medication for the previous 5 days (i.e. sick days rules have not been applied in the preceding 5 days) they will attend the clinic on the morning of the visit. If sick day rules have been applied in the previous 5 days then the visit should be postponed until the subject has been receiving their normal medication for 5 days. Subjects must attend this visit after fasting from 21:00 hours the previous evening.

If the end of study visit is within 3 months after a scheduled 6-monthly visit then only minimal safety assessments (AE and SAE collection only) will be performed.

The subject will be asked to return all packs of study medication, including any unused medication, and the number of capsules used and unused will be counted and recorded in the eCRF so compliance can be calculated. The safety pack should also be returned and checked, with any rescue medication use being recorded.

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

- Subjects will be asked about any AEs and concomitant medications changes since the last visit.
- Signs and symptoms of adrenal insufficiency (see checklist in Appendix 4) and any occurrences of adrenal crises or implementation of sick day rules.
- Urine sample will be taken for a urine pregnancy test in females of childbearing potential (note: females presenting with oligomenorrhoea or amenorrhoea who are aged ≤55 years of age should be considered potentially fertile and should therefore undergo pregnancy testing like all other female subjects).
- A physical examination will be conducted and weight, BMI, and waist circumference recorded.
- Vital signs (blood pressure, heart rate, respiratory rate and body temperature) will be recorded.
- Record the time and dose of the last dose of Chronocort® taken prior to attending for this visit.
- Blood samples taken for serum CTX, osteocalcin, hsCRP, HbA1c, testosterone, fasting insulin and glucose, and safety laboratory tests.
- Blood sample taken for PRA after the subject has been supine for 30 minutes.
- Blood samples will be taken at 09:00 and 13:00 hours for testing of 17-OHP and A4 level.
- Completion of the following questionnaires: MAF, SF-36® and EQ-5D™

Once all the above assessments have been completed, the subject will be discharged. If the subject discontinues from the study early then as many of the above assessments as possible should be completed. The investigator must ensure that continuing therapy for CAH is given according to best practice using either commercially available Chronocort® (assuming a successful licensing application) or standard therapy.

11.1.11 Telephone call (30 days after the final visit)

At the end of the study subjects will have the option to enter a second long-term study (DIUR-015) to enable them to continue to receive open-label Chronocort® until it is commercially available in their region or it is decided to stop Chronocort® treatment. Subjects who decide to enter the DIUR-015 study immediately following this DIUR-006 study do not require a telephone call 30 days after the end of this study. If there is a gap between finishing this DIUR-006 study and entering the DIUR-015 study of greater than 30 days, then the 30-day telephone call is required.

If this call is required, subjects will be asked about any AEs at this call and any AEs reported will be recorded in the eCRF. Any AEs experienced after this 30-day period should only be reported if the Investigator suspects a causal relationship to Chronocort® and treatment with Chronocort® has stopped. Any ongoing AEs at this point will be followed to resolution or stabilisation if resolution is not expected.

11.1.12 Unscheduled Visits or telephone calls

If any unscheduled visits are 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 (note that the local laboratory normal reference ranges will then be needed). Additional telephone calls may also be required in between visits to maintain contact with the subject and to ensure AEs and use of any sick day rules are being noted. Any information collected in such calls must be recorded in the eCRF.

11.2 Study Assessments

- **Vital signs**
  - Blood pressure, heart rate, respiratory rate and body temperature will be measured according to normal clinical practice at the investigational sites and the results recorded in the eCRF.

- **Blood samples**
  Will be taken by suitably qualified study personnel for:
  - routine safety laboratory tests (see Appendix 1).
  - measurement of serum CTX, osteocalcin, hsCRP, HbA1c, testosterone, fasting insulin and glucose. The fasting samples should be taken as soon as possible after the subject arrives for the visit before any food is consumed.
  - measurement of PRA after the subject has been supine for 30 minutes
  - blood samples will be taken at 09:00 and 13:00 hours for testing of 17-OHP and A4 levels.
  - A blood sample for genotyping will be obtained, if necessary, from subjects entering from study DIUR-003, but if previous genotyping has been performed the patient will be asked for their permission for this information to be taken from their medical records and recorded in the eCRF.

To minimise the risk of anaemia associated with the withdrawal of multiple blood samples for laboratory testing, the planned blood volume to be drawn at each visit will be limited to a maximum of 49 mL. The date and time of collection of all blood samples will be recorded in the subject's eCRF. Copies of laboratory accreditation certificates and reference ranges will be provided prior to the analysis of the first subject sample.

All laboratory analyses will be carried out by the central laboratory [redacted]. If laboratory results are needed urgently for safety reasons during the study, these can be processed at the local laboratory but the results must be recorded in the eCRF.

- **Urinalysis**

  A pregnancy test in females of childbearing potential will be done locally at the site using a dipstick test (note: females presenting with oligomenorrhoea or amenorrhoea who are aged ≤55 years of age should be considered potentially fertile and should therefore undergo pregnancy testing like all other female subjects).

- **DEXA scans (except Germany)**
  To be performed at baseline for subjects entering from study DIUR-003 and then annually for all subjects (except in Germany) (note: subjects with a gap between completing study DIUR-005 and starting study DIUR-006 do not require an additional DEXA scan at the time they enter study DIUR-006). The DEXA scans will be performed according to the site's standard clinical procedures.

- **Quality of life questionnaires (QoL)**
  QOL questionnaires (MAF, SF-36® and EQ-5D™) will be administered and completed in a quiet environment.

- **Waist circumference, height and weight**
  Waist circumference, height and weight will be measured according to each site's normal clinical practice and the result recorded in the eCRF. The subject's BMI will be calculated automatically.

- **Physical examination**
  A full physical examination to assess the subject's general appearance and overall health will be carried out at the baseline visit, every 6 months throughout the study, and at the last visit in the study. Significant findings that are present **prior to** the start of study drug must be included in the relevant medical history/current medical status section of the eCRF and significant findings made **after** the start of study drug which meet the definition of an AE must be recorded as AEs in the eCRF.

11.3 Sick Day Rules

All subjects will be educated regarding "sick day rules". "Sick day rules," a written guideline regarding what to do during any illness, will be given to the subjects (as is done for all CAH subjects). Where sites have a standard set of "sick day rules" these will be supplied to subjects at that site routinely along with an emergency pack of medication (see Appendix 3 for an example of sick day rules that can be used for this study if a site choses to do so). Use of sick day rules will be recorded in eCRF, including both duration, dose of steroid and use of injection. Sick day rules from each site will be collected prior to the beginning of recruitment and placed on file by the Sponsor.

11.4 Early Withdrawal from Treatment

If a subject withdraws or is withdrawn prior to the last scheduled visit, all efforts should be made to perform the end of study assessments. Additional follow-up by telephone may be required to obtain information regarding follow-up of AEs (both non-serious and serious) ongoing at the time of study discontinuation.

The date the subject withdraws/is withdrawn from the study and the reason(s) for discontinuation will be recorded on the subject's eCRF.

11.5 Criteria for Withdrawal of Study Treatment

Subjects may withdraw from the study at any time without stating a reason and without prejudice to further treatment. The investigator may withdraw a subject from the study and discontinue study treatment and assessments at any time. Events that will result in discontinuation of treatment include:

1. Inability to tolerate Chronocort® secondary to perceived or observed side effects.
2. Pregnancy (not due to safety reasons but because pregnancy may interfere with the study endpoints) – see Section 11.7 Pregnancy for further details on withdrawal due to pregnancy.
3. Any other changes to clinical signs or changes in laboratory values, physical status or AEs that could compromise the subject's status if they were to continue with the study or if the investigator feels that it is not in the best interests of the subject.

The Sponsor reserves the right to request the withdrawal of a subject due to protocol violations, administrative or other reasons, or in the event of emergence of adverse risk data on the product.

If a subject withdraws from the study prior to study completion, the reason for withdrawal should be sought and recorded on the eCRF. AEs should be followed up until resolution.

11.6 Replacement of Withdrawn Subjects

There will be no replacement of withdrawn subjects.

11.7 Pregnancy

Female subjects who are pregnant or lactating will not be allowed to enter the study. However, no specific contraception requirements are required by the protocol during the study since this is a long-term study and subjects all need to be on continuous hydrocortisone treatment for their underlying condition, and therefore the risks of pregnancy whilst receiving Chronocort® are perceived to be no greater than the risks of pregnancy on standard hydrocortisone treatment. If Chronocort® leads to improved hormonal control, this may be more likely to confer an advantage in subjects who want to become pregnant. If a subject is sexually active, the investigator will provide counselling on contraception and pregnancy, where appropriate, on an individual basis. Urine pregnancy tests will be conducted at each visit to monitor for pregnancy cases.

Since hydrocortisone is a well-established product, no pre-clinical reproductive toxiciology studies have been conducted or are planned with Chronocort®. However, information from the Summary of Product Characteristics (SmPC) of hydrocortisone should be noted (http://www.medicines.org.uk/emc/medicine/27652).

If a subject becomes pregnant during the study they should be withdrawn – not due to safety reasons but because pregnancy may interfere with the study endpoints. However, subjects who withdraw from the study due to pregnancy can re-enter the study, if they choose to do so, at least 6 weeks 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). Subjects who chose to re-enter the study will retain the same subject number.

As soon as the pregnancy is confirmed, the Investigator will conduct as many of the evaluations included in the early withdrawal visit as possible (Section 11.1.10) and the subject 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 subject from Chronocort onto standard of care therapy in line with the "DIUR-006 Participant Pregnancy: Advice to Investigators" document circulated to all Investigators in January 2020. AEs will be collected for 30 days after the early withdrawal visit and a follow-up telephone call will be conducted at 30 days, as detailed in Section 11.1.11. No other data will be collected while the subject is off study due to the pregnancy unless the Investigator considers any AEs are related to Chronocort 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 [redacted]

If the subject decides to re-enter the study after the pregnancy, 2 post-pregnancy visits must be conducted:

- Post-pregnancy baseline visit, comprising the following:
  - Re-consent for re-entry into the study.
  - Review of the inclusion/exclusion criteria to ensure the subject is still eligible for the study.
  - The tests detailed for the basline visit will be conducted (Section 11.1.2) to establish a new second post-pregnancy baseline (note: the androgen results will reflect the standard of care treatment only so the results will not be used to inform dose titration decisions)
  - The Chronocort dose used after re-entry should be determined using the hydrocortisone equivalent of the subject's standard of care dose at the end of the pregnancy/breast-feeding period. The first dose of Chronocort after re-entry should be taken in the evening of the first dosing day.
- Post-pregnancy Week 4 Visit (Section 11.1.3) and subsequent telephone call (Section 11.1.4)

On completion of the Post-pregnancy Week 4 Visit, subjects will attend their following study visits based on the schedule determined by their original baseline date (i.e. not using the new post-pregnancy baseline date).

Further details on data collection during pregnancy are provided in Section 12.12.

11.8 Study Duration and Completion of the Study

The length of the study will be 5.5 years from the date of the first subject entering the study, so subjects will be treated for a maximum of 5.5 years. The end of the study will be the final telephone call (30 days after the last visit) of the last subject or the date the last subject enters the DIUR-015 extension study, which ever is the latest. All subjects must be enrolled by 31 October 2018, with no subjects allowed to enter the study after this date.

11.9 Overdose

In the event of an overdose, the subject should immediately contact the Investigator or Study Nurse for advice. There is no antidote available for Chronocort®.

11.10 Subject Diaries

Subjects will be provided with an ad hoc diary in which they will be asked to record any use of sick day medications and to record any AEs that occur between study visits.

11.11 COVID-19 Procedures

Appropriate measures have been put in place to enable the study to continue during the COVID-19 restrictions. Therefore, if necessary, visits can be performed remotely (via telephone or video call) and IMP shipments can be made directly to the subject's home. Safety and endocrine blood sampling can also be performed locally if required (which could include nurses/phlebotomists performing home visits or subjects attending local doctor/general practitioner's office, local endocrinologist's office and local patient centres or clinics) for scheduled 6-monthly visits and dose titrations, to maintain patient safety and consideration of local environmental factors. If local laboratories are used, then normal ranges and certification of the local laboratories will be required. However, prior to implementation of any of these measures Sponsor approval must be obtained.

12 Adverse Events and Toxicity Management

12.1 Adverse Event Definition

An AE is defined as (21CFR312.32): "Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related." An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. This includes any newly occurring event or previous condition that has increased in severity or frequency since the administration of study drug.

12.2 Adverse Event Collection

AEs will be collected for all subjects from the time of consent up to 30 days after the last visit or the early withdrawal visit. Any AEs experienced after this 30-day period should only be reported if the Investigator suspects a causal relationship to Chronocort®. Any ongoing AEs at this point will be followed to resolution or stabilisation if resolution is not expected. Only treatment emergent AEs (i.e. those that started or worsened during Chronocort® treatment in this study) will be included in the main safety analysis: other AEs will be listed.

Details of any AEs, signs, and symptoms will be collected, including details of onset, resolution, frequency, severity, seriousness, relationship to the drug, effect on the study drug, treatments administered, and outcome. All AEs will be followed, whenever possible, until they return to the baseline conditions or become stable with no further changes expected. In the event of any abnormalities considered to be clinically significant by the investigating physician, subjects will be followed up with appropriate medical management until values are considered to be clinically acceptable. Referral or collaborative care will be organised if required.

12.3 Reporting of Adverse Events

Individual AEs should be evaluated by the investigator and recorded in the eCRF. AEs must be reported regardless of whether the investigator thinks the AEs are related to the study treatment.

12.3.1 Diagnoses vs. signs/symptoms

Each AE should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values if not constituting AEs themselves) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded as the AE(s).

12.3.2 Laboratory values

Changes in laboratory values may be considered AEs if they are judged to be clinically significant (i.e., if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiological fluctuation). If abnormal laboratory values are the result of pathology for which there is an overall diagnosis (e.g., increased creatinine in renal failure), the diagnosis only should be reported as an AE.

12.3.3 Pre-existing conditions

Pre-existing conditions (present before the start of the AE collection period) are considered concurrent medical conditions and should NOT be recorded as AEs. However, if the subject experiences a worsening or complication of such a concurrent condition, the worsening or complication should be recorded as an AE. Investigators should ensure that the AE term recorded captures the change in the condition (e.g., "worsening of….").

12.3.4 Pre-planned surgeries or procedures

Pre-planned procedures (surgeries or therapies) that were scheduled prior to the start of AE event collection are not considered AEs. However, if a pre-planned procedure is performed early (e.g., as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be captured as an AE.

12.3.5 Insufficient clinical response (lack of efficacy)

Insufficient clinical response, efficacy, or pharmacological action, should NOT be recorded as an AE. The investigator must make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy.

12.3.6 Overdose

Cases of drug overdose without manifested side effects are NOT considered AEs.

12.4 Assessment of Adverse Event Severity

The following guidelines for rating severity of AEs should be used:

Mild:
Awareness of signs or symptoms, but easily tolerated; are of minor irritant type; no loss of time from normal activities; symptoms would not require medication or a medical evaluation; signs and symptoms may be transient, disappearing during continued treatment with study medication.

Moderate:
Discomfort enough to cause interference with usual activities; the study medication may have been interrupted.

Severe:
Incapacitating with inability to do work or do usual activities; signs and symptoms may be of systemic nature or require medical evaluation; the study drug may have been stopped, and treatment for the event may be required.

The term "severe" is often used to describe the intensity of a specific event, as in mild, moderate, or severe myocardial infarction; the event itself, however, may be of relatively minor medical significance, such as severe headache. This is not the same as serious, which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning.

12.5 Assessment of Adverse Event Causality/Relatedness

All AEs will be assigned one of the following assessments of causality:

- Not related
- Related to Chronocort®
- Related to sick day medication
- Related to an interaction between Chronocort® and sick day medication
- Related to either Chronocort® or sick day medication
- Related to study medication from previous Chronocort® study

All AEs judged by either the investigator or the sponsor as having a reasonable suspected causal relationship to Chronocort®, or are due to an interaction with Chronocort®, qualify as adverse drug reactions (ADRs).

Appendix 2 provides a comprehensive list of events that are anticipated to occur in the targeted study entry population of subjects with CAH undergoing hydrocortisone replacement therapy. During the course of the trial, if aggregate analyses indicate that the events are occurring more frequently than anticipated, the sponsor will notify Regulatory Authorities expeditiously as appropriate.

12.6 Assessment of Adverse Event Expectedness

An AE is considered "unexpected" if it is not listed in the Reference Safety Information (RSI) in the Investigator's Brochure or is not listed at the specificity or severity that has been observed.

The concept of expectedness does not refer to what may occur in the course of the treated disease such as in the case of disease progression and/or lack of drug effect.

12.7 Serious Adverse Event Definitions

An AE is considered ''serious'' if, in the view of either the investigator or sponsor, it results in any of the following outcomes (21CFR312.32):

- Death.
- Is life-threatening. Life-threatening, in the definition of serious, refers to an event in which the subject 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.
- Requires inpatient hospitalisation or prolongation of existing hospitalisation.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered serious when, based upon appropriate medical judgment, they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

12.8 Suspected Unexpected Serious Adverse Reaction

The definition of Suspected Unexpected Serious Adverse Reaction (SUSAR) includes a suspected causal relationship with administration of the test preparation (thus, a causality assessment of unrelated is not a SUSAR).

12.9 Serious Adverse Event Reporting

As with all AEs, the investigator is responsible for the collection of SAE data. All SAEs should be recorded on the SAE form and the eCRF. Any SAE that occurs between informed consent being signed and 30 days after the last dose of the study treatments (or until the first dose of Chronocort® in the second extension study DIUR-015 for subjects who do not need the 30-day telephone call) must be reported promptly to the sponsor or designee not later than 24 hours after the study site becomes aware of its occurrence, using the SAE form provided. Any SAEs experienced after the 30-day reporting period should only be reported if the Investigator suspects a causal relationship to Chronocort® and treatment with Chronocort® has stopped. All SAEs should be monitored until they are resolved or stabilised.

The initial report shall be promptly followed by detailed, written reports using the SAE report form provided. The initial and follow-up reports shall identify the trial subjects by unique code numbers assigned to the subject. The investigator shall supply the sponsor and the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) with any additional requested information.

The report must be made by telephone, facsimile, or email to the following contacts at the following numbers:

SAEs must be notified immediately (and within 24 hours) by telephone or email to the sponsor's responsible Medical Monitor, [redacted]. This should be done even if the required information is incomplete or if the investigator is awaiting laboratory or diagnostic reports. This should be followed by a written report within 3 working days.

The SAE form requires the following information (at a minimum):

- Subject ID (case number, gender, date of birth, initials [unless date of birth and initials are not allowed to be collected according to local law])
- Trial no.
- Study therapy (dose, route, form regime, start date, end date)
- Concomitant medication (including dose, route, form, regime, start date where available)
- Nature of SAE (overall diagnosis where available or alternatively signs and symptoms)
- Severity of SAE
- Date and time of occurrence
- Any associated factors (concomitant disease or medication)
- Proposed relationship to study therapy
- Outcome
- Identification of the reporter
- Action in relation to study (withdrawn, suspended, none).

Investigators may be asked for additional information for any report of an SAE. An SAE form indicated as a follow-up report with attached documents (if necessary) should be forwarded to the sponsor/designee as soon as the additional information is available. The sponsor will submit to the Regulatory Authority(ies) all safety updates and periodic reports, as required by applicable regulatory requirement(s).

Some of the AEs likely to occur in subjects with CAH, are of special interest, and whilst they may not be defined as SAEs, they will be reported in the same manner in order to capture the data in real time, together with additional data, if this should be required. However these events will not be reported to the Regulatory Authorities unless they are defined as SAEs. These events will include, but not be limited to, Addisonian crisis and events causing implementation of 'sick day rules'.

Addisonian or adrenal crisis is defined as follows (based on Allolio 2015):

- (A): Major impairment of general health with at least two of the following signs/symptoms:
  - Hypotension (systolic blood pressure <100 mmHg)
  - Nausea or vomiting
  - Severe fatigue
  - Fever
  - Somnolence
  - Hyponatraemia (<132 mmol/L) or hyperkalaemia (as judged by characteristic electrocardiogram [ECG] changes)
  - Hypoglycaemia
- (B): Parenteral glucocorticoid (hydrocortisone) administration followed by clinical improvement:
  - Grade 1: outpatient care only
  - Grade 2: hospital care (general ward)
  - Grade 3: admission to intensive care unit

Grade 4: death from adrenal crisis (with or without parenteral glucocorticoid administration)

In addition, some events may occur that represent an improvement in the subject's condition e.g. restoration of menses. These events are of special interest and should be recorded as AEs of special interest, clearly stating that the event is an improvement in the condition, and these events will be coded as 'Unexpected Therapeutic Effect'. Whilst these events are not SAEs, they should be reported in the same manner as SAEs in order to capture the data in real time, together with additional data, if this should be required. However these events will not be reported to the regulatory authorities as SAEs.

12.10 Serious Adverse Event Expedited Reporting

The sponsor or designee will expedite the reporting to the appropriate Regulatory Authority(ies) of all ADRs that are both serious and unexpected. Such expedited reports should comply with the applicable regulatory requirement(s) (i.e., 21CFR312.32).

12.10.1 Standards for Expedited Reporting

For each SAE/SUSAR, the investigator and sponsor (or designee) will independently assess whether there is a reasonable possibility that the event may have been caused by the study drug ("drug-related"). If the SAE is assessed to be both drug-related and unexpected, the sponsor or designee will report it to the appropriate Regulatory Authorities and notify investigators as required by applicable local regulations. The sponsor or designee will report SAEs to the US FDA as required by 21 CFR 312.32, and EU Competent Authorities as per EU requirements.

SUSARs are required to be reported within 7 calendar days for life threatening events and those resulting in death, or 15 calendar days for all others. These timeframes begin with the first notification of the SUSAR to the sponsor/designee.

All events qualifying as SAEs and SUSARs will be reported by the Pharmacovigilance (PV) Contract Research Organisation (CRO), as necessary, to Regulatory Authorities and IEC/IRB (the latter may be through the local investigator, as required by local regulations). The PV CRO for this study is Bionical-Emas up to the end of March 2022, then Pharmalex from April 2022 onwards.

12.10.2 Expedited Reporting Guideline for Other Observations

Other safety issues that might be considered for expedited reporting when they could materially alter the current benefit-risk assessment of the IMP (sufficient to consider changes in the administration or in the overall conduct of the trial) include, for example:

- An increase in the rate of occurrence of an expected serious ADRs, which is judged to be clinically important
- Post-study SUSARs that occur after the subject has completed a clinical trial and are reported by the investigator to the sponsor
- New event relating to the conduct of the trial or the development of the IMP likely to affect the safety of the subjects, such as a SAE which could be associated with the trial procedures and which could modify the conduct of the trial

12.11 Sponsor's Responsibilities

The sponsor is responsible for the ongoing safety evaluation of the IMP. The PV CRO is responsible for ensuring that expedited reports are made to the Regulatory Authority(ies) and all applicable investigators of all ADRs that are both serious and unexpected, of findings that could adversely affect the health of subjects, impact on the conduct of the trial or alter the competent authority's authorisation to continue the trial.

Such expedited reports should comply with the applicable regulatory requirements (e.g., 21CFR312.32). The sponsor should submit to the Regulatory Authority all safety updates and periodic reports, as required by applicable regulatory requirements.

The PV CRO is responsible for arranging structures and written standard operating procedures to ensure that the necessary quality standards are observed in every step of the case documentation, data collection, validation, evaluation, archiving and reporting. The PV CRO will assign a case number to be used in all future correspondence regarding the event and will forward the case to Diurnal Ltd within one working day.

All events qualifying as SUSARs will be reported by the PV CRO, as necessary, to Regulatory Authorities and ethics committees/IRB (the latter may be through the local investigator, as required by local regulations).

12.12 Procedures for Reporting Pregnancy Exposure and Birth Events

Should a female subject become pregnant or be suspected of being pregnant while participating in this study they must be withdrawn from the study immediately (not due to safety reasons but because pregnancy may interfere with the study endpoints) (see Section 11.7). The event must be reported to the sponsor immediately upon receipt of information by the study staff using the pregnancy form. While the pregnancy itself is not considered to be an AE or SAE, any pregnancy complications should be recorded as AEs or SAEs (if applicable). Any pregnancy will be followed through delivery for the observation of any SAEs. Fatalities and spontaneous abortions must be reported as SAEs.

12.13 Data Safety Management Board

An independent DSMB will meet on a regular basis during the study in order to review safety data. The DSMB will operate in accordance with a charter.

13 Statistical Considerations

A detailed and comprehensive statistical analysis plan (SAP) will be prepared and signed-off before the first subject has given informed consent for this extension study. Minor changes to the statistical methods set out in this protocol need not be recorded as a protocol amendment but must be documented in the SAP and in the study report.

Interim data analyses are expected to be required for regulatory review as part of any marketing authorisation applications. No changes to the overall study conduct and no changes to the planned formal statistical analyses are anticipated as a result.

The statistical analysis will be undertaken by [redacted] The statistical analysis and report will conform to the relevant ICH requirements, including but not limited to those set out in ICH documents E3 and E9. SAS version 9.2 or later will be used for the analysis.

13.1 Conventions and Methods

13.1.1 Summary Tables, Listings and Figures

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). Geometric mean and coefficient of variation will also be presented for variables which will subsequently be log-transformed during the analysis.

Summary tables and figures will be supported by full subject listings.

Data will be summarised according to time since first dose of Chronocort® treatment (which may have been in the feeder study for study DIUR-005). Time slotting will be described in the SAP.

Safety and efficacy parameters will be explored based on previous treatment in the feeder study and by previous standard therapy. Exploratory analyses will also be undertaken to assess the relationship between disease control and the proportion of daily dose given at night. Further details will be provided in the SAP.

For subjects who re-enter the study post-pregnancy, data collected during the post-pregnancy phase will be listed only. Only data up to the time of first study withdrawal will be included in summary tables and figures. Individual subject profiles will be created to support discussion of data from this small subset of subjects in the clinical study report.

Disruptions due to the COVID-19 pandemic will be summarised by feeder study and previous treatment. The summary will include an overview of study visit or study medication disruptions due to the COVID-19 pandemic, as well as including whether the scheduled visit was delayed or scheduled assessments were not done. Detailed listings of study visit disruptions and study medication disruptions will be produced.

13.1.2 Hypothesis Testing and Confidence Intervals

Since all subjects participating in this trial will be receiving Chronocort®, there will be no formal treatment comparisons. Summaries over time will be produced for safety and efficacy parameters.

13.1.3 Missing Outcome Data

Blood samples for analysis of 17-OHP and A4 values are to be taken at 09:00 and 13:00, with a window of +/- 1 hour allowed. Missing 17-OHP and A4 values (including those considered missing due to being taken outside the permitted time window) will not be imputed. In calculating the mean of the 09:00 and 13:00 SDS, if one value is missing, then only the non-missing value will be used. If both values are missing, the mean value will be missing.

13.2 Analysis Sets

The full analysis set comprises all subjects who entered the study and who subsequently

received at least one dose of Chronocort®. Subjects in the full analysis set will be analysed according to the actual treatment received.

The interim analysis set is a subset of the full analysis set. In addition to entering the study and receiving at least one dose of Chronocort®, subjects must also have completed the Week 24 (Visit 4) assessment or discontinued early from treatment and withdrawn from the study (Interim Analysis 1). For subsequent interim analyses, a data cut-off date will be defined for each interim analysis set. At the time of interim analyses, all primary, secondary and exploratory endpoints will be summarised using the interim analysis set. Subjects in the interim analysis set will be analysed according to the actual treatment received.

13.3 Endpoints

13.3.1 Primary Endpoint

The primary objective of summarising the safety of Chronocort® over time will be assessed using but not limited to the following endpoints:

1. Signs and symptoms of adrenal insufficiency or over-treatment throughout the study.
2. Use of sick day rules throughout the study.
3. Occurrence of adrenal crises throughout the study.
4. Occurrence of AEs throughout the study.
5. Change from pre-Chronocort® baseline in safety laboratory assessments at each visit throughout the study.
6. Change from pre-Chronocort® baseline in vital signs, weight, BMI, and waist circumference at each visit throughout the study.

13.3.2 Secondary Endpoints

To assess the long-term efficacy of Chronocort®, the following secondary endpoints will be assessed:

1. Total daily dose of Chronocort® in mg/day of hydrocortisone and by BSA
2. Disease control throughout the study as assessed by 17-OHP levels in the optimal range at 09:00 and again at 13:00, and by the proportion of dose given at night
3. Disease control throughout the study as assessed by A4 levels in the normal range at 09:00 and again at 13:00, and by the proportion of dose given at night
4. Change from pre-Chronocort® baseline at each visit in SDS of 17-OHP and A4 at 09:00, 13:00 and the mean of the two timepoints.
5. Change from pre-Chronocort® baseline at each visit in the absolute values of 17-OHP and A4 at 09:00 and 13:00
6. Change from pre-Chronocort® baseline at each visit in:
    a. Bone turnover markers - CTX, osteocalcin
    b. Testosterone (total) – analysed separately by males and females
    c. Fasting insulin and blood glucose levels, and HbA1c
    d. hsCRP and PRA
    e. Body composition (DEXA)(fat mass, lean mass and total bone density) (except in Germany)
    f. Quality of life – SF-36®, MAF, EQ-5D™
7. Incidence of dose titrations

13.4 Analysis of the Conduct of the Study

Data concerning the conduct of the study (subject disposition/withdrawals, compliance, study termination/duration) will be listed and summarised descriptively. Details will be described in the SAP.

13.5 Demographic and other baseline characteristics

Demographic and other baseline characteristics for all enrolled subjects will be listed and summarised.

Baseline values are defined as pre-Chronocort® values:

- for subjects entering from study DIUR-003, baseline values are defined as those taken at Visit 1 of this DIUR-006 study
- for subjects entering immediately from study DIUR-005 who received comparator treatment, baseline values are defined as those taken at the last visit in the feeder study i.e. V4 (week 24) in study DIUR-005
- for subjects entering immediately from study DIUR-005 who received Chronocort®, baseline values are defined as the pre-Chronocort® values recorded at Visit 1 in study DIUR-005
- for subjects who delayed entering study DIUR-005 and received standard glucocorticoid therapy in the gap between the DIUR-005 and DIUR-006 studies, baseline values are defined as those taken at Visit 1 of this DIUR-006 study.

13.6 Efficacy and Safety Analyses

13.6.1 Safety

Signs and symptoms of adrenal insufficiency or over-treatment will be summarised over time. A listing of all signs and symptoms of adrenal insufficiency will be produced, flagging any significant findings as well as a listing of significant findings related to under/over replacement of steroid.

AEs will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). Data will be summarised using preferred term (PT) and primary system organ class (SOC). Only treatment-emergent AEs, i.e. AEs with an onset at or after the first administration of Chronocort®in this study and up to 30 days after the end of the study or the early withdrawal visit, will be presented in summary tables. Where changes in severity are recorded in the eCRF, the most severe incidence of the AE will be reported in the tables. Frequency tables will be provided concerning severity and drug relationship.

Each site will have a set of sick day rules where certain AEs will result in emergency hydrocortisone being taken. All AEs leading to use of “sick day rules” will be summarised (frequency and percentage of subjects) by SOC and PT. Use of sick day medication will be summarised.

All AEs leading to adrenal crises will be summarised (frequency and percentage of subjects) by SOC and PT.

All AEs of unexpected therapeutic benefit will be summarised (frequency and percentage of subjects) by PT, lower level term, and treatment group. There will be a separate listing showing details of all AEs of unexpected therapeutic benefit.

Absolute and change from baseline in safety laboratory variables will be summarised over time. Shift tables from baseline to the maximum and minimum on-treatment values will be presented. The 3 x 3 cross tabulations (from low, normal and high to low, normal and high) will be presented. Values outside the normal ranges will be flagged in the subject data listings.

Changes from baseline in vital signs data, weight, BMI, and waist circumference will be summarised over time. Abnormal findings in the physical examination will be tabulated by body system showing the frequency and percentage of subjects with an abnormal finding.

13.6.2 Efficacy

The total daily dose of Chronocort® in mg/day of hydrocortisone and by BSA will be summarised over time.

Disease control will be based on whether 17-OHP levels are in the optimal range and also whether the A4 levels are in the normal range (both analysed separately). A subject will be considered a responder (i.e. disease controlled) if their 09:00 results are in the optimal range for 17-OHP and then separately if their 09:00 results for A4 are in the normal range. The number and percentage of subjects achieving results in the optimal range will be presented at each visit and by the proportion of dose given at night. This will be repeated for the 13:00 values.

DEXA scans will be performed at baseline for subjects entering from study DIUR-003 and then annually for all subjects, except in Germany. Summary statistics will be produced for the absolute values and change from pre-Chronocort® baseline for fat mass, lean mass, total bone density, T scores and Z scores at each visit. Due to the length of the study, it is possible that there will be changes in the DEXA scanners used at some sites. Therefore, the above summary tables will be repeated excluding data collected after a scanner change and an analysis of variance (ANOVA) model will be created to explore whether there is any statistically significant difference in the DEXA results before and any scanner changes.

13.6.3 SDS

The SDS is defined as the absolute (unsigned) number of standard deviations above or below the average of the lower and upper limit of normal. For each of the 17-OHP and A4 concentrations at each visit at each time point (09:00, 13:00), the natural logarithm will be taken and the SDS will be calculated by counting the number of standard deviations which are above or below the mean of the log transformed range. Further details will be provided in the SAP. The mean and standard deviation values to be used for these calculations will be pre-specified. Change from baseline at each visit in these values will be summarised over time.

In addition to presenting change from baseline SDS at 09:00 and 13:00 separately, an arithmetic mean of the SDS at the two timepoints will be calculated and summarised over time. Change from baseline at each visit in the absolute values of 17-OHP and A4 at 09:00 and 13:00 will also be summarised over time.

All other efficacy endpoints (change from baseline in bone turnover markers, testosterone, fasting insulin, blood glucose levels, HbA1c, hsCRP, PRA, DEXA, QoL questionaires) will be summarised over time.

Exposure to Chronocort® (time since first dose) and the incidence of dose titrations will be summarised.

13.7 Power and Sample Size Considerations

Since this is an open label extension study to gather long term safety and efficacy data on Chronocort®, no formal power or sample size calculations have been performed. All eligible subjects from study DIUR-003 (16 subjects) and DIUR-005 (122 subjects) may enter this study, giving a maximum of 138 subjects. Subjects from study DIUR-003 can be enrolled at any time (since this study has been completed), but subjects from study DIUR-005 will be enrolled when they complete Visit 4 of study DIUR-005. However, in some cases there may be a delay between a subject completing study DIUR-005 and starting study DIUR-006 during which the subject receives standard glucocorticoid therapy. In this case the subject should be entered into study DIUR-006 as soon as possible. All subjects must be enrolled by 31 October 2018, with no subjects allowed to enter the study after this date.

13.8 Data Review Meeting

The sponsor will convene a Data Review Meeting after the data has been cleaned and before the database is locked and the 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 may include, but will not be limited to:

- a review of missing data and of outliers
- a review of the distribution of the efficacy variables, considering any implications for the proposed method of statistical analysis
- revisions to SAP in light of any Data Review Meeting findings

13.9 Deviations from the Planned Statistical Analysis

All deviations from the planned statistical analysis will be documented in the clinical study report.

14 Responsibilities

14.1 Investigator Responsibilities

The investigator agrees to:

1. Conduct the study in accordance with the protocol and make changes only after notifying the sponsor, except to protect the safety, rights or welfare of subjects.
2. Personally conduct or supervise the study (or investigation).
3. Inform any subjects enrolled in the study that the drug is being used for investigational purposes.
4. Ensure that the requirements relating to obtaining informed consent and IEC/IRB review and approval meet EU and US Federal guidelines, as stated in 21 CFR, parts 50 and 56.
5. Report to the sponsor any AEs that occur during the course of the study, in accordance with ICH guidelines and 21 CFR 312.64 (US sites only).

6. Have read and understood the Investigator's Brochure, including potential risks and side effects of the drug.
7. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
8. Maintain adequate and accurate records (in accordance with 21 CFR 312.62 for US sites) and to make those records available for inspection with the sponsor, their designated representative, the FDA or any agency authorised by law.
9. Ensure that an IEC/IRB that complies with the requirements of ICH Good Clinical Practice (GCP) guidelines and local law (and 21 CFR 56 in the US) will be responsible for initial and continuing review and approval of the clinical study.
10. Report promptly to the IEC/IRB and the sponsor all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and IND safety reports).
11. The investigator should not implement any deviation from or changes in the protocol without agreement by the sponsor and prior review and documented approval/favourable opinion from the IEC/IRB of an amendment, except where necessary to eliminate an immediate hazard to trial subjects, or when the change involves only logistical or administrative aspects of the trial (e.g., change in monitor, change of telephone numbers etc.). The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol. If the investigator implements a deviation from the protocol to eliminate an immediate hazard without prior IEC/IRB approval/favourable opinion, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment should be submitted as soon as possible to the IRB/IEC for review and approval/favourable opinion, to the sponsor for agreement and, if required, to the regulatory authorities.
12. Comply with all other requirements regarding the obligations of the clinical investigators and all other pertinent requirements listed in in ICH GCP and 21 CFR 312 (US sites).

14.2 Ethical Conduct of the Study

The trial will be conducted in accordance with this protocol, the principles that have their origins in the Declaration of Helsinki, as well as ICH GCP and applicable regulatory requirements, including the US Code of Federal Regulations on Protection of Human Rights (21 CFR 50) for US sites. All essential documents will be archived for a minimum of 5 years after completion of the study. Note in Sweden all essential documents will be archived for a minimum of 10 years.

14.3 Ethics Committee and Institutional Review Board approval

The final study protocol and subject informed consent form will be reviewed and approved by each of the participating institution's IEC/IRB prior to the initiation of subject recruitment. Any changes to the protocol will be formally documented in protocol amendments and approved by the IEC/IRB prior to implementation, except in the case of changes made to protect subject safety, which will be implemented immediately. In addition, progress reports will be submitted to the IEC/IRB by the investigator as indicated by IRB/IEC guidelines.

Each IRB/IEC must meet the FDA/EMEA, ICH, and any additional national requirements for composition, documentation, and operational procedures. The investigator shall provide the Sponsor with the IRB/IEC written notification of approval along with the membership list and/or statement that the IRB/IEC operates in accordance with GCP.

14.4 Informed Consent

The principles of informed consent as laid down in the Declaration of Helsinki, in the current requirements of GCP published by the ICH, and in local regulation, whichever affords the greater subject protection, will be implemented before any protocol-specified procedures or interventions are carried out.

A signed and dated informed consent form (ICF) shall be obtained from each subject prior to entering the study. The investigator is responsible for obtaining written informed consent from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol specific screening procedures or any study medications are administered. Information should be given in both oral and written form whenever possible and deemed appropriate by the IEC/IRB. Subjects will also be asked to consent to allow the sponsor, sponsor representative or external regulatory auditor to review their medical records to confirm compliance with GCP. All information sheets and consent forms will be provided in local language.

The acquisition of informed consent(s) should be documented in the subject's medical record and the ICF should be signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion (not necessarily by the investigator). The original signed ICF will be retained with the medical records at each site, a copy retained in the Investigator Site File and a further copy of the signed consent will be provided to the subject prior to participation in the trial.

14.5 Subject Data Protection

The ICF will explain that study data will be stored in a computer database, maintaining confidentiality in accordance with national data legislation. All data computer processed by Diurnal Ltd. Will be identified by subject number/study code. The ICF will also explain that for data verification purposes, authorised representatives of Diurnal Ltd., a Regulatory Authority, and/or an IEC/IRB may require direct access to parts of the hospital or practice records relevant to the study, including subjects' medical history.

Extra precautions are taken to preserve confidentiality and prevent genetic information being linked to the identity of the subject. This involves coding of the samples and data. For coded samples this will mean that there is segregation of the databases containing coded genotypic and clinical information with protection of confidentiality achieved by limited access.

14.6 Case Report Forms and QoL questionnaires

All data will be collected using an eCRFs, which will automatically enter the data into a validated computerised clinical data management system.

Each subject will complete the QoL Questionnaires during the clinic visits. The answers to the questionnaires will then be transcribed into the eCRF by the study site staff.

Laboratory data received electronically from the central laboratory will be merged with the database and not entered from the eCRF.

Analysis of the data will only be performed after all queries have been resolved using appropriate software for analysis.

14.7 Data Management

Data management will be undertaken by [redacted] who will:

- Generate the database to include data collected in the eCRF, the QoL questionnaires and the laboratory data in accordance with the CRO's standard operating procedures.
- Complete efficacy and endpoint reporting.
- Generate safety data listings to include AEs coded using the latest version of the MedDRA coding dictionary. These will be produced on an ongoing basis for review by the DSMB.

14.8 Drug Reconciliation

The CRA will perform drug reconciliation of supplies received on site, used, and destroyed or returned. The medication provided for this study is for use only as directed in the protocol. It is the investigator/institution's responsibility to establish a system for handling study treatments, including IMPs, so as to ensure that:

- Deliveries of such products from Diurnal Ltd are correctly received by a responsible person
- Such deliveries are recorded
- Study treatments are handled and stored safely and properly as stated on the label
- Study treatments are only dispensed to study subjects in accordance with the protocol
- Any unused products are either returned for destruction or destroyed on site in liaison with the CRA and following approval from the sponsor of the destruction procedure

At the end of the study, it must be possible to reconcile delivery records with records of usage and destroyed/returned stock. Records of usage should include the identification of the person to whom the study treatment was dispensed and the quantity and date of dispensing. This record is in addition to any drug accountability information recorded on the eCRF. Any discrepancies must be accounted for on the appropriate forms. Certificates of delivery and return must be signed, preferably by the investigational pharmacist, and copies retained in the Investigator Site File.

All unused medication should be either returned for destruction or destroyed on site following appropriate drug accountability procedures.

14.9 Inspections

The sponsor or sponsor representative or external regulatory agency may at any time during or after completion of the study conduct a GCP audit. Notice will be given to the site in advance of a planned GCP audit.

14.10 Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in the protocol.

14.11 Sponsor Responsibilities

14.11.1 Indemnity and Compensation

Diurnal Ltd agrees to abide by the compensation requirements described in the current ABPI Guidelines for medical experiments. Terms for the provision of indemnity and for the provision and maintenance of insurance will be documented in contracts between Diurnal Ltd and the relevant parties.

14.11.2 Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to subjects in the study, may be made only by Diurnal Ltd in conjunction with Principal Coordinating Investigator. All protocol modifications, except when the change involves only logistical or administrative aspects of the trial (e.g., change in monitor, change of telephone numbers etc.). must be submitted to the IEC/IRB in accordance with local requirements. Approval by the sponsor, Regulatory Authorities, and IEC/IRB must be obtained before changes can be implemented.

If a deviation from the protocol is implemented to eliminate an immediate hazard without prior IEC/IRB approval/favourable opinion, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment should be submitted as soon as possible to the IRB/IEC for review and approval/favourable opinion, and, if required, to the regulatory authorities.

14.12 Study Monitoring

The CRO will be responsible for the monitoring of the study. A risk-based monitoring approach will be used for monitoring the study sites with details included in the Monitoring Plan. Remote monitoring may also be conducted, if required.

[redacted] with reasonable advance notice and at reasonable times, the site will permit the sponsor or its designee(s) to monitor the conduct of the research, as well as to audit source documents containing raw data.

The information in original documents and records (e. g. patient files, laboratory results, QoL questionnaires, etc.) are defined as source data, as detailed for each site in their source data agreement and will be reviewed by the monitor for source data verification (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. If remote monitoring is being conducted, SDV against the source documents will be conducted using remote access to the subject's electronic medical records or using scanned documents, if either are permitted. All subject identifiers must be redacted prior to scanning (further details are provided in the Monitoring Contingency Plan).

At all sites the study monitor will review the progress of the study on a regular basis (using a risk-based monitoring approach), with reasonable advance notice and at reasonable times to ensure adequate and accurate data collections. Monitoring site visits to review eCRFs, subject case notes, administrative documentation including the Investigator Site File and frequent telephone communications with site will be performed throughout the study. At each study

monitoring visit the investigator will make available all records pertaining to the study. To allow sufficient time to assemble documentation for the study monitor, monitoring visits will be confirmed in advance of planned visits.

All key communications between the sponsor, designated study representative, and investigators should be documented and retained within the Trial Master File (TMF).

14.13 Publication Policy

This section details the collaboration contractual terms relating to the data ownership and publication policy for Diurnal Ltd and the participating investigators stemming from the data generated from this study.

The study results will be published irrespective of the study outcome. The sponsor and Principal Coordinating Investigator will jointly arrange for the preparation of one or more manuscripts. The sponsor's and investigator's comments on the proposed publication(s) shall be considered in good faith by the authors. Publication of the results will not include company confidential information without the permission of the sponsor.

The sponsor may announce summary data in order to comply with Financial and other Regulatory Authorities, whilst ensuring that release of such data will not compromise the investigator's ability to publish the data in appropriate scientific forms. Announcements made prior to the first scientific publication of the data will be reviewed and approved by the Principal Coordinating Investigator.

Data from individual study sites (unless the only site of a study, or a circumscribed sub-study) will not be published separately unless exceptional circumstances prevail.

14.14 Clinical Study Report

The results of the study will be presented in an integrated clinical study report according to GCP and ICH-E3 guidance.

14.15 Data Retention and Availability

The investigator is required to maintain all study documentation, including regulatory documents, copies of eCRFs, signed ICFs, and records for the receipt and disposition of study medications, for a period of two years following approval date of a New Drug Application or a Marketing Authorisation Application for the drug, or until 15 years after completion of the study, whichever is later.

During the study, the investigator must make study data accessible to the sponsor, IEC/IRBs, and appropriate Regulatory Authorities. A file for each subject must be maintained that includes the signed ICF and copies of all source documentation related to that subject. The investigator must ensure the availability of source documents from which the information on the eCRF was derived.

At the end of the study, archiving will be authorised by the Sponsor following submission of the end of study report. The trial documents the sponsor will be responsible for archiving and the trial documents the CRO will be responsible for archiving will be documented in a separate

agreement. All essential documents will be archived for a minimum of 5 years after completion of trial. Destruction of essential documents will require authorisation from the sponsor.

14.16 Study Termination

The study may be terminated prior to completion at the request of the sponsor, the investigator, the IEC/IRB or Regulatory Authority or by mutual agreement. Conditions that may warrant early termination include, but are not limited to, insufficient adherence to the protocol requirement, the discovery of a significant, unexpected and unacceptable risk to the subjects, attainment of study objectives, or at the discretion of the sponsor. Procedures for terminating the study will be agreed upon by both the sponsor and the investigator.

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Appendix 1 – Standard Safety Haematology and Clinical Chemistry Parameters

Clinical Chemistry

Sodium, potassium, chloride, total CO_2, creatinine, glucose, blood urea nitrogen (BUN), albumin, total calcium, total magnesium, inorganic phosphorus, alkaline phosphatase, ALT/GPT, AST/GOT, total bilirubin, direct bilirubin, lactate dehydrogenase (LDH), total protein, total creatine kinase (CK), uric acid, total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, triglycerides.

Haematology

Complete blood count (CBC):
Red blood cell count (RBC), red cell distribution width (RDW), haemoglobin (Hb), haematocrit (Hct), mean corpuscular volume (MCV), mean cell haemoglobin (MCH), mean cell haemoglobin concentration (MCHC) platelet count, white blood cell count (WBC), WBC differential count (% and absolute).

Appendix 2 - Expected Adverse Events

The active ingredient of Chronocort® is hydrocortisone. The safety profile of hydrocortisone is well characterised in humans and there is extensive clinical experience with the use of hydrocortisone in subjects with CAH. The excipients used in the Chronocort® formulation are also well-characterised and approved for use in humans at the proposed levels. The risks of Chronocort® are, therefore, expected to be no greater than the risks of an equivalent dose of cortisol.

[redacted]: The active ingredient of Chronocort® is hydrocortisone. The safety profile of hydrocortisone is well characterized in humans and there is extensive clinical experience with the use of hydrocortisone in subjects with CAH. The excipients used in the Chronocort® formulation are also well-characterized and approved for use in humans at the proposed levels. The risks of Chronocort® are, therefore, expected to be no greater than the risks of an equivalent dose of cortisol. **However, until the safety, efficacy and tolerability of this formulation in the treatment of individuals with CAH has been proven, the risk is considered to be greater than minimal rsk with the prospect of direct benefit in indidivual subjects**.

The following is reproduced from section 4.8 of a generic hydrocortisone SmPC:

The incidence of predictable undesirable effects, including hypothalamic-pituitary-adrenal suppression correlates with the relative potency of the drug, dosage, timing of administration and the duration of treatment. The following side effects may be associated with the long-term systemic use of corticosteroids:

Gastrointestinal:
Dyspepsia, peptic ulceration with perforation and haemorrhage, abnormal distension, oesophageal ulceration, candidiasis, acute pancreatitis.

Musculoskeletal:
Proximal myopathy, osteoporosis, vertebral and long bone fractures, avascular osteonecrosis, tendon rupture.

Fluid and electrolyte disturbance:
Sodium and water retention, hypertension, potassium loss, hypokalaemic alkalosis.

Dermatological:
Impaired healing, skin atrophy, bruising, striae, acne, telangiectasia.

Endocrine/metabolic:
Suppression of the hypothalamo-pituitary-adrenal axis, growth suppression in infancy, childhood and adolescence, menstrual irregularity and amenorrhoea. Cushingoid facies, hirsutism, weight gain, impaired carbohydrate tolerance with increased requirement for antidiabetic therapy, negative protein and calcium balance, and increased appetite.

Neuropsychiatric:
Euphoria, psychological dependence, depression, insomnia and aggravation of schizophrenia. Increased intracranial pressure with papilloedema in children (pseudotumour cerebri), usually after treatment withdrawal. Aggravation of epilepsy.

Ophthalmic:
Increased intra-ocular pressure, glaucoma, papilloedema, posterior subcapsular cataracts, corneal or scleral thinning, exacerbation of ophthalmic viral or fungal diseases.

Cardiovascular:
Myocardial rupture following recent myocardial infarction.

General:
Hypersensitivity, including anaphylaxis has been reported. Nausea, malaise, leucocytosis, thromboembolism.

Withdrawal symptoms:
Too rapid a reduction of corticosteroid dosage following prolonged treatment can lead to acute renal insufficiency, hypotension and death. A withdrawal syndrome may also occur including fever, myalgia, arthralgia, rhinitis, conjunctivitis, painful itchy skin modules and weight loss.

A wide range of psychiatric reactions including affective disorders (such as irritable, euphoric, depressed and labile mood, and suicidal thoughts), psychotic reactions (including mania, delusions, hallucinations, and aggravation of schizophrenia), behavioural disturbances, irritability, anxiety, sleep disturbances, and cognitive dysfunction including confusion and amnesia have been reported. Reactions are common and may occur in both adults and children. In adults, the frequency of severe reactions has been estimated to be 5-6%. Psychological effects have been reported on withdrawal of corticosteroids; the frequency is unknown.

In addition, 3 out of 16 subjects in a phase 2 study of Chronocort® had symptoms of carpal tunnel syndrome (median nerve compression), which may be related to fluid retention secondary to Chronocort® treatment.

Appendix 3 - Sick Day Rules

Each site should follow their own sick day 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 10mg **Hydrocortisone** three times a day in addition to the usual daily dose of Chronocort®.

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

Vomiting: If you vomit, wait one half-hour and then take 20mg of hydrocortisone for sick day rules from your packet provided. If you vomit the Chronocort® dose do not take another dose of Chronocort® 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 - 2mL 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 behaviour, 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 4 - 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 5 - SF-36®

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.
Thank you for completing this survey!

For each of the following questions, please tick the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c. Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d. Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e. Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f. Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g. Walking more than a mile	☐ 1	☐ 2	☐ 3
h. Walking several hundred yards	☐ 1	☐ 2	☐ 3
i. Walking one hundred yards	☐ 1	☐ 2	☐ 3
j. Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?

None	Very mild	Mild	Moderate	Severe	Very severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e. Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f. Have you felt downhearted and low?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g. Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h. Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i. Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get ill more easily than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

Appendix 6 - MAF

MULTIDIMENSIONAL ASSESSMENT OF FATIGUE (MAF) SCALE

Instructions: These questions are about fatigue and the effect of fatigue on your activities.

For each of the following questions, circle the number that most closely indicates how you have been feeling during the past week.

For example, suppose you really like to sleep late in the mornings. You would probably circle the number closer to the "a great deal" end of the line. This is where I put it:

Example: To what degree do you usually like to sleep late in the mornings?

1	2	3	4	5	6	7	(8)	9	10
Not at all								A great deal	

Now please complete the following items based on the past week.

---

1. To what degree have you experienced fatigue?

1	2	3	4	5	6	7	8	9	10
Not at all								A great deal	

If no fatigue, stop here.

2. How severe is the fatigue which you have been experiencing?

1	2	3	4	5	6	7	8	9	10
Mild								Severe	

3. To what degree has fatigue caused you distress?

1	2	3	4	5	6	7	8	9	10
No distress								A great deal of distress	

MULTIDIMENSIONAL ASSESSMENT OF FATIGUE (MAF) SCALE (Continued)

Circle the number that most closely indicates to what degree fatigue has interfered with your ability to do the following activities in the past week. For activities you don't do, for reasons other than fatigue (e.g. you don't work because you are retired), check the box.

In the past week, to what degree has fatigue interfered with your ability to:

(NOTE: Check box to the left of each number if you don't do activity)

☐ 4. Do household chores

[1] [2] [3] [4] [5] [6] [7] [8] [9] [10]
Not at all A great deal

☐ 5. Cook

[1] [2] [3] [4] [5] [6] [7] [8] [9] [10]
Not at all A great deal

☐ 6. Bathe or wash

[1] [2] [3] [4] [5] [6] [7] [8] [9] [10]
Not at all A great deal

☐ 7. Dress

[1] [2] [3] [4] [5] [6] [7] [8] [9] [10]
Not at all A great deal

☐ 8. Work

[1] [2] [3] [4] [5] [6] [7] [8] [9] [10]
Not at all A great deal

☐ 9. Visit or socialize with friends or family

[1] [2] [3] [4] [5] [6] [7] [8] [9] [10]
Not at all A great deal

MULTIDIMENSIONAL ASSESSMENT OF FATIGUE (MAF) SCALE (Continued)

(NOTE: Check box to the left of each number if you don't do activity)

☐ **10. Engage in sexual activity**

1 2 3 4 5 6 7 8 9 10

Not at all — A great deal

☐ **11. Engage in leisure and recreational activities**

1 2 3 4 5 6 7 8 9 10

Not at all — A great deal

☐ **12. Shop and do errands**

1 2 3 4 5 6 7 8 9 10

Not at all — A great deal

☐ **13. Walk**

1 2 3 4 5 6 7 8 9 10

Not at all — A great deal

☐ **14. Exercise, other than walking**

1 2 3 4 5 6 7 8 9 10

Not at all — A great deal

15. Over the past week, how often have you been fatigued?

4 Every day
3 Most, but not all days
2 Occasionally, but not most days
1 Hardly any days

16. To what degree has your fatigue changed during the past week?

4 Increased
3 Fatigue has gone up and down
2 Stayed the same
1 Decreased

Appendix 7 – EQ-5D Health Questionnaire

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

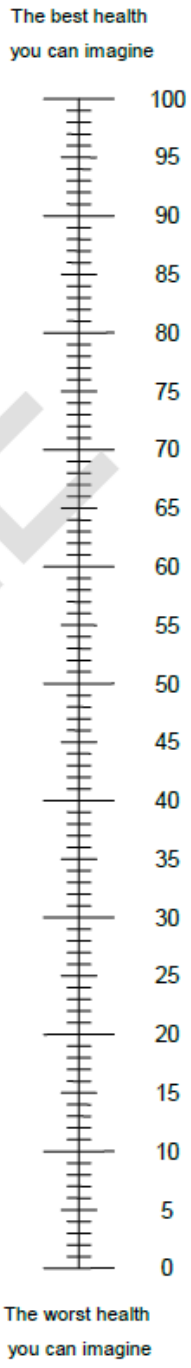
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix 8 – Labelling of IMP and Rescue Medication

Examples of the label text are provided below.

EU Primary (Blister) label (version number: DIUR-006.IMP.EU.01.001)

Chronocort® Hydrocortisone Modified Release Capsules X mg
Sponsor: Diurnal Ltd., [redacted]
PI: [redacted]
CRO: [redacted]
Dose instruction: The morning dose of Chronocort® should be taken on an empty stomach at least 1 hour before a meal and the evening dose should be taken at least 2 hours after the last meal of the day
Batch No.: XXXX
Protocol No.: DIUR-006
Subject No.: YY
EudraCT No. 2015-005448-32
Keep out of reach of children

EU Secondary label (version number: DIUR-006.IMP.EU.02.001)

Chronocort® Hydrocortisone Modified Release Capsules X mg
Quantity: 100 capsules
Batch No.: XXXX
Storage: Store at no more than 25°C
Expiry: MM/YYYY
Protocol No.: DIUR-006
Subject No.: YY
Pack No.: YY
Directions for use: For oral administration. The morning dose of Chronocort® should be taken on an empty stomach at least 1 hour before a meal and the evening dose should be taken at least 2 hours after the last meal of the day
For clinical trial use only
Investigator: [redacted]
Sponsor: Diurnal Ltd., [redacted]
CRO: [redacted]
EudraCT No. 2015-005448-32
No special precautions for unused product: refer to accompanying documents
Keep out of reach of children

EU Primary (Bottle) label (version number: DIUR-006.IMPBOT.EU.01.003)

Chronocort® Hydrocortisone Modified Release Capsules X mg
Sponsor: Diurnal Ltd., [redacted]
PI: [redacted]
Dose instruction: The morning dose of Chronocort® should be taken on an empty stomach at least 1 hour before a meal and the evening dose should be taken at least 2 hours after the last meal of the day
Quantity: 50 capsules
Batch No.: XXXX
Expiry: MM/YYYY
Protocol No.: DIUR-006
Subject No.: YY
Bottle/Pack No.: XX/YYYY
EudraCT No. 2015-005448-32
Keep out of reach of children

EU Secondary label (version number: DIUR-006.IMPBOT.EU.02.003)

Chronocort® Hydrocortisone Modified Release Capsules X mg
Quantity: 100 capsules
Batch No.: XXXX
Storage: Store at no more than 25°C
Expiry: MM/YYYY
Protocol No.: DIUR-006
Subject No.: YY
Pack No.: YY
Directions for use: For oral administration. The morning dose of Chronocort® should be taken on an empty stomach at least 1 hour before a meal and the evening dose should be taken at least 2 hours after the last meal of the day
For clinical trial use only
Investigator: [redacted]
Sponsor: Diurnal Ltd., [redacted]
EudraCT No. 2015-005448-32
No special precautions for unused product: refer to accompanying documents
Keep out of reach of children

EU safety pack label (version number: DIUR-006.SAFE.EU.02.003)

Protocol No.: DIUR-006
Subject No.: YY
Contents: YY
Sponsor: Diurnal Ltd., [redacted]
PI: [redacted]
EudraCT-No. 2015-005448-32

US Primary (Blister) label (version number: DIUR-006.IMP.US.01.001)

Chronocort® Hydrocortisone Modified Release Capsules X mg
Sponsor: Diurnal Ltd., [redacted]
PI: [redacted]
CRO: [redacted]
Dose instruction: The morning dose of Chronocort® should be taken on an empty stomach at least 1 hour before a meal and the evening dose should be taken at least 2 hours after the last meal of the day
Batch No.: XXXX
Protocol No.: DIUR-006
Subject No.: YY
IND No.: 076485
Keep out of reach of children
CAUTION: New Drug Limited by Federal (or United States Law) for Investigational Use

US Secondary label (version number: DIUR-006.IMP.US.02.001)

Chronocort® Hydrocortisone Modified Release Capsules X mg
Quantity: 100 capsules
Batch No.: XXXX
Storage: Store at no more than 25°C
Expiry: MM/YYYY
Protocol No.: DIUR-006
Subject No.: YY
Pack No.: YY
IND No.: 076485
Directions for use: For oral administration. The morning dose of Chronocort® should be taken on an empty stomach at least 1 hour before a meal and the evening dose should be taken at least 2 hours after the last meal of the day
Investigator: [redacted]
Sponsor: Diurnal Ltd., [redacted]
CRO: [redacted]
No special precautions for unused product: refer to accompanying documents
Keep out of reach of children
CAUTION: New Drug Limited by Federal (or United States Law) for Investigational Use

US Primary (Bottle) label (version number: DIUR-006.IMPBOT.US.01.003)

Chronocort® Hydrocortisone Modified Release Capsules X mg
Sponsor: Diurnal Ltd., [redacted]
PI: [redacted]
Dose instruction: The morning dose of Chronocort® should be taken on an empty stomach at least 1 hour before a meal and the evening dose should be taken at least 2 hours after the last meal of the day
Quantity: 50 capsules
Batch No.: XXXX
Expiry: MM/YYYY
Protocol No.: DIUR-006
Subject No.: YY
Bottle/Pack No.: XX/YYYY
IND No.: 076485
Keep out of reach of children
CAUTION: New Drug Limited by Federal (or United States Law) for Investigational Use

US Secondary label (version number: DIUR-006.IMPBOT.US.02.003)

Chronocort® Hydrocortisone Modified Release Capsules X mg
Quantity: 100 capsules
Batch No.: XXXX
Storage: Store at no more than 25°C
Expiry: MM/YYYY
Protocol No.: DIUR-006
Subject No.: YY
Pack No.: YY
IND No.: 076485
Directions for use: For oral administration. The morning dose of Chronocort® should be taken on an empty stomach at least 1 hour before a meal and the evening dose should be taken at least 2 hours after the last meal of the day
Investigator: [redacted]
Sponsor: Diurnal Ltd., [redacted]
No special precautions for unused product: refer to accompanying documents
Keep out of reach of children
CAUTION: New Drug Limited by Federal (or United States Law) for Investigational Use

US safety pack label (version number: DIUR-006.SAFE.US.02.003)

Protocol No.: DIUR-006
Subject No.: YY
Contents: YY
Sponsor: Diurnal Ltd., [redacted]
PI: [redacted]
IND No.: 076485

Appendix 9 – Protocol Amendment History

Protocol Version 1.0 dated 22 December 2015
Original protocol.

Protocol Version 2.0 dated 20 June 2016

The following changes were made to the protocol:

1) The Sponsor signatory was changed from [redacted] to [redacted].

2) In response to comments from the MHRA, it has been clarified that the assessments at Week 18 and then 3-monthly thereafter are not a formal study visits and just comprise telephone calls to check on the welfare of the subject. This has been added as a footnote to Table 1 and revised text in Section 11.1.9.

3) The protocol originally stated that subjects would continue in the study until a decision was reached concerning a marketing authorisation for Chronocort® in the relevant territory. This open-ended study design was not considered acceptable to the MHRA so the protocol has been revised to state that the length of the study will be 2.5 years from the date of the first subject entering the study, so subjects will be treated for a maximum of 2.5 years. If after this time point a decision has not been reached concerning a marketing authorisation for Chronocort®, a further extension of the study through a protocol amendment may be considered.

Protocol Version 3.0 dated 26 July 2016

1) Different clinicians use different conversion factors for dexamethasone to hydrocortisone. The protocol states that 'The initial dose setting at the start of Chronocort® treatment will be made on hydrocortisone dose equivalent of baseline therapy, with the hydrocortisone dose calculated as dexamethasone dose multiplied by 80'. Investigators and Diurnal have been concerned that this may lead to a safety issue that if patients on a higher dose of dexamethasone were converted by x80 they would be exposed to excess hydrocortisone, therefore a greater mineralocortiocoid effect, and be at risk of being overdosed. Therefore the protocol was amended to state that the current conversion rate of x80 should be used as per protocol up to a maximum starting dose of Chronocort® 30mg (split 20mg at night and 10mg in the morning). The justification for the maximum of 30mg Chronocort® is based on the fact this was the starting dose for all patients in the Phase 2 study (DIUR-003) (Mallappa 2015) and is in line with recommendations for hydrocortisone dosing in CAH (Speiser 2010). If the investigator has any concerns regarding the starting dose in a patient then these can be discussed with the Medical Monitor.

2) Subjects entering from study DIUR-005 had to have genotyping conducted at entry to the DIUR-005 feeder study or the information could be retrieved from the patient notes if genotyping had been done in the past. However, subjects were not required to have genotyping at entry into study DIUR-003. As a result, this protocol was amended to either obtain a blood sample for genotyping at screening, if necessary, or if previous genotyping had been performed the patient was to be asked for their permission for this information to be taken from their medical records.

3) Subjects who routinely work night shifts and so do not sleep during the usual nighttime hours was added to the exclusion criteria.

4) In the synopsis, Section 8 (Study Design) and Section 10.4 (Dose Adjustment) it was stated that 'Dose adjustment will not take place without measurement of androgens at an inpatient visit, unless the local investigator considers it is indicated by the severity of symptoms.' However, this statement was considered confusing and also seemed to mandate the measurement of androgens at an unscheduled dose adjustment, which was not the case. The text was therefore revised to say 'No dose adjustments outside of the protocol-defined dose adjustments should be conducted, unless clinical signs and symptoms indicate an immediate need. In such cases the Sponsor's medical monitor must be contacted (preferably before any dose changes are implemented). Any such unscheduled dose adjustments should be based on clinical symptoms only, with repeated androgen testing discouraged and must be pre-approved by the Sponsor's medical monitor.'

5) In Section 11.2 for DEXA scans, it is stated that a DEXA scan has to be conducted at the final visit. This is an error since DEXA scans are required annually and not automatically at the final visit.

6) A follow-up telephone call 30 days after the final visit has been added to collect information on any AEs occurring within this 30-day post-treatment period. This change has been made to the study schedule in Table 1 and in Section 11.1.11.

7) The maximum planned blood volume to be drawn at each visit has been increased from 20 mL to 40 mL following a recalculation of the volume of blood needed at each visit.

8) The AE reporting period after the last dose of study medication was extended from 7 days to 30 days.

9) Clarified that the statement "If the Chronocort® dose is changed at any point, the subject should have an interim visit which includes the assessments noted for Week 4, after which they will then continue with visits every 6 months" only applies after the Week 24 visit onwards. The text has therefore been revised to the following "If the Chronocort® dose is changed at any point **after the Week 24 visit**, the subject should have an interim visit which includes the assessments noted for Week 4, after which they will then continue with visits every 6 months."

10) The term 'safety analysis set' used in Section 13.2 to describe the analysis population was renamed 'full analysis set' to match the statistical analysis plan.

11) The telephone number of [redacted] was added and the international dialing code was added to the fax number.

Protocol Version 4.0 dated 23 September 2016

The following changes were made to the protocol:

1) The Sponsor signatory was changed from [redacted] to [redacted].

2) The Chronocort® capsules may now be supplied in either blister packs or bottles. Therefore, Section 10.2.2 (Packaging and Labelling) and Appendix 9 (Labelling) were updated.

3) For accountability purposes, all used and unused packs of study medication will be stored in a secure location. However, this does not have to be in the pharmacy. Section 10.2.4 has therefore been amended to correct this.

Protocol Version 5.0 dated 04 November 2016

The following changes were made to the protocol:

1) Section 11.7 states that subjects who become pregnant during the study may continue to receive Chronocort® outside of the study after discussion with the sponsor and if the investigator considers this is in the best interest of the subject. However, in Sweden use of Chronocort® is not allowed for pregnant women once they are withdrawn from the study so it has been added that all subjects who become pregnant in Sweden must be switched to standard care.

2) Section 11.7 stated that data would be collected on subjects continuing Chronocort® through the pregnancy, although not all the assessments required in this study will be performed (e.g. DEXA scans will not be performed). This text was removed and replaced with a link to Section 12.12, which describes in more detail the collection of data during pregnancy.

3) Protocol Version 3.0 (dated 26 July 2016) extended the AE reporting period at the end of the study from 7 days to 30 days. As such the definition of the end of the study in Section 11.8 has been revised to say that the end of the study will be the final telephone call (30 days after the last visit) of the last subject. Section 12.2 has also been revised to state that AEs will be collected for all subjects from the time of consent up to 30 days after the last visit, rather than as previously stated up to 30 days after the end of the study.

4). Section 14.2 states that all essential documents will be archived for a minimum of 5 years after completion of the study. However, according to Swedish legislation the minimum reporting period is 10 years, so this has been added to this section.

5). The responsible statistician was changed from [redacted] to [redacted].

Protocol Version 6.0 dated 12 May 2017 (non-substantial amendment for France only)

1) It was noted that the first inclusion criterion was worded slightly differently in the synopsis and in the main protocol. The wording in the main protocol was therefore revised to match the synopsis and now states "Subjects with CAH who have successfully completed the DIUR-003 or DIUR-005 clinical trials with the current formulation of Chronocort®."

Protocol Version 7.0 dated 21 June 2017

The following changes were made to the protocol:

1) Due to delays in the supply of study medication for this study, some subjects entering from study DIUR-005 had to be treated with standard glucocorticoid therapy for a short period. Such subjects will then need to have the safety blood tests and adrenal hormone levels assessed at the baseline visit for study DIUR-006 rather than using the results from Visit 4 of study DIUR-005 i.e. these subjects will be treated in the same way as subjects who are entering from study DIUR-003, with the exception that a DEXA scan at the DIUR-006 baseline visit will not be needed for subjects with a gap between completing study DIUR-005 and starting study DIUR-006. In all cases where a gap occurs, the subject should be entered into study DIUR-006 as soon as possible. This change has been implemented in various sections of the protocol.

2) The sample size in study DIUR-005 was increased from 110 to 120 subjects due to a higher level of protocol deviations than originally anticipated. As such, the maximum number of subjects eligible to enter this extension study is increased from 126 to 136 subjects.

3) It was noted that the first inclusion criterion was worded slightly differently in the synopsis and in the main protocol. The wording in the main protocol was therefore revised to match the synopsis and now states "Subjects with CAH who have successfully completed the DIUR-003 or DIUR-005 clinical trials with the current formulation of Chronocort®." Note: this change was implemented in France in protocol version 6.0.

4) Clarification has been added that female subjects presenting with oligomenorrhoea or amenorrhoea who are aged ≤55 years of age should be considered potentially fertile and therefore should still undergo pregnancy testing like all other female subjects.

5) Some events may occur during the study that represent an improvement in the subject's condition e.g. restoration of menses. To ensure sufficient details of such events are recorded, Section 12.9 has been updated to state that these events will be reported in the same manner as SAEs in order to capture the data in real time, together with additional data, if this should be required. However these events will not be reported to the regulatory authorities as SAEs.

6) After the Week 24 visit, the study visits should occur every 6 months, with interim telephones at approximately 3 months in between each visit. However, Week 24 is not a full 6 months so the visits do not fall regularly at 6-monthly intervals thereafter. To overcome this, the visit windows from Week 18 onwards will be extended to ±2 weeks to allow flexibility in scheduling the visits so they can occur at 6-monthly intervals.

7) The change added in protocol amendment 4 to allow Chronocort® capsules to be supplied in either blister packs or bottles has been removed since Chronocort® capsules will now only be supplied in blister packs.

8) The definition of pre-Chronocort® baseline in the synopsis and Section 7.2 was revised to match the SAP as following:
Pre-Chronocort® baseline means prior to the first dose of continuous Chronocort® which

is:

- The reassessed baseline under DIUR-006 for subjects entering from study DIUR-003 and those subjects from DIUR-005 who had a gap between completing study DIUR-005 and starting study DIUR-006,
- Visit 4 (Week 24) from the feeder study for subjects who received standard glucocorticoid replacement therapy in study DIUR-005 and immediately entered DIUR-006,
- Prior to the first Chronocort® dose in study DIUR-005 for subjects who received Chronocort® in study DIUR-005 (i.e. DIUR-005 baseline visit) and immediately entered DIUR-006.

9) In the synopsis, it incorrectly stated that summary statistics for vital signs and laboratory values would be presented by dose. This analysis by dose is not included in later sections of the protocol or the SAP so this has also been removed from the synopsis for consistency.

10) In Section 13.6.1 it was stated that shift tables from baseline to each time point would be presented. However, to bring this in line with the SAP this has been changed to state that shift tables from baseline to the maximum and minimum on-treatment values will be presented.

11) Interim data analyses are expected to be required for regulatory review as part of any marketing authorisation applications. However, no changes to the overall study conduct and no changes to the planned formal statistical analyses are anticipated as a result. As such a statement to this effect was added to the statistical methods section of the synopsis and in Section 13.

Protocol Version 8.0 dated 23 August 2017 (administrative local amendment for US only)

Following comments from the IRB, an additional statement has been added in Appendix 2 (Expected Adverse Events) amending the risk category from 'minimal risk with the prospect of direct benefit to individual subjects' to 'greater than minimal risk with the prospect of direct benefit to individual subjects'. This is administrative change at the [redacted] in the US only and has arisen due to an error in the NIH IRB classification at the beginning of the study (i.e. there is no actual change to the benefit/risk assessment).

Protocol Version 9.0 dated 08 November 2017

The following changes were made to the protocol:

1) Due to a clerical error, the maximum amount of blood to be drawn at any one study visit was incorrectly stated as 40 mL in the protocol, but in fact up to 49 mL was taken for some visits as per the laboratory manual. The protocol has therefore been corrected so it is consistent with the laboratory manual and describes the maximum allowable amount of blood that can be taken at any one visit.

2) Section 11.1.9 has been revised to allow for subjects to be issued with 6 months supply of Chronocort® at each visit after Week 18 rather than subjects having to return to the study centre to collect new supplies every 3 months. The option to collect supplies from a local pharmacy instead has been removed since this was not practical in terms of drug

accountability and put adequate control of shipping conditions at risk. This change has also been made to Table 1 and at all other relevant places in the protocol.

3) Section 13.2 (Analysis Sets) has been updated to include an interim analysis set which will be used for any interim analyses carried out in this study.

4) Clarified in the protocol that any use of medication from the safety pack will be recorded for drug accountability purposes and any such use should also be recorded on the sick day medication page of the eCRF.

5) In Table 1 an 'X' has been added at the Screening Visit for collection of AE and SAEs to be consistent with footnote 12 (which states AEs and SAEs are recorded from the time of informed consent). Footnote 8 also revised to clarify that dose adjustments also take into account clinical symptoms assessed using the signs and symptoms of adrenal insufficiency questionnaire.

6) Clarified in Section 11.1.1 and Table 1 that any prior genotyping information collected from DIUR-003 subjects will be recorded in the eCRF.

7) Clarified in Section 11.1.2 and in Table 1 that the last glucocorticoid dose taken prior to the baseline visit should be recorded, with details of the drug(s), dose and time of administration being recorded in the eCRF.

8) Clarified in Section 11.1.2 that the prednisone conversion to Chronocort® of x5 should also apply to prednisolone, i.e. prednisone and prednisolone dose multiplied by 5.

9) Clarified in Section 14.12 that all communications between the sponsor, designated study representative, and investigators should be documented in the TMF.

10) Clarified in Section 14.15 that the investigator is required to maintain all study documentation for two years following the approval date of a Marketing Authorisation Application, as well as for a New Drug Application.

11) Some of the dates of the protocol amendments in Appendix 9 were incorrect so these have been corrected.

Protocol Version 10.0 dated 21 August 2018

The following changes were made to the protocol:

1) Project Manager changed from [redacted] to [redacted].

2) Since a decision concerning a marketing authorisation for Chronocort® has not yet been reached, the estimated end of the study has been extended by 1 year. Thus the total length of the study will be now be 3.5 years from the date of the first subject entering the study i.e. from August 2016 until February 2020.

3) An end date for enrolment has been added to ensure all patients are enrolled promptly and sufficient data are obtained before the end of the study. So it is now specified all subjects must be enrolled by 31 October 2018, with no subjects allowed to enter the study after this date.

4) Section 5.5 (Overview of Chronocort® clinical studies): description of study DIUR-007 has been updated to reflect the final design of this study.

5) Section 10.2.1 (Chronocort® formulation) has been revised to state that the Chronocort® capsules may be printed with either 'CHRONOCORT 5mg/10mg/20mg' or 'CHC 5mg/10mg/20mg' on the capsule body.

6) Sections 10.2.2 (Packaging and Labelling) and 10.5 (Other Study Medications [Non-Investigational Medicinal Products]): Some centres do not allow the pharmacist to write the subject numbers on the safety packs (printed labels have to be used) so the sentence "The subject number will be written on the study pack by the pharmacist" has been deleted.

7) Section 10.5 (Other Study Medications [Non-Investigational Medicinal Products]): the wording of the first bullet point has been revised to make the statement more general, thus just stating that a supply of oral hydrocortisone will be provided that would allow dosage of up to 20 mg three times daily.

8) Section 11.7 states that subjects who become pregnant during the study may continue to receive Chronocort® outside of the study after discussion with the sponsor and if the investigator considers this is in the best interest of the subject. Previously it was added that in Sweden, the use of Chronocort® is not allowed for pregnant women once they are withdrawn from the study, so subjects who become pregnant in Sweden must be switched to standard care. The criterion has now been added for the US as well, so subjects who become pregnant in Sweden and the US must be switched to standard care.

Protocol Version 11.0 dated 25 January 2019

The IRB at the NIH centre in the US requested details of study DIUR-007 to be removed from the protocol since this study is currently suspended. This change is considered an administrative change only. A few other minor administrative changes were also made at the same time as follows:

1) The Sponsor signatory was changed from [redacted] to [redacted].

2) The Project Manager was changed from [redacted] to [redacted].

3) The contact details for the Sponsor's Medical Expert were updated.

4) Section 5.5 (Overview of Chronocort® clinical studies) has been revised to remove the reference to study DIUR-007, since this study is currently suspended. The paragraph on study DIUR-005 has also been revised since this study has now been completed and reporting of the results is ongoing.

Protocol Version 12.0 dated 04 September 2019

The following changes were made to the protocol:

1) The statistician has changed from [redacted] to [redacted].

2) The name of the CRO being used has changed its name from [redacted] to [redacted] so this has been changed throughout.

3) Synopsis, Section 9.1 (Number of Subjects and Subject Selection) and Section 13.7 (Power and Sample Size Considerations) - since study DIUR-005 has now finished, the actual number of participants enrolled in this study can be added (a total of 122 participants). As such, the maximum number of subjects potentially eligible to enter this extension study is increased from 136 to 138 subjects.

4) Synopsis and Section 11.8 (Study Duration and Completion of the Study) - since a decision concerning a marketing authorisation for Chronocort® has not yet been reached, the estimated end of the study has been extended until February 2022. Thus the total length of the study will be now be approximately 5.5 years from the date of the first subject entering the study i.e. from August 2016 until February 2022.

5) Synopsis, Section 8 (Study Design), Section 8.1 (Dose Titration Algorithm), Section 10.4 (Dose Adjustments), Section 11 (Study Procedures), Section 11.1.4 (Telephone call (within 2 weeks of Visit 2)), Section 11.1.6 (Telephone call (within 2 weeks of Visit 3)), Section 11.1.7 (Week 24 and then every 6-months (± 2 Weeks)), and Section 11.1.8 (Telephone call (within 2 weeks of previous visit)) - if the Chronocort® dose is changed at any point after the Week 24 visit, the subject was previously required to have an interim dose titration visit where the assessments noted for Week 4 were required to be repeated. However, this has now been replaced with an option to perform either an interim dose titration visit or a telephone call to check on the well-being of the subject. The same assessments as noted for the Week 4 visit will be performed at the interim dose titration visit. If an interim dose titration telephone call is used instead, blood sampling for 17-OHP and A4 and the urine pregnancy test will not be performed but all other Week 4 assessments will be performed.

6) Synopsis, Section 6.2 (Secondary Objectives), Section 7.2 (Secondary Endpoints), Section 13.3.2 (Secondary Endpoints) and Section 13.6.2 (Efficacy) - during the interim analyses for this study, two additional exploratory analyses were added to the SAP to further explore the pattern of Chronocort® dosing (based on the proportion of the dose given at night and the dose by body surface area). These new analyses have therefore been added to the protocol for consistency with the SAP.

7) Section 5.5 (Overview of Chronocort® clinical studies) - summary of the results from study DIUR-005 added.

8) Section 10.2.2 (Packaging and Labelling) and Appendix 8 (Labelling of IMP and Rescue Medication) - the Chronocort® capsules may now be supplied in either blister packs or bottles so these sections have been updated. In addition, the label text in Appendix 8 has been updated to the latest label text.

9) Section 12.5 (Assessment of Adverse Event Causality/Relatedness) - a new category of "related to study medication from previous Chronocort study" has been added for any AEs that might occur in participants who have recently joined the DIUR-006 study from one of the feeder studies.

10) Section 12.6 (Assessment of Adverse Event Expectedness) - the definition of “unexpected” was updated to reference the RSI in the Investigator's Brochure.

11) Section 13.2 (Analysis Sets) - clarified the different definitions for the 'Interim Analysis 1' data set and subsequent interim analysis data sets.
12) Section 13.3.2 (Secondary Endpoints) - clarified the testosterone will be analysed for males and females separately.
13) Section 14.12 (Study Monitoring) - study monitoring will be moved to a risk-based monitoring approach, with full details of this methodology included in the Monitoring Plan.
14) Appendix 2 (Expected Adverse Events) - the reference to the SmPC of hydrocortisone for expected AEs has been removed since this is no longer used in the RSI.

15) Some minor administrative and consistency changes have been made throughout the protocol.

Protocol Version 13.0 dated 24 October 2019

The following changes were made to the protocol:

1) Section 4 (Investigators and Administrative Structure) and Appendix 8 (Labelling of IMP and Rescue Medication) - the CRO has been changed from [redacted] to [redacted]

2) Appendix 5 (SF-36®) - the script version of the SF-36® was replaced with the validated paper questionnaire.

3) Appendix 8 (Labelling of IMP and Rescue Medication) - the pack number has been added to the EU and US primary bottle labels.

Protocol Version 14.0 dated 17 Apr 2020

The following changes were made to the protocol:

1) Section 11 (Study Procedures) - footnote 11 added to DEXA scan assessment to make it clear the DEXA scans are only needed once a year

2) Section 11 (Study Procedures) - new footnote 17 added to indicate that Baseline and Week 4 visits are repeated for subjects who re-enter the study post-pregnancy.

3) Section 11.7 (Pregnancy) - subjects who become pregnant must still be withdrawn from the study, but they are now allowed to re-enter the study 6 weeks after the pregnancy is complete (i.e. 6 weeks post-partum regardless of outcome or 6 weeks after abortion or

termination) or 6 weeks after they have finished lactating and are no longer breast feeding. Details of re-entry into the study and of the post-pregnancy visits are also included.

4) Section 4 (Investigators and Administrative Structure), Section 11.7 (Pregnancy), Section 12.9 (Serious Adverse Event Reporting) and Section 12.10.1 (Standards for Expedited Reporting) - updated [redacted] to [redacted] and updated email address [redacted]

5) Section 4 (Investigators and Administrative Structure) and Section 12.9 (Serious Adverse Event Reporting) - contact details for [redacted] (Medical Monitor) updated.

6) Appendix 8 (Labelling of IMP and Rescue Medication) - expiry date and bottle number added to the example bottle labels to reflect the bottle labels being used.

Protocol Version 15.0 dated 17 Aug 2020

1) Section 11.7 (Pregnancy) - clarified that the time period before pregnant subjects can re-enter the study is at least 6 weeks.

2) Section 11.8 (Study Duration and Completion of the Study) - clarified that the end of the study will be the final telephone call (30 days after the last visit) of the last subject, i.e. March 2022.

3) Section 11.10 (Subject Diaries) - added that subject will be provided with an ad hoc diary in which they will be asked to record any use of sick day medications and to record any AEs that occur between study visits.

4) Section 11.11 (COVID-19 Procedures) - new section added to describe the interim measures put in place to enable the study to continue during the COVID-19 restrictions.

5) Section 13 (Statistical Considerations) - section updated in line with changes made to the SAP (Version 4.0 dated 13 Jul 2020).

6) Section 13.1.3 (Missing Outcome Data) - the window around the blood sampling times for analysis of 17-OHP and A4 at 09:00 and 13:00 have been increased from half an hour to 1 hour.

7) Section 14.12 (Study Monitoring) - the option to conduct remote monitoring has been added, with SDV conducted using the subject's electronic medical records or using scanned documents, if either are permitted.

Protocol Version 16.0 dated 28 Jun 2021

1) Section 4 (Investigators and Administrative Structure) – address for [redacted] updated.

2) Section 10.6 (Permitted Concomitant Medications/Treatments) - clarification has been added for what should happen if a participant receives a COVID-19 vaccine to bring the

protocol in line with the latest MHRA guidance on COVID-19 vaccinations and clinical trials.

3) Section 11 (Study Procedures) and Section 11.1.10 (Final Visit or Early Withdrawal Visit) – added that if the end of study visit is within 3 months after a scheduled 6-monthly visit then only minimal safety assessments (AE and SAE collection only) will be performed.

4) Section 11.1 (Visit Schedule) – added that if a participant has received the COVID-19 vaccine then the next visit must be scheduled at least 5 days post-vaccine.

5) Section 11.7 (Pregnancy) – added that the first dose of Chronocort after re-entry following pregnancy should be taken in the evening of the first dosing day.

6) Section 11.11 (COVID-19 Procedures) – clarified that the specified COVID-19 measures can only be implemented after Sponsor approval has been obtained.

7) Appendix 8 (Labelling of IMP and Rescue Medication) – bottle labels updated to reflect current labels in use.

Protocol Version 17.0 dated 29 Apr 2022

1) Section 4 (Investigators and Administrative Structure), Section 11.7 (Pregnancy), Section 12.9 (Serious Adverse Event Reporting) and Section 12.10.1 (Standards for Expedited Reporting) – added that SAE and pregnancy reporting will change to [redacted] from April 2022 onwards.
2) Signature page, Section 4 (Investigators and Administrative Structure) – name and contact details for [redacted] statistician updated.

Protocol Version 18.0 dated 25 May 2022 (applicable for USA and France only)
Protocol signed off but not submitted - voided and protocol amendment 19 implemented instead.

Protocol Version 19.0 dated 15 June 2022 (applicable for USA and France only)

1) Synopsis, Section 8 (Study Design), Section 11 (Study Procedures), Section 11.1.11 (Telephone call (30 days after final visit)) – added that at the end of the study subjects will have the option to enter a second long-term study (DIUR-015) to enable them to continue to receive open-label Chronocort® until it is commercially available in their region or it is decided to stop Chronocort® treatment. Subjects who decide to enter the DIUR-015 study immediately following this DIUR-006 study do not require a telephone call 30 days after the end of this study. If there is a gap between finishing this DIUR-006 study and entering the DIUR-015 study of greater than 30 days, then the 30-day telephone call is required.
2) Section 11 (Study Procedures), Section 11.1.11 (Telephone call (30 days after final visit)), Section 12.9 (Serious Adverse Event Reporting) – clarified that AEs and SAEs are reported until 30 days after the last dose of Chronocort® or until the subject starts receiving Chronocort® in the second long-term extension study (DIUR-015) if this is less than 30 days after the end of dosing in this DIUR-006 study.

Protocol Version 20.0 dated 16 June 2022 (applicable for USA and France only)

1) Section 11.8 (Study Duration and Completion of the Study) – end of study definition expanded to include the date the last subject enters the DIUR-015 extension study since these subjects won't have the final telephone call 30 days after the last visit.