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CLINICAL STUDY PROTOCOL PLUS AMENDMENT 6
(administrative local amendment for US only)

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

IND No.: **76485**
Protocol No.: **DIUR-005**
EUDRACT No.: **2015-000711-40**
Version No.: **Final 7.0**
Date of Protocol: **23 August 2017**

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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 Address:	[redacted]
Tel: Fax: Email:	[redacted]

I, the undersigned, have reviewed this protocol, plus amendment 6, and 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]

Date: [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*
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I, the undersigned, have reviewed this protocol, plus amendment 6, 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

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Statistician: Address:	[redacted]
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I, the undersigned, have reviewed this protocol, plus amendment 6, 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] Date: [redacted]

1. Protocol Synopsis

PROTOCOL TITLE:	A Phase III study of efficacy, safety and tolerability of Chronocort® compared with standard glucocorticoid replacement therapy in the treatment of congenital adrenal hyperplasia (CAH)
PROTOCOL No:	DIUR-005
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	Parallel arm, randomised, open study

INCLUSION CRITERIA

1. Known CAH due to 21-hydroxylase deficiency (classic CAH) diagnosed in childhood with documented (at any time) elevated 17-hydroxyprogesterone (17-OHP) and/or androstenedione (A4) and currently treated with hydrocortisone, prednisone, prednisolone or dexamethasone (or a combination of the aforementioned glucocorticoids) on a stable glucocorticoid therapy for a minimum of 6 months.
2. Male or female subjects aged 18 and above.
3. Provision of signed written informed consent.
4. Non-pregnant, non-lactating females who are post menopausal, naturally or surgically sterile, or of childbearing potential with a negative urinary pregnancy test and using a medically acceptable method of contraception (Note: females presenting with oligomenorrhoea or amenorrhoea who are aged ≤55 years of age should be considered potentially fertile and therefore, as well as undergoing pregnancy testing like all other female subjects, will be expected to be using an acceptable method of contraception).
5. Plasma renin activity (PRA) less than 1.5 times the upper limit of normal (ULN) at screening or within 3 months prior to screening, except in subjects who have been diagnosed with hypertension where the renin is not being used to monitor fludrocortisone replacement.

EXCLUSION CRITERIA

1. Co-morbid condition requiring daily administration of a medication (or consumption of any material) 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 (ALT or AST >2 times the ULN).
3. Subjects on regular daily inhaled, topical, nasal or oral steroids for any indication other than CAH.
4. Subjects with any other significant medical or psychiatric conditions that in the opinion of the investigator would preclude participation in the trial.
5. History of malignancy (other than basal cell carcinoma successfully treated >6 months prior to entry into the study).
6. Participation in another clinical trial of an investigational or licensed drug or device within the 3 months prior to inclusion in this study.
7. Subjects with a history of bilateral adrenalectomy.
8. Subjects having previously been exposed to Chronocort®.
9. Subjects who routinely work night shifts and so do not sleep during the usual nighttime hours.
10. Subjects unable to comply with the requirements of the protocol.

STUDY DURATION:

After screening and baseline evaluation, subjects will either be randomised to Chronocort® or continue their standard therapy. Treatment will continue for 6 months, during which times the glucocorticoid dose in both treatment groups will be titrated according to an agreed algorithm to optimise control of the disease. After

completion of the 6-month study period, all subjects may then enter a period of open-label treatment with Chronocort® as part of an open-label extension study (to be conducted under a separate protocol).

NUMBER OF SUBJECTS:
A sample size of 102 subjects provides greater than 95% power and 2-sided alpha 5% to demonstrate a fall in the logarithm of the mean daily unsigned standard deviation score of 17-OHP relative to the standard glucocorticoid replacement therapy group. It is assumed that (i) the mean fall in the Chronocort® group will be the same (0.78) as that observed in the phase II study (DIUR-003) (ii) the mean fall in the standard therapy group will be 0.2 (approximately 25% of the Chronocort® phase II study fall) and (iii) the standard deviation of the fall (0.681) is that seen in the phase II study. The study is powered to ensure that there can be a reasonable description of the comparison of Chronocort® with a variety of standard therapies. 120 subjects will be randomised to this study which will account for an inevaluability rate of 15%. Individual sites should not recruit more than 25 subjects without first consulting the sponsor.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION:	Chronocort® will be provided as 5mg, 10mg and 20mg capsules for oral administration. The starting dose for each subject will be based on the subject's previous glucocorticoid therapy dose and then dose titrated to effect. The morning dose of Chronocort® (approximately 1/3rd of the total daily dose) should be taken at 07:00 hours on an empty stomach at least 1 hour before a meal and the evening dose (approximately 2/3rd of the total daily dose) should be taken at 23:00 hours at least 2 hours after the last meal of the day.
REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION:	Continuing previous oral glucocorticoid therapy titrated to effect.

OBJECTIVES:
Primary Objectives:
To demonstrate the superior efficacy of Chronocort® compared with standard glucocorticoid replacement therapy in the treatment of CAH based on 17-OHP.
Secondary Objectives:
In adult subjects with CAH:

- To assess the safety and tolerability of Chronocort® treatment in adult subjects with CAH over a 6-month period.
- To assess the efficacy of Chronocort® with regard to the effect on A4 over the 6-month treatment period.
- To assess the impact of Chronocort® on body composition (using dual energy X-ray absorbtimetry [DEXA]) – fat mass, lean mass and total bone density – at selected sites.

Exploratory Objectives:

- To assess the efficacy of Chronocort® with regard to the effect on testosterone levels over the 6-month treatment period.
- To assess the impact of Chronocort® on cardiovascular (CV) risk (evaluated using high-sensitivity C-reactive protein [hsCRP]).
- To assess the impact of Chronocort® on bone markers of serum C-terminal cross-linked telopeptide (CTX) and osteocalcin (after fasting).
- To assess changes from baseline in glucose and insulin in the morning (after fasting)
- To assess changes from baseline in glycated haemoglobin (HbA1c) and PRA in the morning.
- To assess the impact of Chronocort® on quality of life (QoL) using SF-36®, Multidimensional Assessment of Fatigue (MAF), and EQ-5D™.
- To assess subject compliance in subjects treated with Chronocort® over a 6-month period.

ENDPOINTS:
Primary Endpoint:
The primary efficacy endpoint is the change from baseline to 24 weeks of the mean of the 24-hour standard deviation score (SDS) profile for 17-OHP. The SDS profile is calculated as the SDS of log-transformed 17-OHP concentration unsigned.

Secondary Endpoints:

1. The change from baseline to 24 weeks of the mean of the 24-hour SDS profile for A4 (calculated in the same way as the primary endpoint).
2. The presentation of 17-OHP and A4 by individual baseline treatment strata in the study will be presented in the same manner as the primary endpoint (using 24-hour SDS profile at 24 weeks).
3. 17-OHP and A4 levels at 09:00 as a responder analysis (i.e. the number of subjects achieving results in the optimal range).
4. Changes relative to standard glucocorticoid replacement therapy in body composition (DEXA) (fat mass, lean mass and total bone density) to be measured at all sites except Germany.

Exploratory Endpoints:

1. Partial area under the curve (AUC) of 17-OHP at 15:00-23:00, 23:00-07:00, and 07:00-15:00 (all refer to actual clock time of sampling).
2. The primary endpoint measure will also be presented for the profiles measured at 4 and 12 weeks for the purposes of titration.
3. Changes relative to standard treatment in the following:
    a. Bone markers – serum CTX and osteocalcin (after fasting)
    b. hsCRP
    c. Assessment of glucose and insulin in the morning (after fasting)
    d. Assessment of HbA1c, total testosterone, and PRA in the morning
    e. QoL using SF-36®, MAF, and EQ-5D™
4. Use of glucocorticoids at beginning and end of the study will be presented both as individual glucocorticoids used, and as calculated hydrocortisone equivalents using accepted conversion constants for the calculations.

Safety Endpoints:

1. Routine haematology, biochemistry, physical examination, vital signs, urinalysis, electrocardiogram (ECG).
2. Clinical adverse events (AEs) – particular note of use of sick day rules and Addisonian crises. Under or over-replacement with glucocorticoids will be considered in the efficacy endpoints.
3. Changes relative to the standard treatment in weight, body mass index (BMI), waist circumference, and blood pressure (BP).

METHODOLOGY:

As part of the baseline assessment, subjects will be admitted overnight for a 24-hour endocrine profile whilst on their standard therapy. Subjects will attend the study site in the morning and have a profile taken: 17-OHP and A4 at 15:00, 17:00, 19:00, 21:00, 23:00, 01:00, 03:00, 05:00, 07:00, 09:00, 11:00, 13:00 and 15:00. Baseline bloods will be taken on the second morning and will include: safety measurements, all secondary endpoints to be measured – PRA, fasting osteocalcin and CTX, DEXA scan for body composition (except Germany) (DEXA scan may be performed at other times up to 2 weeks before baseline if scheduling proves difficult), insulin and glucose, HbA1c, QoL, height, weight (BMI to be calculated) and waist circumference. After these measurements have been taken, the subject will be randomised to Chronocort® or to continue on their standard care. Randomisation will be stratified by baseline treatment:

1. hydrocortisone only or
2. prednisone or prednisolone, alone or in combination with hydrocortisone
3. dexamethasone only or in combination with any other glucorticoid

The initial dose setting at the start of the Chronocort® treatment will be based on hydrocortisone dose equivalent of baseline therapy in accordance with standard clinical practice. Further dose refinement/titration will be conducted in both treatment groups as necessary after 4 weeks and 12 weeks using a standardised titration algorithm after the subject has been re-admitted for further 24-hour profiles, to include 17-OHP and A4. Safety endpoints and PRA will also be measured at the 07:00 morning sample at each profile.

At 6 months, all the baseline tests will be repeated (including the 24-hour profile). All subjects may then continue on Chronocort®, whatever their randomised treatment, as part of an open-label extension study (to be conducted under a separate protocol).

Blinding: The decision to change doses in both treatment groups will be made by an independent blinded physician but the actual change in dose will be made by the local investigator looking after the subject. 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 is currently recommended to clinical practice.

Stress doses of hydrocortisone will be given for intercurrent illnesses as medically indicated according to "sick day rules". Fludrocortisone dose adjustment will be allowed if medically indicated and will be based on

BP measurements and laboratory data (goal supine PRA above the lower limit and <1.5 times ULN).

- Dose changes in both treatment groups will be under the direction of an independent blinded physician and will be made following an inpatient assessment of symptoms and androgen levels.
- Dose adjustment will be based on clinical symptoms using the "signs and symptoms of adrenal insufficiency questionnaire" and the measurement of the 17-OHP and A4 profiles.
- The 5 samples taken between 01:00 and 09:00 will reflect the glucocorticoid dose taken in the evening or last thing at night on standard or Chronocort® therapy and the 5 samples taken between 11:00 and 19:00 will reflect the morning glucocorticoid dose on standard or Chronocort® therapy. Dose adjustments will be considered if 3 or more of the 5 sample times show out of range values for 17-OHP or A4.

For subjects continuing on standard therapy the local investigator can change the daytime and evening doses of the standard therapy (within the limits set by the independent blinded physician) but the timing and the drugs used must not be changed. Dose adjustment will use the lowest dose adjustment available with the specific therapy, so generally for hydrocortisone this will be 5mg, for prednisolone 1mg and dexamethasone 0.25mg.

Where 17-OHP and A4 show inconsistent trends the A4 parameter will take precedence in directing dose adjustment.

If required, dose adjustments will be made within 2 weeks of the week 4 and week 12 visits when biochemical results are reviewed.

- All subjects (whether or not there has been a titration) will receive a telephone call one week after any dose adjustments to enquire as to whether there have been any AEs, and reinforce any other protocol requirements.
- 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.The rationale for any dose adjustment, by both the independent blinded physician and also any changes made by the local investigator, will be recorded in the electronic case report form (eCRF).
- In subjects who have undetectable androgens at baseline on their regular medication, caution will be taken over dose reduction so as to avoid the risk of suppressed pituitary-adrenal axis occurring in these subjects.

STATISTICAL METHODS:

The Statistical Analysis Plan (SAP) must be finalised before any subject is randomised into the trial.

Efficacy: The primary efficacy endpoint is the change from baseline to 24 weeks in the primary efficacy variable (natural logarithm of the mean over the 24-hour SDS profile for 17-OHP). The primary efficacy endpoint will be compared between treatment groups within a Normal linear analysis of covariance (ANCOVA) model with baseline treatment category and baseline SDS as covariates. Exploratory analyses will investigate the sensitivity of the results to the transformation of the endpoint and to the form of the model. Secondary endpoints will also be analysed as a change from pre-randomisation baseline to end-of-study. To ensure that the treatment effect of Chronocort® is not all as a result of non-hydrocortisone based regimes being different in achieving control, the effect of Chronocort® within baseline treatment subgroups will be presented.

Safety: Summary vital signs change from baseline data will be presented in tabular form, by dose level across time, with N, mean, standard deviation (SD), median, quartiles, minimum and maximum as appropriate.

Summary ECG (heart rate, PR interval, QRS width, QT interval and QTC interval) change from baseline data will be presented in tabular form, by dose level across time, with N, n, mean, SD, median, minimum and maximum as appropriate.

AEs will be coded using the latest version of the MedDRA drug dictionary. Data will be summarised using preferred term and primary system organ class. Only treatment-emergent AEs, being events with an onset at or after the first administration of study drug, 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.

Absolute and change from baseline laboratory variables (haematology, biochemistry) will be summarised by treatment group (N, n, mean, SD, median, quartiles, minimum and maximum) at each time point. Shift tables from pre-dose to each time point for laboratory variables (haematology, biochemistry) will be presented. The 3 x 3 cross tabulations (from low, normal and high to low, normal and high) will be presented by treatment group. Urinalysis variables will be listed by subject and time point. 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
AE	Adverse event
ACTH	Adrenocorticotropic hormone
ADR	Adverse drug reaction
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AUC	Area under the curve
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
CAH	Congenital adrenal hyperplasia
CBC	Complete blood count
CK	Creatine kinase
C_{max}	The maximum concentration achieved after a single dose
CRA	Clinical Research Associate
CRADA	Cooperative Research and Development Agreement
eCRF	Electronic case report form
CRH	Corticotropin-releasing hormone
CRO	Contract Research Organisation
CTX	C-terminal cross-linked telopeptide
CV	Cardiovascular
CYP	Cytochrome P
DEXA	Dual Energy X-ray Absorptiometry
dL	Decilitre
DSMB	Data Safety Management Board
ECG	Electrocardiogram
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
HR	Heart rate
hsCRP	High sensitivity c-reactive protein
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICF	Informed consent form
IMP	Investigational medicinal product

IPI	Identifiable private information
IR	Immediate release
IRB	Institutional Review Board
IUD	Intrauterine device
IUS	Intrauterine system
IWRS	Interactive Web Response System
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
QoL	Quality of life
PK	Pharmacokinetics
PP	Polypropylene
PRA	Plasma renin activity
RBC	Red blood cell
RDW	Red cell distribution width
REC	Research Ethics Committee
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SDS	Standard deviation score
SF-36®	Medical Outcome Short Form Health Survey Form 36 (Subject Questionnaire)
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
T_{max}	Time taken to reach C_{max}
ULN	Upper limit of normal
WBC	White blood cell
WHO	World Health Organisation

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]

Safety reporting

[redacted]

5. Introduction

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 et al. 2014).

There is currently no standard treatment for this condition, and 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 the 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. The proposed study will 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]).

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.

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). The risks of Chronocort® are, therefore, expected to be no greater than the risks of an equivalent dose of cortisol.

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 (IR) hydrocortisone 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).

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 (20mg) and 07:00 hours (10mg), 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).

Overview of Chronocort® clinical studies

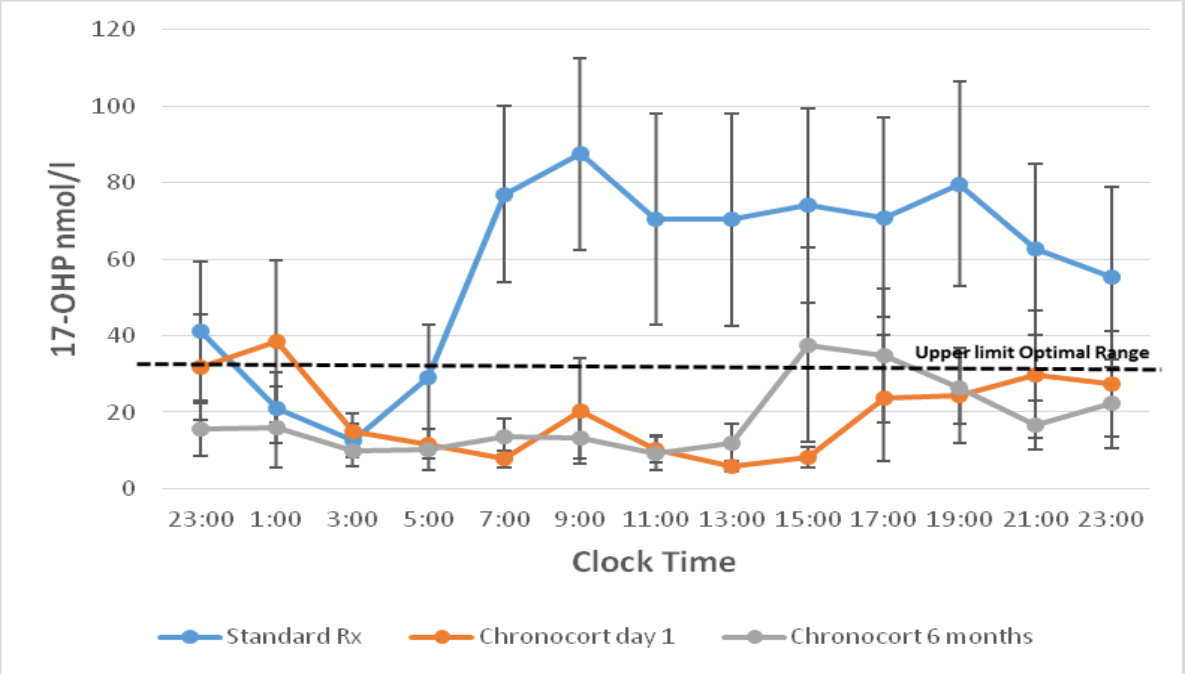
One Phase I study has been completed to assess the pharmacokinetics (PK) of Chronocort® (study DIUR-002) (Whitaker 2014). Study DIUR-002 fully characterised the PK performance and dose proportionality of Chronocort®. The target PK criteria, commensurate with the endogenous circadian profile for cortisol, were as follows: mean C_{max} >300nmol/L (>10.8 mcg/dL) for the 20mg dose, T_{max} approximately 6-8 hours post-dosing to prime waking, mean cortisol level >100nmol/L (>3.6mcg/dL) up to 16:00 hours, mean cortisol level <100nmol/L (>3.6mcg/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 National Institutes of Health (NIH) Clinical Center in Bethesda, Maryland, USA (Mallappa 2015). DIUR-003 evaluated the PK profile of cortisol following short-term twice-daily administration of Chronocort® (20mg at night and 10mg 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 30mg daily (given as 10mg at 07:00 and 20mg 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 20mg at 23:00 and 10mg 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 28mg and on Chronocort® was 26mg. 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 cases of anaemia and 4 cases of 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 are currently being analysed, but preliminary PK data indicate that food may have an effect on the dosing of Chronocort®. Thus in this study 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. 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 no there was no causal relationship with the study drug.

Proposed study
The proposed study aims to build on the results of study DIUR-003 and further evaluate whether Chronocort® can provide improved control of serum androgen levels (using 17-OHP and A4 as markers) compared to current glucocorticoid treatment regimens.

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 these risks are then negligable. 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 total blood volume to be withdrawn during this study has been limited to a maximum of 427mL. 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 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 cortisol 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 is receiving at entry into this study. However, the delivery of hydrocortisone with Chronocort® has been demonstrated to produce a cortisol profile more similar to the endogenous cortisol profile than current 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 Objectives

- To demonstrate the superior efficacy of Chronocort® compared with standard glucocorticoid replacement therapy in the treatment of CAH based on 17-OHP.

6.2 Secondary Objectives

In adult subjects with CAH:

- To assess the safety and tolerability of Chronocort® treatment in adult subjects with CAH over a 6-month period.
- To assess the efficacy of Chronocort® with regard to the effect on A4 levels over the 6-month treatment period.
- To assess the impact of Chronocort® on body composition (using dual energy X-ray absorbtimetry [DEXA]) – fat mass, lean mass and total bone density – at selected sites.

6.3 Exploratory Objectives

- To assess the efficacy of Chronocort® with regard to the effect on testosterone levels over the 6-month treatment period.
- To assess the impact of Chronocort® on cardiovascular (CV) risk (evaluated using high-sensitivity C-reactive protein [hsCRP]).
- To assess the impact of Chronocort® on bone markers of serum C-terminal cross-linked telopeptide (CTX) and osteocalcin (after fasting).
- To assess changes from baseline in glucose and insulin in the morning (after fasting)
- To assess changes from baseline in glycated haemoglobin (HbA1c) and plasma renin activity (PRA) in the morning.
- To assess the impact of Chronocort® on quality of life (QoL) using SF-36®, Multidimensional Assessment of Fatigue (MAF), and EQ-5D™.
- To assess subject compliance in subjects treated with Chronocort® over a 6-month period.

7. Study Endpoints

7.1 Primary Endpoint

The primary efficacy endpoint is the change from baseline to 24 weeks of the mean of the 24-hour standard deviation score (SDS) profile for 17-OHP. The SDS profile is calculated as the SDS of log-transformed 17-OHP concentration unsigned.

7.2 Secondary Endpoints

1. The change from baseline to 24 weeks of the mean of the 24-hour SDS profile for A4 (calculated in the same way as the primary endpoint).
2. The presentation of 17-OHP and A4 by individual baseline treatment strata in the study will be presented in the same manner as the primary endpoint (using 24-hour SDS profile at 24 weeks).
3. 17-OHP and A4 levels at 09:00 as a responder analysis (i.e. the number of subjects achieving results in the optimal range).
4. Changes relative to standard glucocorticoid replacement treatment in body composition (DEXA) (fat mass, lean mass and total bone density) to be measured at all sites except Germany.

7.3 Exploratory Endpoints

1. Partial area under the curve (AUC) of 17-OHP at 15:00-23:00, 23:00-07:00, and 07:00-15:00 (all refer to actual clock time of sampling).
2. The primary endpoint measure will also be presented for the profiles measured at 4 and 12 weeks for the purposes of titration.
3. Changes relative to standard treatment in the following:
    a. Bone markers – serum CTX and osteocalcin (after fasting)
    b. hsCRP
    c. Assessment of glucose and insulin in the morning (after fasting)
    d. Assessment of HbA1c, total testosterone, and PRA in the morning
    e. QoL using SF-36®, MAF, and EQ-5D™
4. Use of glucocorticoids at beginning and end of the study will be presented both as individual glucocorticoids used, and as calculated hydrocortisone equivalents using accepted conversion constants for the calculations.

7.4 Safety Endpoints

1. Routine haematology, biochemistry, physical examination, vital signs, urinalysis, electrocardiogram (ECG).
2. Clinical AEs – particular note of use of sick day rules and Addisonian crises. Under or over-replacement with glucocorticoids will be considered in the efficacy endpoints.
3. Changes relative to the standard treatment in weight, body mass index (BMI), waist circumference, and blood pressure (BP).

8. Study Design

This study is designed as a parallel arm, randomised, open-label study, including dose titration and admissions for four overnight stays for 24-hour endocrine profiles. It will compare the efficacy, safety and tolerability of Chronocort® with standard glucocorticoid replacement therapy in the treatment of CAH over a treatment period of 6 months.

A previous phase II study (a two-part, single cohort, open label multiple dose protocol [DIUR-003]) demonstrated that Chronocort®, when given in a twice a day regimen in subjects with CAH, enables physiological replacement of cortisol, which results in improved control of androgens without increasing glucocorticoid exposure (Mallappa 2015). Chronocort®, in contrast to hydrocortisone IR, achieved a physiological profile. Dosing times for study DIUR-003 were 23:00 hours and 07:00 hours, and these timings will be continued for the present phase III study. Subject reported outcomes were used in study DIUR-003, which are

also to be included in this phase III study. The results gained in the phase II protocol have been used in the design of this phase III study with regard to dosage, endpoint selection and sample size. Additionally, a phase I food effect study has recently been completed, with preliminary results indicating that food may have an effect on the dosing of Chronocort®. Thus in this study 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.

There is a wide variation in standard therapy for this indication. In order to ensure treatment is standardised, the protocol requires that subjects are on a stable glucocorticoid therapy for a minimum of 6 months prior to study participation, and it is this period that will characterise the subjects and their baseline characteristics, and is effectively the run-in period for the study.

Due to the wide variance in standard therapy for this condition, this study has been designed as an open study rather than a blinded study. The randomisation either to Chronocort® or to continue on their original therapy will be stratified with regard to the subject's prior treatment. The number of subjects in the study will be closely monitored via the interactive web response system (IWRS) system until a total of 120 subjects are randomised in the study. This number of subjects provides greater than 95% power, with a 2-sided alpha of 5% to demonstrate a fall in the mean daily unsigned standard deviation SDS of 17-OHP, which is 20% less than that seen in the phase II study.

Dose titration decisions in both treatment groups will be made by an independent blinded physician, blinded to the treatment arm. This will be carried out within 2 weeks of each profiling visit at weeks 4 and 12 using a standard titration algorithm after the subject has been re-admitted for 24-hour profiles that include 17-OHP and A4. The use of an independent blinded physician will minimise bias in the management of subjects in this open study. Each treatment arm will be subject to the same titration rules throughout the study, ensuring that opportunities for optimisation and control of androgens are the same in both groups. It is intended that dose adjustment should optimise control of CAH according to the current standard of care based on subject symptoms and measurement of androgens as is currently recommended for clinical practice.

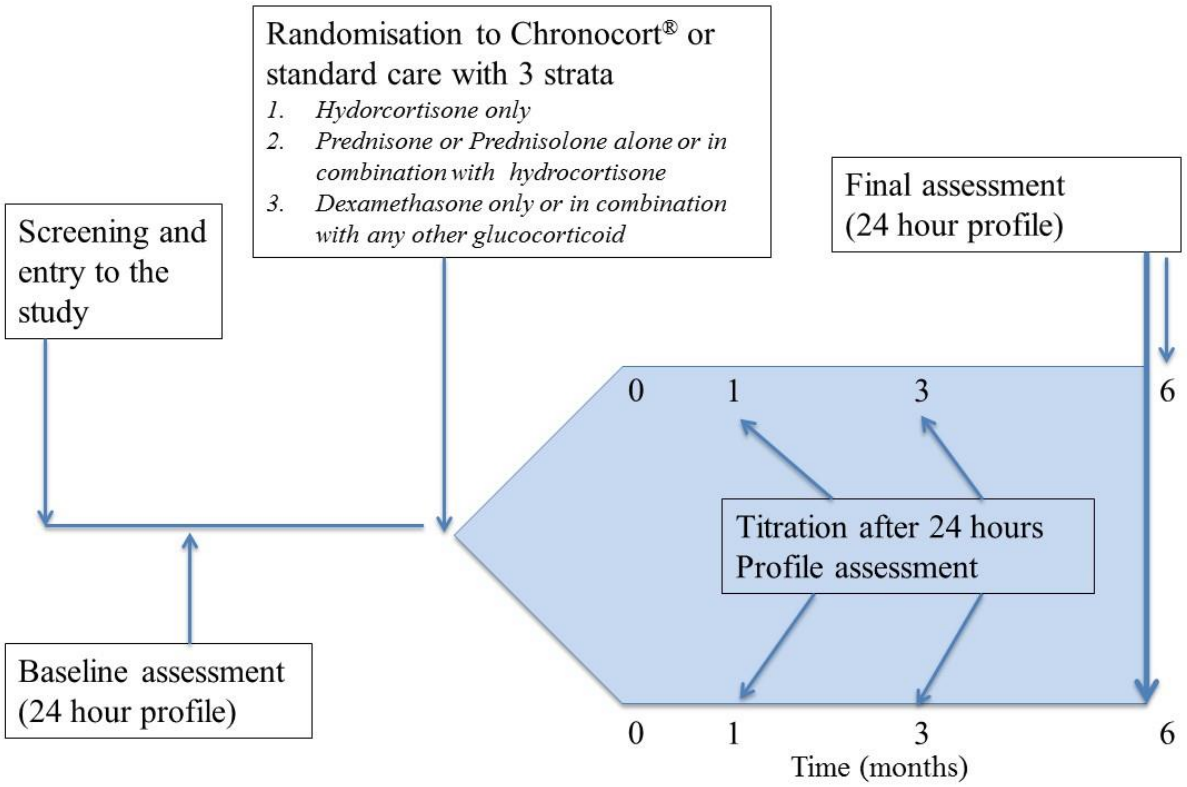
As this is an open study, measures have been taken to minimise any potential bias as follows:

1. Records will be kept of any subjects screened, whether or not they enter the study. This will enable an assessment of the representative nature of the subjects randomised.
2. Randomisation will be carried out by IWRS, stratified by 3 baseline treatment groups according to the subjects current treatment:
    a. hydrocortisone only or
    b. prednisone or prednisolone alone or in combination with hydrocortisone
    c. dexamethasone only or in combination with any other glucorticoid
3. The titration of the subject's dose of study treatment following the hormone profiles at 4 weeks and 12 weeks will be directed by an independent blinded physician, minimising bias in the management of subjects.
4. Care will be taken not to dose adjust for the Chronocort® arm of the study at baseline by selecting the initial dose following randomisation on the equivalent glucocorticoid dose at baseline, rather than basing it on hormone levels or symptoms. By using this method both arms will effectively continue on their baseline glucocorticoid dosage.

5. The primary endpoint is an objective biochemical measure that is not subject to bias in its ascertainment.
6. Efforts will be made to ensure that all subjects remain in the study and are evaluable. Subjects completing the study will become eligible for an open extension study, in which all subjects will be offered Chronocort® (this will be conducted under a separate protocol).
7. The statistical analysis plan (SAP) will be completed before randomisation of the first subject to the study.
8. There will be rigorous monitoring of sites to ensure compliance with all study procedures.
9. Treatment will be allocated using block randomisation. The block size will be determined by an independent statistician and will not be communicated to the study team.

Written informed consent for the study will be obtained from subjects who have been stable on their current treatment for a minimum of 6 months. Subjects will be screened and entered in the study provided they meet the inclusion/exclusion criteria. 120 subjects will be randomised into this study (see Subject Stratification below) to obtain 102 evaluable subjects (individual sites should not recruit more than 25 subjects without first consulting the sponsor).

Figure 2: Overview of DIUR-005 Study Schema



Study Inclusion

Following written informed consent and screening tests (Visit 0), suitable subjects will be called back for the baseline visit. The diagnosis of 21-hydroxylase deficiency and adequacy of the subject's CAH management will be confirmed by examination of prior medical records prior to Visit 1.

Baseline Assessment and Randomisation (2-day visit)

Subjects will be called in for the Baseline Visit (Visit 1) and admitted overnight for a 24-hour endocrine profile whilst remaining on their standard therapy. Subjects will have 17-OHP and A4 measured at 13 time points. On the second morning baseline bloods will be taken together with all safety measures and all secondary endpoint measurements (see Section 11).

After the completion of the baseline profile, the subject will be randomised either to receive Chronocort® or to continue on standard care. 120 subjects will be randomised (see Section 11).

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 prednisone 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) Chronocort® will be given at 23:00 hours (approximately 2/3rd of the total daily dose) and 07:00 hours (approximately 1/3rd of the total daily dose). The first dose of Chronocort® will be taken at 23:00 hours on Day 2 of the baseline visit. Subjects will be asked to write on the pack the dose, date and time they took the first dose of study medication (Chronocort® or standard therapy).

Dose Adjustment

Dose adjustment in both treatment groups will be made, if necessary, within 2 weeks of Visits 2 (4 weeks) and 4 (12 weeks). The decision to change dose will be made by an independent blinded physician but the actual treatment change will be made by the local investigator. The independent blinded physician will determine either that no change is required or that an increase/decrease in the morning/midday/evening medication is needed. In the event that a change in the midday dose is advised for a subject who is receiving Chronocort or in a subject who is receiving twice daily dosing of standard therapy, the local investigator must decide to make this dose change at the most appropriate timepoint in their judgement (morning or evening), in addition to any changes already advised for morning and evening doses, so that the total change advised is accommodated within the day. For each subject, the independent blinded physician will record whether or not a treatment change is required in the electronic case report form (eCRF). The local investigator will be informed so they can make the change to the prescription and the local investigator will document whether or not a change is required in the subject notes, using the eCRF as the source document for this information. All subjects will receive a telephone call to inform them whether or not their dose will change. The local investigator will ensure the subject receives clear instructions in writing (emails are acceptable) following the telephone call. All subjects will receive a further telephone call one week after the first call (whether or not dose adjustment has been recommended) to assess any AEs and reinforce any other protocol requirements.

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. Rationale for any dose adjustment, by both the independent blinded physician and also any changes made by the local investigator, will be recorded in the eCRF. With intercurrent illness, sick day rules apply (see Appendix 4 for an example). In subjects with undetectable androgen

levels at baseline who are on regular medication, caution will be taken over dose reduction so as to avoid the risk of adrenal insufficiency in subjects with a suppressed pituitary-adrenal axis.

Dose adjustment by the independent blinded physician will be based on clinical symptoms using the "signs and symptoms of adrenal insufficiency questionnaire" (Appendix 5) and the measurement of the 17-OHP and A4 profiles. The adrenal insufficiency questionnaire should only be used to determine if symptoms of under or over replacement of glucocorticoids have occurred since the last visit – it should not be used to record AEs due to other causes.

- The independent blinded physician will review the signs and symptoms of adrenal insufficiency questionnaire and if there is evidence the subject is undertreated with glucocorticoid the glucocorticoid dose will not be reduce and if there is evidence of over treatment the glucocorticoid dose will not be increased.

The 5 samples taken between 01:00 and 09:00 will reflect the glucocorticoid dose taken in the evening or last thing at night on standard and Chronocort® therapy and the 5 samples taken between 11:00 and 19:00 will reflect the morning glucocorticoid dose on standard and Chronocort® therapy. Dose adjustments will be considered if 3 or more of the 5 sample times show out of range values for 17-OHP or A4.

For subjects continuing on standard therapy the local investigator can change the daytime and evening doses of the standard therapy (within the limits set by the independent blinded physician) but the timing and the drugs used must not be changed. Dose adjustment will use the lowest dose adjustment available with the specific therapy, so generally for hydrocortisone this will be 5mg, for prednisolone 1mg and dexamethasone 0.25mg.

Where 17-OHP and A4 show inconsistent trends, the A4 parameter will take precedence in directing dose adjustment.

The dose adjustment is to optimise control of CAH according to current standard of care based on subject symptoms and the measurement of androgens as is currently recommended for clinical practice. No other glucocorticoid dose adjustments will be allowed apart from sick day rules. Fludrocortisone dose adjustment will be allowed if medically indicated and will be based on BP measurements and laboratory data (goal supine PRA above the lower limit and <1.5 times upper limit of normal [ULN]).

At 24 weeks, all the baseline tests will be repeated, including the 24-hour profile. All subjects who complete the study may then continue to an open-label extension study where they will be offered Chronocort®, whatever their randomised treatment (to be conducted under a separate protocol).

9. Subject Population

9.1 Number of Subjects and Subject Selection

120 adult subjects will be randomised into this study to account for any dropouts and provide an evaluable dataset of 102 (see Section 11). Individual sites should not recruit more than 25 subjects without first consulting the sponsor. Subjects that are screened and not entered will be documented, along with the reasons for screen failure, and will be included in the database. To

be eligible for enrolment, subjects must comply with the inclusion and exclusion criteria listed in sections 9.2 and 9.3.

9.2 Inclusion Criteria

1. Known CAH due to 21-hydroxylase deficiency (classic CAH) diagnosed in childhood with documented (at any time) elevated 17-OHP and/or A4 and currently treated with hydrocortisone, prednisone, prednisolone or dexamethasone (or a combination of the aforementioned glucocorticoids) on a stable glucocorticoid therapy for a minimum of 6 months.
2. Male or female subjects aged 18 and above.
3. Provision of signed written informed consent.
4. Non-pregnant, non-lactating females who are:
    a. Post menopausal (defined as at least 12 months natural spontaneous amenorrhoea or at least 6 weeks following surgical menopause, i.e. bilateral oophorectomy)
    b. Naturally or surgically sterile (hysterectomy, bilateral oophorectomy, bilateral tubal ligation with surgery at least 6 weeks prior to study initiation)
    c. Of childbearing potential with a negative urinary pregnancy test and using a medically acceptable method of contraception (see Section 11.7 for details)

    Note: females presenting with oligomenorrhoea or amenorrhoea who are aged ≤55 years of age should be considered potentially fertile and therefore, as well as undergoing pregnancy testing like all other female subjects, will be expected to be using an acceptable method of contraception as noted above.
5. PRA less than 1.5 times ULN at screening or within 3 months prior to screening, except in subjects who have been diagnosed with hypertension where the renin is not being used to monitor fludrocortisone replacement.

9.3 Exclusion Criteria

1. Co-morbid condition requiring daily administration of a medication (or consumption of any material) 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 (ALT or AST >2 times ULN).
3. Subjects on regular daily inhaled, topical, nasal or oral steroids for any indication other than CAH.
4. Subjects with any other significant medical or psychiatric conditions that in the opinion of the investigator would preclude participation in the trial.
5. History of malignancy (other than basal cell carcinoma successfully treated >6 months prior to entry into the study).
6. Participation in another clinical trial of an investigational or licensed drug or device within the 3 months prior to inclusion in this study.
7. Subjects with a history of bilateral adrenalectomy.
8. Subjects having previously been exposed to Chronocort®.
9. Subjects who routinely work night shifts and so do not sleep during the usual nighttime hours.
10. Subjects unable to comply with the requirements of the protocol.

10. Study Medication and Administration

10.1 Randomisation and Blinding

There will be a fully stratified randomisation of subjects using an IWRS system. Stratification will be based on subjects' current treatment at the time of entering the study. This is an open-label study so there will be no blinding or unblinding procedures. Subjects will be allocated an identifying number sequentially per site in the following format: Study No./Site No./Screening No. (for example D005/1/001, D005/1/002 etc. for site 1; D005/2/001 etc. for site 2). When the subject is randomised, a separate randomisation number will be allocated, which will be used internally for the purposes of treatment allocation and stratum identification. The screening number will still be used for subject identification purposes, so there will be gaps in subject ID numbers for screen failures.

10.2 Description and Handling of IMPs

The Investigational Medicinal Products (IMP) for this study are:

- Chronocort® (Hydrocortisone Modified Release Capsule). In this study Chronocort® will be supplied in three unit dose strengths of 5mg, 10mg and 20mg per capsule.
- the standard glucocorticoid replacement therapy that the subject is receiving will be used for subjects randomised to the comparator arm

Diurnal Ltd will supply the study sites with adequate bulk study medication of Chronocort® for the entire study period. Diurnal will also supply the standard glucocorticoid replacement therapy used at each site to ensure that subjects remain on the same products throughout the study.

10.2.1 Chronocort® Formulation

Chronocort® is a modified-release formulation of hydrocortisone for oral administration. Chronocort® is available in dose strengths of 5, 10 and 20mg hydrocortisone. The 5mg formulation will be presented in white opaque body/blue opaque cap size 1 hard gelatin capsules, printed with 'CHRONOCORT 5mg' on the capsule body. The 10mg formulation will be presented in white opaque body/green opaque cap size 1 hard gelatin capsules, printed with 'CHRONOCORT 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 'CHRONOCORT 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 pack contains 100 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 1 x 100-count bottle. A treatment pack for each subject randomised to Chronocort® will be assembled by the pharmacy using the required number of clinical packs according to the individual subject prescription. Each dose

strength will be identifiable by the unique colour hard gelatin capsule and product/dose identifier printed on the capsule.

Chronocort® Treatment pack 1 will be dispensed by the study site pharmacy on Day 2 and taken home by the subject. Treatment pack 1 consists of a cardboard carton containing one clinical pack of each dose strength (5, 10 and 20mg Chronocort®), with each pack containing 100 Chronocort® capsules. The initial Chronocort® dose regimen will be determined according to the individual subject prescription, based on the hydrocortisone dose equivalent of the subject's previous therapy, with the hydrocortisone dose calculated as prednisone 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).

Treatment pack 2 (dispensed at Visit 2 after 4 weeks) and Treatment pack 3 (dispensed at Visit 3 after 12 weeks) will be dispensed by the study site pharmacy. Treatment packs 2 and 3 will be assembled based on individual prescribed dosing regimen, including any dose adjustment required.

Chronocort® will be labelled as shown in Appendix 9. The subject number will be written on the study pack by the pharmacist.

Diurnal will also provide appropriate labels for the standard glucocorticoid replacement therapy that the pharmacy can use to label the drugs dispensed to subjects (See Appendix 9). The subject number will be written on the study pack by the pharmacist. The batch numbers of the standard glucocorticoid replacement therapy must be recorded by the pharmacist.

10.2.3 Storage

Chronocort® will be securely stored in the study site pharmacy at a temperature not exceeding 25°C. Subjects dispensed with treatment packs will be advised to store Chronocort® securely in a cool (room temperature) and dry place out of the reach of children. The comparator of standard glucocorticoid replacement treatment will be stored in line with the manufacturer's labelling.

10.2.4 Accountability

Subjects randomised to Chronocort® will return treatment pack 1 to the study team at Visit 2, treatment pack 2 to the study team at Visit 3 and treatment pack 3 to the study team at Visit 4. The study team will count the number of capsules remaining at each of these visits and enter the information in the eCRF, so compliance can be calculated against the treatment and titration prescriptions. At Visits 2 and 3 the study team will transfer empty treatment packs to the returns pharmacy at the site. At Visit 4 the study team will transfer all supplies returned by the subject to the returns pharmacy at the site. All used and unused Chronocort® will be stored at the returns pharmacy 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 within 8 weeks of completion of the study unless otherwise instructed. If a subject is continuing on the follow-on study, they will be consented for this study and undergo the relevant procedures for the first visit and then a separate treatment pack that will provide sufficient capsules to last until the next visit will be dispensed.

Dispensing of the comparator treatment will be in accordance with the site's usual procedure, but used and unused medication must be returned to the study site at each visit and

accountability conducted along similar lines to that detailed above for Chronocort®. Accountability must also be performed at each visit for the safety pack, which should be used in conjunction with the sites "sick day rules". Any use of the medications in the safety pack should be recorded in the eCRF, along with the reason for use.

10.3 Dosage and Administration

Subjects will be randomised on Day 2 of the baseline visit, following the 24-hour endocrine profile and baseline blood tests. Further 24-hour endocrine profiles will be carried out at weeks 4 and 12, and any dose titrations required will be assessed centrally by an independent blinded physician.

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. Subjects will be asked to self-administer the dose of Chronocort® provided at 23:00 hours (approximately 2/3rd of the total daily dose) and 07:00 hours (approximately 1/3rd of the total daily dose) with a small drink of water.

The comparator of standard glucocorticoid replacement treatment will be dosed in line with the site's usual practice.

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" (Appendix 4 for an example). Other dose adjustments will not be allowed, unless the local investigator judges that there is a medical reason to alter the dose, and if so this will be recorded in the subject notes and the eCRF (see also last bullet point below).

- Dose adjustment will be based on clinical symptoms using the "signs and symptoms of adrenal insufficiency questionnaire" (Appendix 5) and the measurement of the 17-OHP, and A4 profile. The adrenal insufficiency questionnaire should only be used to determine if symptoms of under or over replacement of glucocorticoids have occurred since the last visit – it should not be used to record AEs due to other causes.
- Dose adjustments in both treatment groups will be made by an independent blinded physician, according to the instructions provided in Section 8 under the heading "Dose Adjustment"
- Dose adjustment will be made within 2 weeks of visits when biochemical results are reviewed. 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 it is practical to see the subject again in the clinic to tell them of the dose adjustment, this is also acceptable.
- All subjects (whether or not there has been a titration) will receive a telephone call one week after any dose-adjustment, to enquire as to whether there have been any AEs, and reinforce any other protocol requirements.
- The rationale for any dose adjustment, by both the independent blinded physician and also any changes made by the local investigator, will be recorded in the subject's notes and in the 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.

Fludrocortisone dose adjustment will be allowed if medically indicated and will be based on BP measurements and laboratory data (goal supine PRA above the lower limit and <1.5 times ULN).

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 one-week supply of 20 mg oral hydrocortisone (in 10mg tablets to allow dosage of up to 20mg 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)

Diurnal will also provide appropriate labels for the safety pack that the pharmacy can use to label the drugs dispensed to subjects (See Appendix 9). The subject number will be written on the safety pack by the pharmacist.

Subjects will continue to take Chronocort® twice daily or standard glucocorticoid replacement therapy at the usual dosing regimen 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 pack.

10.6 Permitted Concomitant Medications/Treatments

The subjects must be instructed that no additional medication will be 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(s). Medication for sick days does not require authorisation. All concomitant medications and treatments will be recorded in the subject's eCRF.

Existing or previous treatments for CAH (last 6 months) will be recorded separately in the eCRF from routine medication as part of the subject's medical history.

11 Study Procedures

The study procedures to be conducted for each subject enrolled in the study are summarised in Table 1. Subjects will be screened up to 2 weeks prior to the baseline visit. Written informed consent must be taken prior to any study related procedures. Subjects will continue on their regular medication for CAH until they are randomised at Visit 1.2 (Day 2 of the baseline visit).

11.1 Visit Schedule

At any visit, if multiple assessments are being conducted, then the measurements should be made in the following order: demographic data and medical history, AEs, signs and symptoms of adrenal insufficiency, waist circumference and weight, physical examination, vital signs, ECG, urinalysis, blood tests, and then dosing.

11.1.1 Visit 0 (Screening Visit)

At Dutch centres only, potential subjects will be approached by their own treating physician. If the treating physician is also the investigator the subject information sheet can be provided immediately. If this is not the case then the treating physician will ask the patient for permission for the investigator to approach them about study participation.

Once subjects have consented to the study, the following assessments will be carried out on all patients and recorded:

- All inclusion and exclusion criteria checked
- Demographic data
- Medical history taken, together with information on concomitant medications
- CAH medication will be recorded separately from other concomitant medications
- AEs
- Signs and symptoms of adrenal insufficiency
- Waist circumference will be measured, together with height and weight, and the BMI calculated
- A physical examination
- Vital signs (BP, heart rate [HR], respiratory rate and body temperature)
- Urine sample for urinalysis (including urine pregnancy test in females of childbearing potential)
- Blood samples will be taken for routine biochemistry and haematology
- Blood sample taken for genotyping if possible, unless genotyping has previously been performed, in which case the patient will be asked for their permission for this information to be taken from their medical records
- Sample taken for PRA after the subject has been supine for 30 minutes (if this has not been done and documented in the subject records during the previous 3 months)

If subjects meets all the inclusion/exclusion criteria they will be asked to attend Visit 1 in a maximum of 3 weeks' (21 days) time. They will be asked to inform the investigator of the time and dose of glucocorticoid taken on the morning they are due to attend for Visit 1.

11.1.2 Visit 1 (Baseline Visit)

Day 1

Subjects will attend the clinic on the morning of Day 1 and must be prepared for an overnight stay. The following assessments will be carried out and recorded:

- Check of inclusion/exclusion criteria
- Subjects will asked about any AEs and concomitant medications changes since the last visit
- Record the time and dose of the last glucocorticoid medication taken prior to attending for this visit
- An abbreviated physical examination, if indicated by AEs
- Vital signs
- DEXA scan (except Germany) – this needs to be performed at Baseline Visit or within 2 weeks prior to Baseline Visit, after inclusion/exclusion criteria are checked

If the subject meets all the study criteria and they have been receiving their normal medication for the previous 5 days (i.e. sick days rules have not been applied in the preceding 5 days) they

will then be admitted to the clinic for their first 24-hour endocrine profile (17-OHP and A4). If sick day rules have been applied in the previous 5 days then the 24-hour profiling should be postponed until subjects have been receiving their normal medication for 5 days. The 24-hour endocrine profile sampling will commence at 15:00 hours on Day 1 followed by 2-hourly serum samples, hence 13 samples will be taken; 15:00, 17:00, 19:00, 21:00, 23:00, 01:00 (Day 2), 03:00, 05:00, 07:00, 09:00, 11:00, 13:00, 15:00h. These blood samples are to be taken within ±10 minutes of the stated timepoints.

Day 2

On the second morning of Visit 1, the following assessments will be conducted (the fasting samples to be taken at 07:00hrs):

- AEs
- Signs and symptoms of adrenal insufficiency
- The following questionnaires will be completed: MAF, SF-36® and EQ-5D™
- Waist circumference will be measured, together with weight, and the BMI calculated
- Vital signs
- ECG
- Urinalysis (including urine pregnancy test for females of childbearing age)
- Blood sample for fasting osteocalcin and CTX, insulin, glucose, HbA1c, lipids, hsCRP and total testosterone
- Blood samples will be taken for routine biochemistry and haematology
- Sample taken for PRA after the subject has been supine for 30 minutes

Following these procedures, the subject will be randomised to Chronocort® or to continue on standard care. Randomisation will be stratified by baseline treatment (see Section 8). Sufficient medication will be dispensed to the subject for the next 4 weeks. Initial dose setting at the start of Chronocort® treatment will be made on hydrocortisone dose equivalent of baseline therapy (see Section 8).

Study drug will be dispensed and the subject will be asked to attend the clinic for Visit 2 in 4 weeks' time. Subjects will be discharged following the end of the endocrine profile. Subjects will be asked to record the date, exact time and amount of the first dose of study medication on the drug packaging. The first dose of Chronocort® should be taken at approximately 23:00 hours on an empty stomach at least 2 hours after the last meal of the day. The first dose of standard therapy should be taken in accordance with the instructions from the investigator.

Table 1: Summary of Study Procedures

	Visit 0 Screening up to 3 wks	Visit 1 Baseline		Visit 2 - 4 weeks ±3days		Telephone (up to V2 D2+2wks)	1 wk after T2.1	Visit 3 - 12 weeks ±3days		Telephone (up to V3 D2+2wks)	1 wk after T3.1	Visit 4 - 24 weeks ±3days or early termination visit[11]		Telephone 30 days after V4[12]
	Screening	V1 Day 1	V1 Day 2	V2 Day 1	V2 Day 2	Call T2.1[10]	Call T2.2	V3 Day 1	V3 Day 2	Call T3.1[10]	Call T3.2	V4 Day 1	V4 Day 2	Call T4
Consent[1]	X													
Medical history	X													
Concomitant medications	X	X		X				X				X		
Demographic data	X													
Inclusion/exclusion criteria	X	X[9]												
Physical examination	X												X	
Abbreviated physical examination (If indicated by AEs)		X		X				X				X		
Vital signs (blood pressure, heart rate, respiratory rate, temperature)[2]	X	X	X	X	X			X	X			X	X	
17-OHP (24-hour hormone profile)[3]		X (x13)		X (x13)				X (x13)				X (x13)		
A4 (24-hour hormone profile)[3]		X (x13)		X (x13)				X (x13)				X (x13)		
Haematology	X		X		X				X				X	
Biochemistry	X		X		X				X				X	
Urinalysis	X		X		X				X				X	
Urine pregnancy test (females)	X		X		X				X				X	
Plasma renin (within last 3 months)[4]	X[4]		X		X				X				X	
Total testosterone			X		X				X				X	
Fasting osteocalcin, CTX, lipids, hsCRP			X		X				X				X	
ECG			X		X				X				X	
DEXA (up to 2 weeks before baseline)[5]	X												X	
Fasting insulin & glucose			X		X				X				X	
HbA1c			X		X				X				X	
Genotyping[6]	X													
QoL (MAF, SF-360®, EQ-5D™)			X										X	
Signs & symptoms of adrenal insufficiency	X		X		X				X				X	
Height, waist circumference, weight[7]	X		X		X				X				X	
Randomisation			X											
Adverse events	X	X		X		X	X	X		X	X	X		X
Dispense study drug			X		X				X					
Dose setting/adjustment[8]			Set dose			Adjust dose				Adjust dose				
Record the time and dose of last glucocorticoid medication taken prior to attending for this visit		X		X				X				X		
Telephone contact (all subjects)						Confirm dose	X			Confirm dose	X			X
Compliance					X				X				X	

Notes:

1 Consent must be obtained prior to any study related procedures, including a DEXA scan (DEXA to be done everywhere except Germany)

2 Vital signs (blood pressure, heart rate, temperature)

3 If the subject has been receiving their normal medication for the previous 5 days (i.e. sick days rules have not been applied in the preceding 5 days) they will be admitted to the clinic for 24 hour endocrine profile (17-OHP and A4). If sick day rules have been applied in the previous 5 days then the 24-hour profiling should be postponed until subjects have been receiving their normal medication for 5 days. Samples to be taken at 15:00, 17:00, 19:00, 21:00, 23:00, 01:00, 03:00, 05:00, 07:00, 09:00, 11:00, 13:00, 15:00h. Exact times of sampling to be recorded in eCRF; samples to be taken within ±10 minutes of stated timepoints. If dosing is done at the same timepoints as the blood sampling, the blood sampling should be conducted first.

4 Plasma renin must be done at screening unless this has been done within 3 months of screening and documented in the patient notes.

5 DEXA is part of Baseline Visit 1 (except for Germany) but can be done up to 2 wks prior to baseline if scheduling difficult; consent must be taken prior to this study related procedure (applies only to Screening period).

6 Blood sample taken for genotyping, if possible, unless genotyping has previously been performed in which case the patient will be asked for their permission for this information to be taken from their medical records

7 Height, waist circumference & weight at first visit, only waist circumference & weight measuremed thereafter

8 First dose of study medication to be taken in evening of Baseline Visit 1 Day 2; dose adjustment must be done within 2 weeks of Visits 2 and 3.

9 Limited review of inclusion/exclusion criteria

10 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.

11 If the subject discontinues from the study early then as many assessments as possible should be completed

12 Only for subjects who do not enter the extension study

11.1.3 Visit 2 (Week 4)

Day 1

Subjects will attend the clinic on the morning of Day 1 and must be prepared for an overnight stay. The following assessments will be carried out and recorded:

- Subjects will asked about any AEs and concomitant medications changes since the last visit
- An abbreviated physical examination, if indicated by AEs
- Record the time and dose of the last glucocorticoid medication taken prior to attending for this visit
- Vital signs

If the subject has been receiving their normal medication for the previous 5 days (i.e. sick days rules have not been applied in the preceding 5 days) they will be admitted to the clinic for their second 24-hour endocrine profile (17-OHP and A4). If sick day rules have been applied in the previous 5 days then the 24-hour profiling should be postponed until subjects have been receiving their normal medication for 5 days. The 24-hour endocrine profile sampling will commence at 15:00h on Day 1 followed by 2-hourly serum samples, hence 13 samples will be taken; 15:00, 17:00, 19:00, 21:00, 23:00, 01:00 (Day 2), 03:00, 05:00, 07:00, 09:00, 11:00, 13:00, 15:00h. These blood samples are to be taken within ±10 minutes of the stated timepoints. If dosing needs to be conducted at the same timepoints as the blood sampling, the blood sampling should be conducted first before the dose of study medication is given.

Day 2

On the second morning of Visit 1, the following assessments will be conducted (the blood samples to be taken at 07:00 hrs before the morning dose of study medication):

- AEs
- Signs and symptoms of adrenal insufficiency
- Waist circumference will be measured, together with weight, and the BMI calculated.
- Vital signs
- ECG
- Urinalysis (including urine pregnancy test for females of childbearing age)
- Blood samples will be taken for routine haematology and biochemistry
- Blood sample taken for fasting osteocalcin and CTX, insulin, glucose, HbA1c, lipids, hsCRP and total testosterone
- PRA after the subject has been supine for 30 minutes

The subject will return all of their medication (Chronocort® and the comparator), including any unused medication, and the number of tablets 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.

Sufficient medication will be dispensed for the next 8 weeks, including an extra amount in case titration is required and the subject will be asked to attend the clinic for Visit 3 in 8 weeks' time. Subjects will be discharged following the end of the endocrine profile. Subjects will be asked to record the date, exact time and amount of the first dose of study medication on the drug packaging. The dose of Chronocort® should be taken at approximately 23:00 hours on an

empty stomach at least 2 hours after the last meal of the day. The first dose of standard therapy should be taken in accordance with the instructions from the investigator.

11.1.4 Telephone call T2.1

Following the assessment of the 4 week 24-hour hormone profile and subject's symptoms and androgen levels, a decision will be made by the independent blinded physician as to whether to adjust the dose for the subject. The actual dose adjustment will be made by the investigator, within 2 weeks of Visit 2. All subjects will be contacted by telephone, whether or not a dose adjustment is to be made. 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.

11.1.5 Telephone call T2.2

All subjects, whether or not they have received a dose adjustment, will receive a telephone call a week after the dose-adjustment call, to enquire as to whether there have been any AEs, and to reinforce any other protocol requirements. Any AEs will be recorded in the eCRF.

11.1.6 Visit 3 (Week 12)

Day 1

Subjects will attend the clinic on the morning of Day 1 and must be prepared for an overnight stay. The following assessments will be carried out and recorded;

- Subjects will asked about any AEs and concomitant medications changes since the last visit
- Record the time and dose of the last glucocorticoid medication taken prior to attending for this visit
- An abbreviated physical examination, if indicated by AEs
- Vital signs

If the subject has been receiving their normal medication for the previous 5 days (i.e. sick days rules have not been applied in the preceding 5 days) they will be admitted to the clinic for their third 24-hour endocrine profile (17-OHP and A4). If sick day rules have been applied in the previous 5 days then the 24-hour profiling should be postponed until subjects have been receiving their normal medication for 5 days. The 24-hour endocrine profile sampling will commence at 15:00 hours on Day 1 followed by 2-hourly serum samples, hence 13 samples will be taken; 15:00, 17:00, 19:00, 21:00, 23:00, 01:00 (Day 2), 03:00, 05:00, 07:00, 09:00, 11:00, 13:00, 15:00 hours. These blood samples are to be taken within ±10 minutes of the stated timepoints. If dosing needs to be conducted at the same timepoints as the blood sampling, the blood sampling should be conducted first before the dose of study medication is given.

Day 2

On the second morning of Visit 3, the following assessments will be conducted (the blood samples to be taken at 07:00 hrs before the morning dose of study medication):

- AEs
- Signs and symptoms of adrenal insufficiency
- Waist circumference will be measured, together with weight, and the BMI calculated Vital signs

- ECG
- Urinalysis (including urine pregnancy test for females of childbearing age)
- Blood samples will be taken for routine haematology and biochemistry
- Blood sample for fasting osteocalcin and CTX, insulin, glucose, HbA1c, lipids, hsCRP and total testosterone
- PRA after the subject has been supine for 30 minutes

The subject will return their medication (Treatment Pack 2 for subjects randomised to Chronocort®) and the number of capsules counted and recorded in the eCRF by the study team so compliance can be calculated (for both Chronocort® and the comparator). The safety pack should also be returned and checked, with any rescue medication use being recorded.

Following the above procedures, subjects will be dispensed sufficient mediation for the next 12 weeks, including an amount in case titration is required (treatment pack 3 for subjects taking Chronocort®). Subjects will be asked to attend the clinic for Visit 4 in 12 weeks' time. Subjects will be asked to record the date, exact time and amount of the first dose of study medication on the drug packaging. The first dose of Chronocort® should be taken at approximately 23:00 hours on an empty stomach at least 2 hours after the last meal of the day. The first dose of standard therapy should be taken in accordance with the instructions from the investigator.

11.1.7 Telephone call T3.1

This telephone call will be the same as for telephone call T2.1 above. All subjects will be contacted, whether or not titration is necessary. Subjects will be asked about any AEs at this call and any AEs reported will be recorded in the eCRF.

11.1.8 Telephone call T3.2

This telephone call will be the same as for telephone call T2.2 above. All subjects will be contacted irrespective of whether titration has taken place. Subjects will be asked about any AEs at this call and any AEs reported will be recorded in the eCRF.

11.1.9 Visit 4 (Week 24) or early termination visit

Day 1

Subjects will attend the clinic on the morning of Day 1 and must be prepared for an overnight stay. The following assessments will be carried out and recorded;

- Subjects will asked about any AEs and concomitant medications changes since the last visit
- An abbreviated physical examination, if indicated by AEs
- Record the time and dose of the last glucocorticoid medication taken prior to attending for this visit
- Vital signs

If the subject has been receiving their normal medication for the previous 5 days (i.e. sick days rules have not been applied in the preceding 5 days) they will be admitted to the clinic for their fourth 24-hour endocrine profile (17-OHP and A4). If sick day rules have been applied in the previous 5 days then the 24-hour profiling should be postponed until subjects have been receiving their normal medication for 5 days. The 24-hour endocrine profile sampling will commence at 15:00 hours on Day 1 followed by 2-hourly serum samples, hence 13 samples will be taken; 15:00, 17:00, 19:00, 21:00, 23:00, 01:00 (Day 2), 03:00, 05:00, 07:00, 09:00,

11:00, 13:00, 15:00 hours. These blood samples are to be taken within ±10 minutes of the stated timepoints. If dosing needs to be conducted at the same timepoints as the blood sampling, the blood sampling should be conducted first before the dose of study medication is given.

Day 2

On the second morning of Visit 4, the following will assessments will be conducted (the blood samples to be taken at 07:00 hrs before the morning dose of study medication):

- AEs
- Signs and symptoms of adrenal insufficiency
- Waist circumference will be measured, together with weight, and the BMI calculated
- The following questionnaires will be completed: MAF, SF-36® and EQ-5D™
- A full physical examination
- Vital signs
- ECG
- Urinalysis (including urine pregnancy test for females of childbearing age)
- Blood sample for fasting osteocalcin and CTX, insulin, glucose, HbA1c, lipids, hsCRP and total testosterone
- Blood samples will be taken for routine biochemistry and haematology
- PRA after the subject has been supine for 30 minutes
- DEXA scan at all sites except in Germany (this can be performed within 2 weeks of Visit 4)

The subject will return their medication (treatment pack 3 for subjects randomised to Chronocort®) and the number of capsules counted and recorded in the eCRF by the study team so compliance can be calculated (for both Chronocort® and the comparator). The safety pack should also be returned and checked, with any rescue medication use being recorded. An appointment will be made for the 30-day follow-up telephone call.

If the subject has completed the 24-week study period, they will then be eligible to take part in the extension study.

If the subject discontinues from the study early then as many of the above assessments as possible should be completed. Subjects who discontinue from the study early are not eligible to take part in the extension study.

11.1.10Telephone call T4

If the subject does not enter into the extension study then they will receive a telephone call 30 days following completion of Visit 4 in which they will be asked about AEs. If the subject enters the extension study then any AEs occurring between the two studies will be collected as part of the entry procedures for the extension study.

11.1.11Unscheduled Visits or telephone calls

If an unscheduled visit is required, e.g. to follow up on an AE, then the details should be recorded in the eCRF, along with the results of any tests carried out. If laboratory results are needed urgently these can be processed at the local laboratory. Additional telephone calls may also be required inbetween 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**
  - BP, HR, 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 biochemistry and haematology tests (see Appendix 2)
  - measurement of PRA after the subject has been supine for 30 minutes (not required at the screening visit if this has been done and documented in the subject's records during the previous 3 months; otherwise required at all visits)
  - genotyping, unless genotyping has previously been performed, in which case the patient will be asked for their permission for this information to be taken from their medical records
  - 24-hour endocring profiles

To minimise the risk of anaemia associated with the withdrawal of multiple blood samples for laboratory testing (as seen in DIUR-003), the planned total blood volume to be withdrawn during this study will be limited to a maximum of 427mL. The date and time of collection of all blood and urine samples will be recorded in the subject's eCRF. With regard to the profile sampling, a draw window of ±10 minutes from the prescribed timepoints for blood sampling is permitted, but exact times of sampling must be recorded in the source documents and eCRF. Copies of laboratory accreditation certificates and reference ranges will be provided prior to the analysis of the first subject sample.

On Day 2 of each overnight stay, blood samples will be taken at 07:00 hrs before the morning dose of study medication, then the study medication will be given at least 1 hour before breakfast. These samples are for fasting osteocalcin, CTX, insulin, glucose, lipids, HbA1c, hsCRP, and total testosterone. Subjects will fast from 23:00 to 0700 hour on Day 1 of each visit until this sample is taken.

All analyses, with the exception of the genotyping, will be carried out by the central laboratory, [redacted]. Genotyping will be carried out by a specialist laboratory. By specific exception agreed with the Sponsor for logistical reasons, sites may use a local laboratory to determine inclusion and exclusion criteria. This must be agreed with the Sponsor prior to the start of the study. In addition, 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**
  Urine samples will be tested for the following;
  - Pregnancy test in females of childbearing potential (this test will be done locally at the site)
  - Protein, glucose, specific gravity, ketones, urobilinogen, bilirubin, pH, blood

- **DEXA scans (except Germany)**
  To be performed up to 2 weeks prior to the baseline visit (Visit 1) and again within 2 weeks of Visit 4. 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 after breakfast on the day when the subject is not fasted and completed in a quiet environment. To be administered at baseline and Visit 4.

- **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 and recorded in the eCRF.

- **ECG**
  ECG will be performed and reported locally, and the result recorded in the eCRF.

- **Physical examination**
  A full physical examination to assess the subject's general appearance and overall health will be carried out at screening 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 in the eCRF. At the other visits, an abbreviated physical examination will be conducted if indicated by AEs, noting any changes from the screening assessment. Any abnormal findings will be recorded on 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 4 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 (as per Visit 4). 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 primary endpoint)
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 violation, 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.

If a subject withdraws from the study they will not be eligible to participate in the extension study.

11.6 Replacement of Withdrawn Subjects

120 subjects will be randomised to account for withdrawals anticipated during the course of the study and to provide 102 evaluable subjects.

11.7 Additional Information for the Study Population

Females presenting with oligomenorrhoea or amenorrhoea who are aged ≤55 years of age should be considered potentially fertile and therefore, as well as undergoing pregnancy testing like all other female subjects, will be expected to be using an acceptable method of contraception as noted below.

Acceptable forms of contraception include:

1. Established use of oral, injected or implanted hormonal methods of contraception (including oestrogen-containing products) – note that use of these methods of contraception must remain the same throughout the study in both nature and dose. The type of contraception should have been ongoing for ≥90 days prior to the study and at least 7 days after the final dose. If <90 days prior to the study, additional use of a double barrier method until 90 days is reached is required.
2. Placement of an intrauterine device (IUD) or intrauterine system (IUS).
3. Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository. The following should be noted:
    - Failure rates indicate that, when used alone, the diaphragm and condom are **not** highly effective forms of contraception. Therefore the use of additional spermicides does confer additional theoretical contraceptive protection.
    - However, spermicides alone are inefficient at preventing pregnancy when the whole ejaculate is spilled. **Therefore, spermicides are not a barrier method of contraception and should not be used alone.**

4. Male sterilisation (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). [For female subjects on the study, the vasectomised male partner should be the sole partner for that subject].
5. True abstinence: When this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence, such as calendar, ovulation, symptothermal, post ovulation methods, and withdrawal are not acceptable methods of contraception

11.8 Completion of the Study

The study will be completed when all subjects have completed the last visit or telephone call of this study.

11.9 Subject Payment Schedule

Reasonable subject travel costs will be reimbursed. Where appropriate, costs for overnight accommodation prior to clinic admittance will be reimbursed, and in some cases a compensation or inconvenience payment may be made to subjects.

11.10 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®.

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 phone call T4 (30 days ± 3 days) following the last visit or, if applicable, the Early Withdrawal visit. Any ongoing AEs post study will be followed to resolution or stabilisation if resolution is not expected. Only treatment emergent AEs 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 it returns to the baseline condition or becomes stable with no further change 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 equally for both study treatments, 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 ECG findings) 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 (note that both Chronocort® and the standard glucocorticoid replacement therapy used in the comparator arm are considered IMPs in this study):

- Not related
- Related to the IMP
- Related to sick day medication
- Related to an interaction between IMP and sick day medication
- Related to either IMP or sick day medication

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

Appendix 3 provides a comprehensive list of events that are anticipated to occur in the targeted study entry population of subjects with congenital adrenal hyperplasia when disease treatment is not optimum. In general, if events as listed in Appendix 3 occur and are considered serious, they will not be reported to regulatory authorities in an expedited safety report since causality will likely be due to the underlying medical condition, rather than to study drug. 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 Investigator Brochure or is not listed at the specificity or severity that has been observed. "Unexpected," as used in this definition, also refers to AEs that are mentioned in the Investigator Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

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 in the eCRF. Any SAE that occurs between administration of the first dose of either of the study treatments and 30 days after the last dose of the study treatments 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. 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 ethics committee/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 physician, [redacted] and to [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 should 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 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 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 Contract Research Organisation (CRO), as necessary, to Regulatory Authorities and ethics committees/IRB (the latter may be through the local investigator, as required by local regulations).

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 adverse reaction, 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 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 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 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 Pharmacovigilance 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 primary endpoint). The event must be reported to the sponsor immediately upon receipt of information by the study staff. 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 Data Safety Management Board (DSMB) will meet on a regular basis during the study in order to review safety data. The DSMB will meet several times during the study, and operate in accordance with a charter, which is a separate document.

13 Statistical Considerations

A detailed and comprehensive SAP will be prepared and signed-off before the first subject has been randomised. 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.

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.

All efficacy variables, vital signs and laboratory assessments, together with their changes from baseline, will be summarised by treatment group (Chronocort®, standard therapy), stratum

(previous stable therapy: hydrocortisone only, prednisone or prednisolone with hydrocortisone [but not dexamethasone], dexamethasone alone or in combination with either prednisolone, prednisone or hydrocortisone) and timepoint.

Baseline and demographic data will be summarised by treatment group and stratum. Shift tables from baseline will be provided for vital signs and laboratory assessments.

Data on dose changes indicated by the independent blinded physician, non-implemented changes and reasons for non-implementation will be presented descriptively by treatment group.

Where appropriate, graphical displays of variables assessed serially over time may be presented.

The summary tables and figures will be supported by full subject listings.

13.1.2 Hypothesis Testing and Confidence Intervals

All significance probabilities will be reported as two tailed. Confidence intervals will be reported as 95% two-sided.

13.1.3 Comparison of Groups

In general, continuous variables will be compared across treatment groups using a Normal analysis of covariance (ANCOVA) linear model including pre-baseline standard therapy and, if appropriate, the baseline assessment of the variable as covariates in the model. In the case of change-from-baseline variables, baseline will always be included as a covariate.

Binary variables, such as response, will be compared using logistic regression with adjustment for covariates as in the continuous data case.

13.1.4 Missing Outcome Data

Missing 17-OHP and A4 values (including those considered missing due to being taken outside the permitted time window) within the 24-hour hormone profile will be imputed by linear interpolation of the two closest non-missing measurements to the scheduled missing time point (including out-of-window measurements). In the event that several values are missing from a single profile, a decision will be made about the validity of the whole profile will be made at the Data Review Meeting on a case-by-case basis (see Section 13.10)

Subjects who withdraw from the study will be assessed on the basis of the latest available 24-hour profile. This is a conservative procedure as subjects enter the study already receiving a suitable dose of their standard therapy.

Exploratory and sensitivity analyses will be performed to assess the effect of any missing data on the efficacy conclusions.

13.2 Analysis Sets

The safety analysis set comprises all subjects who were randomised into the study and who subsequently received at least one dose of Chronocort® or standard therapy.

The full analysis set comprises all subjects who were randomised into the study, who received at least one dose of Chronocort® or standard therapy, and who have at least one post-randomisation 17-OHP 24-hour hormone profile.

The efficacy evaluable analysis set comprises all subjects who were randomised into the study, who received at least one dose of Chronocort® or standard therapy, and who have a week 24 17-OHP 24-hour hormone profile, and who have no major protocol violations.

The efficacy evaluable analysis set is the primary analysis set for the evaluation of efficacy. The final determination of the membership of analysis sets will be made at a data review meeting convened by the sponsor before database lock.

13.3 Efficacy and Safety Variables

13.3.1 Definitions

Standard Deviation Score
The SDS is the absolute (unsigned) number of standard deviations above or below the average of the lower and upper limit of normal, with the value of the limits and standard deviation – which may depend on age and gender – being obtained from the laboratory and reference range.

Mean over a 24-hour SDS profile
The mean over a 24-hour profile is the arithmetic mean over all the 24-hour SDS with the first and last observations weighted one half relative to intermediate observations (this definition is equivalent to a normalised AUC calculated by the trapezoidal rule).

13.3.2 Primary Efficacy Variable

The primary efficacy variable is the natural logarithm of the mean over the 24-hour hormonal profile of the SDS for the natural logarithm of 17-OHP.

13.3.3 Secondary Efficacy Variables

The secondary efficacy variables are:

1. The change from baseline to 24 weeks of the mean of the 24-hour SDS profile for A4 (calculated in the same way as the primary endpoint).
2. The presentation of 17-OHP and A4 by individual baseline treatment strata in the study will be presented in the same manner as the primary endpoint (using 24-hour SDS profile at 24 weeks).
3. 17-OHP and A4 levels at 09:00 as a responder analysis (i.e. the number of subjects achieving results in the optimal range).
4. Changes relative to standard treatment in body composition (DEXA) (fat mass, lean mass and total bone density) to be measured at all sites except Germany.

13.3.4 Exploratory Efficacy Variables

The exploratory efficacy variables are:

1. The natural logarithm of the means over the partial profiles of 17-OHP at 15:00-23:00, 23:00-07:00, and 07:00-15:00 (all refer to actual clock time of sampling).
2. The primary endpoint measure will also be presented for the profiles measured at 4 and 12 weeks for the purposes of titration.
3. Changes relative to standard treatment in the following:
   a. Bone markers – serum CTX and osteocalcin

b. hsCRP
c. Assessment of glucose and insulin morning and evening (after fasting), HbA1c, total testosterone, and PRA
d. QoL using SF-36®, MAF, and EQ-5D™

5. Use of glucocorticoids at beginning and end of the study will be presented both as individual glucocorticoids used, and as calculated hydrocortisone equivalents using accepted conversion constants for the calculations.

13.3.5 Safety Variables

The safety variables are:

1. weight, BMI and waist circumference
2. routine haematology and clinical chemistry
3. physical examination
4. vital signs
5. urinalysis
6. ECG
7. the incidence, nature, severity, relatedness, duration, outcome and seriousness of treatment emergent AEs
8. the incidence, nature, severity, relatedness, duration, outcome and seriousness of 'sick days' and Addisionian crises.

13.4 Analysis of the Conduct of the Study

Data concerning the conduct of the study (e.g. allocation to analysis sets, inclusion/exclusion criteria, subject disposition/withdrawals, compliance, protocol deviations, study termination/duration) will be listed and summarised descriptively. Details will be described in the SAP.

Protocol Violations/Deviations

As will be described in the SAP, following trial completion, but prior to database lock, any/all protocol deviations will be reviewed and classified as either ‘minor’ (unlikely to appreciably affect trial outcomes) or ‘major’ (likely to affect outcomes) and this classification will be utilised to define the various study populations for analysis purposes.

13.5 Demographic and other baseline characteristics

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

13.6 Efficacy Analyses

13.6.1 Primary Efficacy Analysis

The primary efficacy analysis is the comparison of the mean change from baseline to 24 weeks in the primary efficacy variable (natural logarithm of the mean over the 24-hour SDS profile for the natural logarithm of 17-OHP) between the Chronocort® treatment group and the standard therapy treatment group within the efficacy evaluable analysis set.

This is the primary efficacy analysis for this study. All other analyses of this outcome variable and all analyses of other efficacy variables are secondary or exploratory analyses.

13.6.2 Secondary Efficacy Analyses

The secondary efficacy analyses are:

1. The primary analysis repeated for A4.
2. The above analyses repeated within each pre-baseline treatment stratum.
3. The comparison of the frequency of the 17-OHP and A4 09:00 responders at 24-weeks (i.e. the number of subjects achieving results in the optimal range).
4. Changes relative to standard treatment in body composition (DEXA) (fat mass, lean mass and total bone density) to be measured at all sites except Germany.
5. The above analyses repeated in the full analysis set.

13.6.3 Exploratory Efficacy Analyses

1. Partial AUCs of 17-OHP at 15:00-23:00, 23:00-07:00, and 07:00-15:00 (all refer to actual clock time of sampling).
2. The primary endpoint measure will also be presented for the profiles measured at 4 weeks and 12 weeks for the purposes of titration.
3. Changes relative to standard treatment in the following:
    a. Bone markers – serum CTX and osteocalcin
    b. hsCRP
    c. Assessment of glucose and insulin morning and evening (after fasting), HbA1c, total testosterone, and PRA
    d. QoL using SF-36®, MAF, and EQ-5D™.
4. The comparison of the dose of individual glucocorticoids used, and as calculated hydrocortisone equivalents, and its change from baseline at 24-weeks.

13.7 Safety Analysis

Safety variables, will be listed and summarised by treatment, stratum and timepoint.

The nature, severity, relatedness, duration, outcome and seriousness and outcome of all AEs will be listed. The subject incidence of treatment emergent AEs will be tabulated by system organ class, preferred term, severity and relatedness. Tables will be provided of AEs of special interest, SAEs, SUSARs, AEs leading to withdrawal and fatal AEs.

Shift tables will be presented for laboratory variables and vital signs. Abnormal findings on physical examination and from ECG will be tabulated. Listings of laboratory data, vital signs, physical examination and ECG will have abnormal findings marked, together with an indication of whether or not that finding was clinically significant.

The versions of the following international dictionaries current at the time of study conduct will be used for medical coding:

- Diagnoses: MedDRA
- Medications: WHO Drug Dictionary including ATC classification
- Adverse events: MedDRA

13.8 Power and Sample Size Considerations

A sample size of 102 subjects provides greater than 95% power and 2-sided alpha 5% to demonstrate a fall in the logarithm of the mean daily unsigned standard deviation score of 17-OHP relative to the standard glucocorticoid replacement therapy group. It is assumed that (i) the mean fall in the Chronocort® group will be the same (0.78) as that observed in the phase

II study (DIUR-003) (ii) the mean fall in the standard therapy group will be 0.2 (approximately 25% of the Chronocort® phase II study fall) and (iii) the standard deviation of the fall (0.681) is that seen in the phase II study. The study is powered to ensure that there can be a reasonable description of the comparison of Chronocort® with a variety of standard therapies. 120 subjects will be randomised to this study which will account for an inevaluability rate of 15%. Individual sites should not recruit more than 25 subjects without first consulting the sponsor.

13.9 Exploratory Analyses

Additional exploratory and sensitivity analyses may include, but are not limited to:

- an assessment of the efficacy results in subgroups;
- an assessment of the effect of missing data on the efficacy conclusions;
- an assessment of the effect of baseline variables on efficacy
- a comparison between the treatment groups of the number of direction of dose changes made during the study period.

Any exploratory analyses not specified in the SAP must be clearly described as such in the clinical study report.

13.10 Data Review Meeting

The sponsor will convene a Data Review Meeting after the data has been cleaned and the database locked but before analysis has commenced. The review will be performed within the framework of the requirements of the ICH Guideline E9.

The terms of reference for the Data Review Meeting will include, but will not be limited to:

- the determination of whether protocol violations are 'major' or 'minor', or not a protocol violation at all
- the allocation of subjects to analysis sets
- 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
- a review of whether additional covariates need to be included in the analyses
- revisions to SAP in light of any Data Review Meeting findings

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

13.11 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 ethics committee/REC review and approval meet EU and/or 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/or 21 CFR 312.64 (US sites only).
6. Have read and understood the Investigator 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 ethics committee/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 ethics committee/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. Not make any changes in the research study without approval, except when necessary to eliminate hazards to the subjects.
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 study will be conducted according to ICH GCP, the Declaration of Helsinki (1996), and ethics committees/IRBs in accordance with the US Code of Federal Regulations on Protection of Human Rights (21 CFR 50) (US site).

14.3 Ethics Committee and Institutional Review Board approval

The final study protocol and subject informed consent form will be approved by the ethics committee/IRB for the site participating in the study. Approval will be received in writing before initiation of the study at site.

Any changes to the study design will be formally documented in protocol amendments and approved by the ethics committee/IRB prior to implementation, except in the case of changes made to protect subject safety, which will be implemented immediately.

14.4 Informed Consent

The principles of informed consent in the Declaration of Helsinki (1996), in the current requirements of GCP published by the ICH and local regulation, whichever affords the greater subject protection will be implemented before any protocol-specified procedures or interventions are carried out.

At Dutch centres only, potential subjects will be approached by their own treating physician. If the treating physician is also the investigator the subject information sheet can be provided immediately. If this is not the case then the treating physician will ask the patient for permission for the investigator to approach them about study participation.

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 ethics committee/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 ethics committee/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 eCRF, 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 (visits 1 and 4). 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 [redacted] standard operating procedures.
- Complete efficacy and end-point reporting.

- Generate safety data listings to include AEs coded using the latest version of the MedDRA coding dictionary.

The exact time of the PK blood draws will be recorded. All deviations will be listed to enable [redacted] to make the necessary adjustments during the PK analysis.

14.8 Drug Reconcilliation

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 must be submitted to the ethics committee/IRB in accordance with local requirements.

Approval by the sponsor, FDA, other regulatory authorities as necessary, and ethics committee/IRB must be obtained before changes can be implemented.

14.12 Study Monitoring

The CRO will be responsible for the monitoring of the study.

[redacted]

At all sites the study monitor will review the progress of the study on a regular basis, 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 communications, between the sponsor, designated study representative, and investigator should be documented for the study file.

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 liability to publish the data in appropriate scientific forms. Announcements made prior to the first scientific publication of the data will be reviewed 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 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, ethics committee/IRB and regulators including the FDA. 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.

14.16 Study Termination

The study may be terminated prior to completion of the specified number of subjects at the request of the sponsor, the investigator, the ethics committee/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 - Sampling Schedule for 24-hour Profiling

Sample Number	Clock time in hours
1	15:00
2	17:00
3	19:00
4	21:00
5	23:00
6	01:00
7	03:00
8	05:00
9	07:00
10	09:00
11	11:00
12	13:00
13	15:00

Endocrine profile: Beginning at 15:00h on Day 1 (Visit 1.1) and finishing 15:00h on Day 2 (Visit 1.2): two hourly serum for:

- 17-OHP
- A4

Exact times of samples to be recorded; allowable deviation from above times is ±10 minutes

The above will be repeated on respective Days for Visits 2 (2.1 and 2.1), 3 (3.1 and 3.2) and 4 (4.1 and 4.2).

If dosing with the study medication needs to be conducted at the same timepoints as the blood sampling, the blood sampling should be conducted first before the dose of study medication is given.

Appendix 2 - 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, glucose, insulin, Hb1Ac, total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, triglycerides, hsCRP, osteocalcin, CTX, plasma renin

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 3 - 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.

For US NIH clinical centre only (new text in bold): 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 Summary of Product Characteristics (SmPC) of hydrocortisone is used as the reference for expected AEs (http://www.medicines.org.uk/emc/medicine/27652). However, some of the data in the hydrocortisone SmPC clearly relates to anti-inflammatory immunosuppressive doses of glucocorticoid, which will not be used in this study of Chronocort®. Should such immunosuppressive events be observed they would be unexpected so are not included.

The following is reproduced from section 4.8 of the 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 4 - 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 5 - Adrenal Insufficiency Checklist

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

Date of assessment (mm/dd/yyyy):	

Please ask subject:	Have you experienced any of the following symptoms more than once per week in the last 4 weeks?

Symptoms	Yes	If Yes, do you believe this to be related to under or over replacement of glucocorticoid? Please state over/under.	No	Any clinically significant findings? Y/N
Sudden weight loss				
Sudden weight gain				
Lack of appetite				
Increased appetite				
Nausea				
Vomiting				
Headache				
Blurred vision				
Fatigue				
Weakness				
Dizziness				
Lightheadedness				
Syncope (sudden loss of consciousness)				
Sleeping difficulties				
Increased acne				
Other				
If yes to Other please specify:				

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Appendix 6 - SF-36®

SF-36v2® HEALTH SURVEY (FOUR-WEEK RECALL)

SCRIPT FOR INTERVIEW ADMINISTRATION

These first questions are about your health now and your current daily activities.

Please try to answer every question as accurately as you can.

1. **In general, would you say your health is...** *[READ RESPONSE CHOICES]*

(Circle one number)

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

2. **Compared to one year ago, how would you rate your health in general now? Would you say it is...** *[READ RESPONSE CHOICES]*

(Circle one number)

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

Now I'm going to read a list of activities that you might do during a typical day.

As I read each item, please tell me if your health now limits you a lot, limits you a little, or does not limit you at all in these activities.

3a. **First, vigorous activities, such as running, lifting heavy objects, participating in strenuous sports. Does your health now limit you a lot, limit you a little, or not limit you at all?** *[READ RESPONSE CHOICES ONLY IF NECESSARY]*

[IF RESPONDENT SAYS S/HE DOES NOT DO ACTIVITY, PROBE: Is that because of your health?]

(Circle one number)

Yes, limited a lot 1
Yes, limited a little 2
No, not limited at all 3

3b. **. . . moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf. Does your health now limit you a lot, limit you a little, or not limit you at all?** *[READ RESPONSE CHOICES ONLY IF NECESSARY]*

[IF RESPONDENT SAYS S/HE DOES NOT DO ACTIVITY, PROBE: Is that because of your health?]

(Circle one number)

Yes, limited a lot 1

Yes, limited a little 2

No, not limited at all 3

3c. **. . . lifting or carrying groceries. Does your health now limit you a lot, limit you a little, or not limit you at all?** *[READ RESPONSE CHOICES ONLY IF NECESSARY]*

[IF RESPONDENT SAYS S/HE DOES NOT DO ACTIVITY, PROBE: Is that because of your health?]

(Circle one number)

Yes, limited a lot 1

Yes, limited a little 2

No, not limited at all 3

3d . **. . . climbing several flights of stairs. Does your health now limit you a lot, limit you a little, or not limit you at all?** *[READ RESPONSE CHOICES ONLY IF NECESSARY]*

[IF RESPONDENT SAYS S/HE DOES NOT DO ACTIVITY, PROBE: Is that because of your health?]

(Circle one number)

Yes, limited a lot 1

Yes, limited a little 2

No, not limited at all 3

3e. **. . . climbing one flight of stairs. Does your health now limit you a lot, limit you a little, or not limit you at all?** *[READ RESPONSE CHOICES ONLY IF NECESSARY]*

[IF RESPONDENT SAYS S/HE DOES NOT DO ACTIVITY, PROBE: Is that because of your health?]

(Circle one number)

Yes, limited a lot 1

Yes, limited a little 2

No, not limited at all 3

3f . **. . . bending, kneeling, or stooping. Does your health now limit you a lot, limit you a little, or not limit you at all?** *[READ RESPONSE CHOICES ONLY IF NECESSARY]*

[IF RESPONDENT SAYS S/HE DOES NOT DO ACTIVITY, PROBE: Is that because of your health?]

(Circle one number)

Yes, limited a lot 1

Yes, limited a little 2

No, not limited at all 3

3g. **. . . walking more than a mile. Does your health now limit you a lot, limit you a little, or not limit you at all?** *[READ RESPONSE CHOICES ONLY IF NECESSARY]*

[IF RESPONDENT SAYS S/HE DOES NOT DO ACTIVITY, PROBE: Is that because of your health?]

(Circle one number)

Yes, limited a lot 1

Yes, limited a little 2

No, not limited at all 3

3h . **. . . walking several hundred yards. Does your health now limit you a lot, limit you a little, or not limit you at all?** *[READ RESPONSE CHOICES ONLY IF NECESSARY]*

[IF RESPONDENT SAYS S/HE DOES NOT DO ACTIVITY, PROBE: Is that because of your health?]

(Circle one number)

Yes, limited a lot 1

Yes, limited a little 2

No, not limited at all 3

3i . **. . . walking one hundred yards. Does your health now limit you a lot, limit you a little, or not limit you at all?** *[READ RESPONSE CHOICES ONLY IF NECESSARY]*

[IF RESPONDENT SAYS S/HE DOES NOT DO ACTIVITY, PROBE: Is that because of your health?]

(Circle one number)

Yes, limited a lot 1

Yes, limited a little 2

No, not limited at all 3

3j. **. . . bathing or dressing yourself. Does your health now limit you a lot, limit you a little, or not limit you at all?** *[READ RESPONSE CHOICES ONLY IF NECESSARY]*

[IF RESPONDENT SAYS S/HE DOES NOT DO ACTIVITY, PROBE: Is that because of your health?]

(Circle one number)

Yes, limited a lot 1

Yes, limited a little 2

No, not limited at all 3

The following four questions ask you about your physical health and your daily activities.

4a. **During the past four weeks, how much of the time have you had to cut down on the amount of time you spent on work or other daily activities as a result of your physical health?** *[READ RESPONSE CHOICES]*

(Circle one number)

All of the time 1

Most of the time 2

Some of the time 3

A little of the time 4

or None of the time 5

4b. **During the past four weeks, how much of the time have you accomplished less than you would like as a result of your physical health?** *[READ RESPONSE CHOICES]*

(Circle one number)

All of the time 1

Most of the time 2

Some of the time 3

A little of the time 4

or None of the time 5

4c. **During the past four weeks, how much of the time were you limited in the kind of work or other regular daily activities you do as a result of your physical health?** *[READ RESPONSE CHOICES]*

(Circle one number)

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

4d. **During the past four weeks, how much of the time have you had difficulty performing work or other regular daily activities as a result of your physical health, for example, it took extra effort?** *[READ RESPONSE CHOICES]*

(Circle one number)

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

The following three questions ask about your emotions and your daily activities.

5a. **During the past four weeks, how much of the time have you had to cut down the amount of time you spent on work or regular daily activities as a result of any emotional problems, such as feeling depressed or anxious?** *[READ RESPONSE CHOICES]*

(Circle one number)

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

5b. **During the past four weeks, how much of the time have you accomplished less than you would like as a result of any emotional problems, such as feeling depressed or anxious?** *[READ RESPONSE CHOICES]*

(Circle one number)

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

5c. **During the past four weeks, how much of the time did you do work or other regular daily activities less carefully than usual as a result of any emotional problems, such as feeling depressed or anxious?** *[READ RESPONSE CHOICES]*

(Circle one number)

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

6. **During the past four weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups? Has it interfered . . .** *[READ RESPONSE CHOICES]*

(Circle one number)

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

7. **During the past four weeks, how much did pain interfere with your normal work, including both work outside the home and housework? Did it interfere . . .** *[READ RESPONSE CHOICES]*

(Circle one number)

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

8. **How much bodily pain have you had during the past four weeks? Have you had . .** *[READ RESPONSE CHOICES]*

(Circle one number)

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

The next questions are about how you feel and how things have been with you during the past four weeks.

As I read each statement, please give me the one answer that comes closest to the way you have been feeling; is it all of the time, most of the time, some of the time, a little of the time, or none of the time?

9a. **How much of the time during the past four weeks . . . did you feel full of life?** *[READ RESPONSE CHOICES]*

(Circle one number)

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

9b. **How much of the time during the past four weeks . . . have you been very nervous?** *[READ RESPONSE CHOICES]*

(Circle one number)

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

9c. **How much of the time during the past four weeks . . . have you felt so down in the dumps that nothing could cheer you up?** *[READ RESPONSE CHOICES ONLY IF NECESSARY]*

(Circle one number)

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

9d. **How much of the time during the past four weeks . . . have you felt calm and peaceful?** *[READ RESPONSE CHOICES ONLY IF NECESSARY]*

(Circle one number)

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

9e. **How much of the time during the past four weeks . . . did you have a lot of energy?** *[READ RESPONSE CHOICES ONLY IF NECESSARY]*

(Circle one number)

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

9f. **How much of the time during the past four weeks . . . have you felt downhearted and depressed?** *[READ RESPONSE CHOICES ONLY IF NECESSARY]*

(Circle one number)

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

9g. **How much of the time during the past four weeks . . . did you feel worn out?** *[READ RESPONSE CHOICES ONLY IF NECESSARY]*

(Circle one number)

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

9h. **How much of the time during the past four weeks . . . have you been happy?** *[READ RESPONSE CHOICES ONLY IF NECESSARY]*

(Circle one number)

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

9i. **How much of the time during the past four weeks . . . did you feel tired?** *[READ RESPONSE CHOICES ONLY IF NECESSARY]*

(Circle one number)

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

10. **During the past four weeks, how much of the time has your physical health or emotional problems interfered with your social activities like visiting with friends or relatives? Has it interfered . . .** *[READ RESPONSE CHOICES]*

(Circle one number)

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

These next questions are about your health and health-related matters.

Now, I'm going to read a list of statements. After each one, please tell me if it is definitely true, mostly true, mostly false, or definitely false. If you don't know, just tell me.

11a. **I seem to get sick a little easier than other people. Would you say that's . . .** *[READ RESPONSE CHOICES]*

(Circle one number)

Definitely true 1
Mostly true 2
Don't know 3
Mostly false 4
or Definitely false 5

11b. **I am as healthy as anybody I know. Would you say that's . . .** *[READ RESPONSE CHOICES]*

(Circle one number)

Definitely true 1
Mostly true 2
Don't know 3
Mostly false 4
or Definitely false 5

11c. **I expect my health to get worse. Would you say that's . . .** *[READ RESPONSE CHOICES]*

(Circle one number)

Definitely true 1
Mostly true 2
Don't know 3
Mostly false 4
or Definitely false 5

11d. **My health is excellent. Would you say that's . . .** *[READ RESPONSE CHOICES]*

(Circle one number)

Definitely true 1
Mostly true 2
Don't know 3
Mostly false 4
or Definitely false 5

DO NOT read the following text to the survey respondent

Important Instruction for Interviewer:

When using this script for interview administration of the SF-36v2 survey, note that items 7 and 8 from the Bodily Pain health domain scale are administered in reverse order from the way they appear on the printed SF-36v2 self-administered paper form. Reversing the order of the presentation of these two items facilitates the flow of the interview administration.

When recording responses from interview administration of the SF-36v2, the response to Item 7 from the interview script should be entered in the Item 8 response area on the paper form, and vice versa.

Note: All QualityMetric scoring solutions only support the scoring of items as ordered on the printed SF-36v2 self-administered paper form.

Appendix 7 - 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 8 - 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

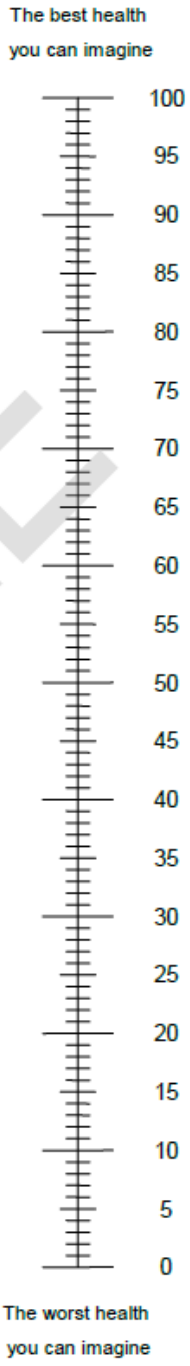
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

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 = ☐



3

Appendix 9 - Labelling of IMP and Rescue Medication

EU Primary (Blister) label (version number: DIUR-005.IMP.EU.01.001)

Chronocort® Hydrocortisone Modified Release Capsules X mg
Sponsor: Diurnal Ltd., Cardiff, U.K. Phone: +44 2920682069
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-005
Subject No.: YY
EudraCT-No. 2015-000711-40
Keep out of reach of children

EU Secondary (Blister) label (version number: DIUR-005.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-005
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., Cardiff, U.K. Phone: +44 2920682069
CRO: [redacted]
EudraCT-No. 2015-000711-40
No special precautions for unused product: refer to accompanying documents
Keep out of reach of children

EU Primary (Bottle) label (version number: DIUR-005.IMPBOT.EU.01.001)

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-005
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., Cardiff Medicentre, Heath Park, Cardiff, U.K. Phone: +44 2920682069
CRO: [redacted]
EudraCT-No. 2015-000711-40
No special precautions for unused product: refer to accompanying documents
Keep out of reach of children

EU comparator label (version number: DIUR-005.COMP.EU.02.001)

Protocol No.: DIUR-005
Subject No.: YY
Sponsor: Diurnal Ltd., Cardiff, U.K. Phone: +44 2920682069
PI: [redacted]
EudraCT-No. 2015-000711-40

EU safety pack label (version number: DIUR-005.SAFE.EU.02.001)

Protocol No.: DIUR-005
Subject No.: YY
Contents: YY
Sponsor: Diurnal Ltd., Cardiff, U.K. Phone: +44 2920682069
PI: [redacted]
EudraCT-No. 2015-000711-40

US Primary (Blister) label (version number: DIUR-005.IMP.US.01.001)

Chronocort® Hydrocortisone Modified Release Capsules X mg
Sponsor: Diurnal Ltd., Cardiff, U.K. Phone: +44 2920682069
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-005
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 (Blister) label (version number: DIUR-005.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-005
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., Cardiff, U.K. Phone: +44 2920682069
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-005.IMPBOT.US.01.001)

Chronocort® Hydrocortisone Modified Release Capsules Xmg
Quantity: 100 capsules
Batch No.: XXXX
Storage: Store at no more than 25°C
Expiry: MM/YYYY
Protocol No.: DIUR-005
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
Keep out of reach of children
No special precautions for unused product: refer to accompanying documents
CAUTION: New Drug Limited by Federal (or United States Law) for Investigational Use
IND No.: 076485
Sponsor: Diurnal Ltd., Cardiff Medicentre, Heath Park, Cardiff, U.K. Phone: +44 2920682069
PI: [redacted]
CRO: [redacted]

US comparator label (version number: DIUR-005.COMP.US.02.001)

Protocol No.: DIUR-005
Subject No.: YY
Sponsor: Diurnal Ltd., Cardiff, U.K. Phone: +44 2920682069
PI: [redacted]
IND No.: 076485

US safety pack label (version number: DIUR-005.SAFE.US.02.001)

Protocol No.: DIUR-005
Subject No.: YY
Contents: YY
Sponsor: Diurnal Ltd., Cardiff, U.K. Phone: +44 2920682069
PI: [redacted]
IND No.: 076485

Appendix 10 - Protocol Amendment History

Protocol Version 1.0 dated 03 July 2015
Original protocol.

Protocol Version 2.0 dated 03 September 2015
The protocol was amended to address MHRA comments on the protocol and to make a small administerative change to the Adrenal Insufficieny Checklist. The following changes were made:

1) Modification of the RSI in the Investigator's Brochure (IB) necessitated an update to Appendix 3 (Expected Adverse Events) in the protocol.
2) Clarification was added that the DSMB is independent.
3) The inclusion criteria of PRA less than 2 x ULN was reduced to PRA less than 1.5 x ULN.
4) Appendix 5 was updated to a newer version of the Adrenal Insufficiency Checklist (minor administrative change).

Protocol Version 3.0 dated 03 December 2015
The protocol was amended to address the Swedish Medicines Agency and the US National Institutes of Health comments on the protocol that a separate benefit/risk assessment should be added. The following changes were made:

1) Section 5: new section added at the end of Section 5 titled Benefit/Risk Assessment.

Protocol Version 4.0 dated 28 May 2016
The following changes were made to the protocol:

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

2) 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 mineralocorticoid 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.

3) The protocol stated that blood samples should be taken for genotyping, unless genotyping had previously been performed. It was clarified that if previous genotyping had been performed the patient has to be asked for their permission for this information to be taken from their medical records.

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

5) At the request of the Dutch ethics committee, the following sentence has been added to the procedures for the screening visit (Section 11.1.1) and also in Section 11.4 (Informed Consent): At Dutch centres only, potential subjects will be approached by their own treating physician. If the treating physician is also the investigator the subject information sheet can be provided immediately. If this is not the case then the treating physician will ask the patient for permission for the investigator to approach them about study participation.

6) It was noted that the terminology for the independent blinded physician was not consistent throughout the protocol so this was corrected throughout.

7) 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.'

Protocol Version 5.0 dated 23 September 2016

The following changes were made to the protocol:

1) The Sponsor signatory was changed from [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.

Protocol Version 6.0 dated 13 April 2017

The following changes were made to the protocol:

1) The statistician was changed from [redacted].

2) The sample size was increased from 110 to 120 patients due to a higher level of protocol deviations than originally anticipated. As such, the inevaluability rate has been increased from 7% to 15%.

3) The titration instructions in Section 8 (Dose Adjustment) has been modified to provide guidance if the independent blinded physician states that a change to the midday dose is needed but the patient is either receiving Chronocort or is receiving twice daily dosing of standard therapy. In such cases the local investigator is instructed to decide whether to

adjust the morning or evening dose, based on their judgement, in addition to any changes already advised for morning and evening doses, thus ensuring that the total change advised is accommodated within the day.

4) The screening period has been extended by 1 week (21 days) to allow extra time for the study site to obtain the results of the screening PRA test.

5) Clarification added to Sections 9.2 and 11.7 and the synopsis that female subjects presenting with oligomenorrhoea or amenorrhoea who are aged ≤55 years of age should be considered potentially fertile and therefore, as well as undergoing pregnancy testing like all other female subjects, will be expected to be using an acceptable method of contraception, as listed in Section 11.7.

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

Protocol Version 7.0 dated 23 August 2017 (administrative local amendment for US only)

Following comments from the IRB, an additional statement has been added in Appendix 3 (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 NIH clinical centre 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).