Title: Statistical Analysis Plan for DIUR-005: A Phase III study of efficacy, safety and tolerability of Chronocort® compared with standard glucocorticoid replacement therapy in the treatment of congenital adrenal hyperplasia

Compound Name/Number: Chronocort®

Effective Date: 13 Sep 2018

Subject: Congenital Adrenal Hyperplasia

Author's Name, Title and Functional Area: [redacted].

[redacted]

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Abbreviations

17-OHP	17-hydroxyprogesterone
A4	Androstenedione
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
ATC	'Anatomical Therapeutic Chemical' drug classification (WHO)
AUC	Area under the curve
BMI	Body mass index
BP	Blood pressure; Bodily pain
BUN	Blood urea nitrogen
CAH	Congenital adrenal hyperplasia
CK	Creatine kinase
C_{max}	The maximum concentration achieved after a single dose
CO_2	Carbon dioxide
CSR	Clinical study report
CTX	C-terminal cross-linked telopeptide
CV	Cardiovascular
DBP	Diastolic blood pressure
DEXA	Dual Energy X-ray Absorptiometry
ECG	Electrocardiogram
EQ-5D™	EQ-5D™ Standardised Health Questionnaire (5-level)
GC	Glucocorticoid
GFI	Global Fatigue Index
GH	General health
Hb	Haemoglobin
HbA1c	Glycated haemoglobin
Hct	Haematocrit
HDL	High density lipoprotein
HOMA-IR	Homeostasis model assessment of insulin resistance
hsCRP	High sensitivity C-reactive protein
IMP	Investigational medicinal product
LDH	lactate dehydrogenase
LDL	low density lipoprotein
LLOQ	lower limit of quantification
LLT	Lowest Level Term (MedDRA®)
LS	Least Squares
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
MH	Mental health
PF	Physical functioning
PK	Pharmacokinetic
PLT	Platelet count
PRA	Plasma renin activity
PT	Preferred term
QoL	Quality of life
QTcB	Bazett's QTc interval
QTcF	Fridericia's QTc interval
RBC	Red blood cell
RDW	Red cell distribution width
RE	Role-emotional
RP	Role-physical
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard deviation
SDS	Standard deviation score
SDTM	Study Data Tabulation Model
SF	Social functioning
SF-36®	Medical Outcome Short Form Health Survey Form 36 (Subject Questionnaire)
SI	International system of units
SOC	System Organ Class
VAS	Visual analogue scale
VT	Vitality
WBC	White blood cell
WHO	World Health Organisation

Trademark Information

SAS	SAS (Statistical Analysis Software) is a registered trademark of SAS Institute Inc.
Chronocort	Chronocort is a registered trademark of Diurnal Ltd
SF-36v2	SF-36v2 is a registered trademark of QualityMetric Incorporated
EQ-5D	EQ-5D is a registered trademark of the EuroQol Research Foundation
QualityMetric Health Outcomes™ Scoring Software 4.5	QualityMetric Health Outcomes™ Scoring Software 4.5 is a registered trademark of QualityMetric Incorporated

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Revision history

Version	Date	Summary of revisions
1.0	30 Sept 2015	Initial version
2.0	11 Sept 2017	**Section 1 Introduction:** Clarified that SAP Version 1.0 was written using Protocol Version 2.0 dated 3 September 2015 and that at the time of writing SAP Version 2.0 the most recent version of the Protocol was Protocol Version 7.0 dated 23 August 2017.
		Section 3 Study design and Section 5 Sample size considerations: The SAP text was updated to reflect the change to the sample size in Protocol Version 6.0 dated 13 April 2017 which states '*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%.*' Note: The original rate of 7% was estimated from a single site 16 subject Phase II study and hence has been updated to reflect the rate expected in a Phase III multiple site study in this patient population.
		Section 3 Study design: Additional information regarding titration instructions which was added to Protocol Section 8 (Dose Adjustment) has been included.
		Section 7.2 Data display (treatments and other subgroups): In Table 7 the Full data display descriptor has been updated to 'Prednisone **or Prednisolone**' for the 'Pre-baseline therapy of prednisone or prednisolone (alone or in combination with hydrocortisone)' stratification factor/subgroup.
		Section 9.1 Premature withdrawal and missing data: Text has been added for imputation/handling of missing or partial dates. Text has been added to specify how middle doses for subjects receiving standard care will be handled.
		Section 9.2.1 Baseline and demographic derivations: Derivation of Age in years has been corrected. Derivation of Time since CAH diagnosis added.
		Section 9.2.2 Derivations of SDS scores: References and justification for Normal reference ranges for 17-OHP and A4 which will be used in the derivation of the SDS scores for 17-OHP and A4. These have been added as footnotes to Tables 2 and 3. Removal of text stating that '*These reference ranges are to be reviewed by the contracted laboratories and are subject to change.*'

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	Section 9.2.3 Conversion factors: Included Finkielstain 2012 reference for conversion factors used. Added restriction for Dexamethasone conversion to Chronocort® from Protocol Version 4.0 in Table 4. Updated text to state that laboratory data will be presented in both SI and conventional units.
	Section 9.2.4 Coding of adverse events, concomitant medications, etc.: Removed physical examinations as these are not coded. Included prior CAH medication which are coded using the World Health Organisation (WHO) Drug Dictionary including Anatomical Therapeutic Chemical (ATC) drug classification
	Section 9.3.1 Definition of permissible time windows: Derivation of actual study day has been updated so that it is appropriate for subjects whose dosing regimen does not include an evening dose. Clarified that all assessments which are performed at the baseline visit (Visit 1, Days 1 and 2) will be considered prior to randomised study treatment Target study day ranges added to Table 7. A per CDISC standards there is no study day 0, hence the target study day for Baseline (Visit 1) has corrected (i.e. updated from target study day 0, 1 to -1, 1).
	Section 10.2 Protocol deviations: Cross-reference to Section 6.2 fixed. Specified that summary and listing would also include protocol category.
	Section 10.3 Demographic and baseline characteristics: Listing of demographic information added. Summary and listing of baseline disease characteristics added. Listing of genotyping information added. Signs and symptoms of adrenal insufficiency moved to new Section 11.7.4 under Section 11.7 Other safety evaluations.
	Section 10.4 Treatment compliance: Derivation of visit intervals updated so they apply to all dosing regimens and do not depend on whether a subject has a morning or evening dose.

	Additional detail added specifying how each interval will be split to take account of dose titrations. Summaries of sick day medications moved to new section - Section 10.7.3 Use of dispensed sick day medications and steroids taken in addition to IMP. Listing of dispensed sick day medication pack accountability added.
	Section 10.5 Primary efficacy analysis: Residuals plots to check model fit of primary analysis model added. As the Normal reference ranges in Table 2 have been finalised the following paragraph was removed '*The reference ranges given in Table 2 are currently under review. The concentration-time plot may need to include separate panels if it is decided that there will be different reference ranges for different groups. If this is the case, the plot of the SDS score will also be produced with a different panel for each group to check the validity of the reference ranges.'*
	Section 10.6.1 Secondary hormonal profile analysis: References and justification for the optimal reference range for 17-OHP and Normal reference range for A4 which will be used to define whether a subject is a responder. These have been added as footnotes to Tables 7. Removal of text stating that '*These reference ranges are to be reviewed by the contracted laboratories and are subject to change.*'
	Section 10.7.2 Bone markers and laboratory assessments of special interest: Biomarkers updated to bone biomarkers in the Section heading and throughout the text in this Section. Shift tables to each visit relative to baseline replaced with shift tables to minimum on-treatment versus baseline and to maximum on-treatment versus baseline.
	Section 10.7.3 Quality of life (QoL) questionnaires: Additional descriptive text has been added for each questionnaire. References have been added for SF-36 and EQ-5D™ (derivation of single index score).
	Section 10.7.4 Use of glucocorticoids Text has been updated to reflect study team requested improvements of these summaries. Table of hydrocortisone dose increments versus baseline added.
	Section 11.1 Extent of exposure: Minor updates made specific to each treatment arm included.

	Section 11.2 Adverse events: Minor correction of typographical errors – 'action taken' updated to 'action taken with study drug' and 'effect of study drug' removed from text. Text added to describe the Overview of AEs summary table which will be produced.
	Section 11.3.1 Use of "sick days rules" Section title updated to 'Use of "sick day **rules**"'. Additional summary table of AEs leading to sick day rules by PT, route and sick day medication included. Listing updated to include information on sick day medications.
	Section 11.3.3 Unexpected therapeutic benefit: New Section added describing the additional summary and listing that will be produced for these events.
	Section 11.4.1 Naming conventions: Biomarkers updated to bone biomarkers.
	Section 11.4.2 Haematology: Clarification added regarding central and local laboratory results and reference ranges. Shift tables to each visit relative to baseline replaced with shift tables to minimum on-treatment versus baseline and to maximum on-treatment versus baseline. Haematology (1) will be summarised together across males and females for all summary tables. Formula to derive RDW-CV(%) using RDW-SD(fL) and MCV added. Formulae to derive 1) WBC differentials as percentages of WBCs when only WBC differential counts and WBC counts are provided and 2) WBC differential counts when only percentages of WBCs and WBC counts are provided, have been added.
	Section 11.4.3 Clinical biochemistry: Clarification added regarding central and local laboratory results and reference ranges. Shift tables to each visit relative to baseline replaced with shift tables to minimum on-treatment versus baseline and to maximum on-treatment versus baseline.
	Section 11.4.4 Urinalysis: Shift table of baseline to worst on-treatment added.

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		Section 11.5 Vital signs: Split by dose level removed from summaries of absolute and change from baseline over time. Shift tables specified as being to minimum on-treatment versus baseline and to maximum on-treatment versus baseline.
		Section 11.6 Electrocardiogram (ECG): Split by dose level removed from summary of abnormal findings.
		Section 11.7.1 Physical examination: Abnormal findings tabulation replaced with shift table. Derivation of 'Normal' physical examination status based on information captured in eCRF added.
		Section 11.7.2 Concomitant medications excluding steroids: Section updated to reflect decision to exclude steroids from concomitant medication summary and listing. Steroids taken in addition to IMP will be summarised alongside use of sick day medications.
		Section 11.7.3 Use of dispensed sick day medications and steroids taken in addition to IMP: New section created using information regarding sick day medication use previously in Section 10.4 and steroids taken in addition to IMP which have been separated out from other concomitant medications.
		Section 11.7.4 Adrenal insufficiency: New section created. Information previously included in Section 10.3 Demographic and baseline characteristics.
		Section 14 Appendix A – List of tables, listings and figures: Minor addition/removal of tables/listings following review of mock shells and SAP updates.
3.0	13 Aug 2018	**Section 1 Introduction:** Added that at the time of writing SAP Version 3.0 the most recent version of the Protocol was Protocol Version 7.0 dated 23 August 2017.
		Section 9.1 Premature withdrawal and missing data Introduction: Subjects who have withdrawn prior to Week 12 will be assessed on the basis of the latest available 24-hour profile.
		Section 9.2.3 Conversion factors: Added conversion factor for PRA.

	Section 9.3.4 Clinical laboratory values below the lower limit of quantification: New section created to outline how to handle values below the LLOQ.
	Section 10.2 Protocol deviations: Text added describing high level categories of protocol deviations that will be implemented.
	Section 10.3 Demographic and baseline characteristics: Text added describing the age categories that will be implemented. Medical history split out into two separate summary tables and listings: CAH medical history and Other medical history excluding CAH events.
	Section 10.4 Treatment compliance: Section updated to reflect decision that only overall treatment compliance will be derived. A listing of treatment compliance will be produced.
	Section 10.7.2 Bone markers and laboratory assessments of special interest: Glucose units in HOMA-IR derivation updated to mmol/L. Boxplots of change from baseline over time added for all bone marker and laboratory assessment of special interest parameters.
	Section 11.1 Extent of exposure: Summary of unplanned dose changes added. Listing of study drug dosing instructions added.
	Section 11.2 Adverse events: Updated text to reflect that AE summaries will include AEs occurring after the last day of study treatment for subjects who enter the extension study or the last day of study treatment plus 30 days for subjects who do not enter the extension study.
	Section 11.2.3 Adrenal crises: Section title updated to '**Adrenal** crises'. Section text updated to replace 'Addisonian' with 'adrenal'.
	Section 11.4.2 Haematology: Boxplots of change from baseline over time added for all haematology parameters.
	Section 11.4.3 Clinical biochemistry:

		Boxplots of change from baseline over time added for all biochemistry parameters.
		Section 11.4.4 Urinalysis: Boxplots of change from baseline over time added for all continuous urinalysis parameters.
		Section 11.5 Vital signs: Boxplots of change from baseline over time added for all vital sign parameters. Reference ranges added for systolic blood pressure and diastolic blood pressure.
		Section 11.6 Electrocardiogram (ECG): Values with a change from baseline > 30 msec in QT interval, QTcB and QTcF will be flagged in the listing. Reference ranges added for all ECG parameters.
		Section 11.7.2 Concomitant medications excluding glucocorticoid steroids: Title updated to 'Concomitant medication excluding **glucocorticoid** steroids'. Table added specifying which glucocorticoid steroids will be excluded from summary and listing.
		Section 12 Changes from the planned analyses: Updated to reflect the version of the SAP the changes from the planned analyses were made.
		Appendix 14.1 List of planned tables: Updated list of planned tables.
		Appendix 14.2 List of planned listings: Updated list of planned listings.
		Appendix 14.3.1 Summary figures: Updated list of planned summary figures.
4.0	11 Sep 2018	**Section 9.3.3 Methods for handling out-of-window observations** In order to use all available endocrine samples the evaluable window was increased from +/- 15 minutes to +/- 60 minutes from the planned time point. The decision to implement this change was based on a case-by-case review of blinded endocrine profiles with 2 or more missing (or out of window) at the Data Review Meeting prior to database lock and

	unblinding of the study. It was judged that this was more appropriate than the existing rule for handling out of window samples. Imputation rule added to handle completely missing endocrine results at the 15:00 planned time points within a 24-hour profile.
	Section 9.3.4 Other clinical laboratory values below the limit of quantification Section header updated to clarify the section does not refer to 17-OHP and A4.
	Signature pages The Sponsor signatory was changed from [redacted]

[redacted]

1. Introduction

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]).

A phase II study (DIUR-003) was conducted in 16 subjects to evaluate the pharmacokinetic (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 PK profile of Chronocort® was characterised by an overnight rise in cortisol levels reaching a maximal concentration approximately 8 hours post-dosing, consistent with the endogenous profile of cortisol reported in normal individuals. The variation in the maximum concentration achieved after a single dose (C_{max}) and area under the curve (AUC) was similar to that seen in physiological cortisol levels in healthy volunteers.

This 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.

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. The purpose of this document is to formally set out the primary, secondary and safety statistical analyses to be conducted for this study. SAP version 1.0 was written using protocol version 2.0 dated 3 September 2015. At the time of writing SAP version 2.0, the most recent version of the protocol is version 7.0 dated 23 August 2017. At the time of writing SAP version 3.0, the most recent version of the protocol is version 7.0 dated 23 August 2017. At the time of writing SAP version 4.0, the most recent version of the protocol was version 7.0 dated 23 August 2017.

2. Study objectives and endpoints

2.1. Study objectives

2.1.1. Primary objective

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

2.1.2. 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 over the 6-month treatment period.
- To assess the impact of Chronocort® on body composition (using dual energy X-ray absorptimetry [DEXA]) – fat mass, lean mass and total bone density – at selected sites.

2.2. Study endpoints

2.2.1. Primary endpoints

The primary efficacy endpoint is the change from baseline to 24 weeks in the natural logarithm 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.

2.2.2. Secondary endpoints

1. The change from baseline to 24 weeks in the natural logarithm 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 or reference range respectively).
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.

2.2.3. 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).

2.3. Statistical hypotheses

2.3.1. Primary hypothesis

The primary comparison of interest is to test the null hypothesis H_0: There is no difference between the mean change from baseline to 24 weeks in the primary efficacy variable (the natural logarithm of

[redacted]

the mean of the 24-hour SDS profile for 17-OHP) in Chronocort® compared to standard glucocorticoid replacement therapy, versus the alternative hypothesis H_1: There is a difference in the mean change from baseline to 24 weeks in the primary efficacy variable in Chronocort® compared to standard glucocorticoid replacement therapy. The difference analysed will be the mean of the primary efficacy analysis variable for Chronocort® minus the mean of the primary efficacy analysis variable for standard glucocorticoid replacement therapy. This means that a negative difference will be in favour of Chronocort®.

2.3.2. Secondary hypotheses

For the secondary endpoint of the change from baseline to 24 weeks of the logarithm of the mean of the 24-hour SDS profile for A4, the same hypothesis as the primary analysis will be tested, with A4 in place of 17-OHP.

The responder analysis will test the null hypothesis H_{01}: The odds of response for Chronocort® is the same as the odds of response for standard glucocorticoid replacement therapy i.e. the odds ratio is 1, versus the alternative hypothesis H_{11}: The odds of response for Chronocort® is different to the odds of response for standard glucocorticoid replacement therapy. An odds ratio of greater than 1 favours Chronocort®. Response is defined as the number of subjects achieving results in the optimal or reference ranges (See 10.6). The hypothesis will be tested separately for 17-OHP and A4.

For the secondary endpoint of the change from baseline in body composition (DEXA), the results from the three tests: fat mass, lean mass, total bone density will be analysed separately. The results from each test will be used in turn to test the null hypothesis H_{02}: There is no difference between the mean change from baseline to 24 weeks in the result for Chronocort® compared to standard glucocorticoid replacement therapy, versus the alternative hypothesis H_{12}: There is a difference in the mean change from baseline to 24 weeks in the result for Chronocort® compared to standard glucocorticoid replacement therapy.

2.3.3. Multiple testing strategy

There will be no adjustment for multiple testing as the primary analysis will be considered the main analysis with the secondary and exploratory endpoints intended as support for the primary analysis.

2.4. Exploratory objectives, endpoints and hypotheses

The purpose of this document is to set out the primary, secondary and safety analyses, however several exploratory objectives will also be addressed in this study. The following were specified in the protocol, other analyses may be added on an ad hoc basis.

2.4.1. 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 type I) 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)
- To assess changes from baseline in plasma renin activity (PRA) in the morning.

[redacted]

- 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.

2.4.2. Exploratory endpoints

1. Partial 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.

3. 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 24 weeks.

An overview of the study plan is illustrated in Figure 1. 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 to obtain 102 evaluable subjects (individual sites should not recruit more than 25 subjects without first consulting the sponsor). The randomisation either to Chronocort® or to continue on their original therapy will be stratified with regard to the subject's prior treatment:

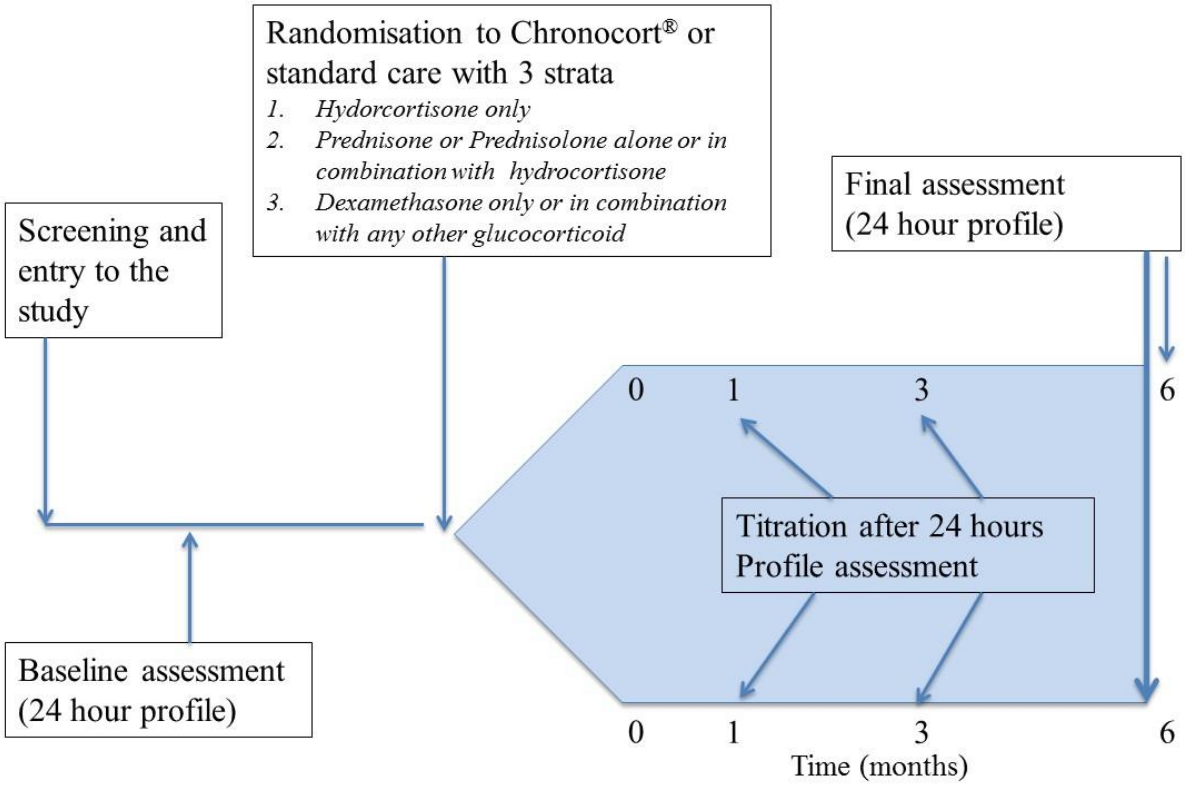
1. Hydrocortisone only
2. Prednisone or prednisolone, alone or in combination with hydrocortisone
3. Dexamethasone only or in combination with any other glucocorticoid

Dose titration decisions will be made within two 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. These decisions will be made by a central independent physician, blinded to the treatment arm to minimise bias. 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.

Subjects completing the study will become eligible for an open extension study, in which all subjects will be offered Chronocort®.

Figure 1: Overview of DIUR-005 Study Schema



4. Timing of planned analyses

4.1. 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 datasets used in the review will be masked to treatment allocation and dummy treatment groups with generic treatment labels will be used. The terms of reference for the Data Review Meeting are outlined in Section 13.10 of the protocol.

4.2. Interim analyses

No formal interim analysis is planned.

4.3. Final analysis

The final analysis will take place after the Data Review Meeting described in Section 4.1.

[redacted]

5. 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 24-hour unsigned SDS 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.

6. Analysis populations

6.1. Full analysis set

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 had at least one evaluable post-randomisation 17-OHP 24-hour hormone profile.

Subjects in the full analysis set will be analysed according to the actual treatment received (the first dose of treatment they actually took post randomisation).

6.2. Efficacy evaluable set

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 an evaluable week 24 17-OHP 24-hour hormone profile, and who have no major protocol violations.

It is difficult to conduct trials in this indication. This is the first comparative trial of a re-formulation of a standard therapy for CAH. The efficacy evaluable analysis set is therefore the primary analysis set for the evaluation of efficacy. The robustness of the conclusions will be assessed by repeating key efficacy analyses using the full analysis set.

The final determination of the membership of analysis sets will be made at a Data Review Meeting convened by the sponsor before database lock.

Subjects in the efficacy evaluable set will be analysed according to the actual treatment received.

6.3. Safety analysis set

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.

Subjects in the safety analysis set will be analysed according to the actual treatment received.

A summary will be produced of the number of subjects in each analysis population, together with reasons for exclusion from each analysis set.

7. Treatment comparisons

7.1. General

The comparison in all analyses will be between the Chronocort® treatment group and standard glucocorticoid replacement therapy.

For the stratified secondary and exploratory analyses and the stratified analysis of the primary endpoint, comparisons will be presented for subgroups defined by the pre-baseline standard treatment.

7.2. Data display (treatments and other subgroups) descriptors

The treatment group descriptors to be used in outputs are listed in Table 1 below. The full data display descriptor is preferred, although the abbreviated option in the third column may be used if there is not enough space on the page.

In general, where subgroups are presented in a table as three separate columns (optionally together with a "Total" column), then these columns should preferably be displayed using the full treatment group descriptor spanning all three columns (four including a "Total" column) as a "super-header" and either the full or abbreviated stratification descriptor underneath.

Table 1: Treatment group and stratification subgroup descriptors

Treatment group/stratification factor	**Full data display descriptor**	**Abbreviated data display descriptor**
Treatment groups		
Chronocort® (Any pre-baseline standard therapy)	Chronocort	Cct
Standard glucocorticoid replacement therapy (All groups combined)	Standard GC therapy	SGC
Stratification factors (subgroups)		
Pre-baseline therapy of hydrocortisone only	Hydrocortisone only	Hydro
Pre-baseline therapy of prednisone or prednisolone (alone or in combination with hydrocortisone)	Prednisone or Prednisolone	Pred
Pre-baseline therapy of dexamethasone (alone or in combination with any other glucocorticoid)	Dexamethasone	Dex
Combined treatment group/subgroups		
Chronocort® with pre-baseline therapy of hydrocortisone only	Chronocort - Hydrocortisone only	Cct - Hydro

[redacted]

Chronocort® with pre-baseline therapy of prednisone or prednisolone (alone or in combination with hydrocortisone)	Chronocort – Prednisone or Prednisolone	Cct - Pred
Chronocort® with pre-baseline therapy of dexamethasone (alone or in combination with any other glucocorticoid)	Chronocort - Dexamethasone	Cct - Dex
Standard glucocorticoid replacement therapy, hydrocortisone only	Standard GC - Hydrocortisone only	SGC - Hydro
Standard glucocorticoid replacement therapy, prednisone or prednisolone (alone or in combination with hydrocortisone)	Standard GC – Prednisone or Prednisolone	SGC - Pred
Standard glucocorticoid replacement therapy, dexamethasone (alone or in combination with any other glucocorticoid)	Standard GC - Dexamethasone	SGC - Dex

8. General considerations for data analyses

All statistical analyses will be performed using the software package SAS® version 9.1 or higher.

8.1. Standard summary statistics

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.

8.2. Standard comparison methods

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.

8.3. Statistical significance and multiple testing strategy

All significance probabilities will be reported as two tailed. Confidence intervals will be reported as 95% two-sided. There will be no adjustment for multiple testing.

8.4. Strata and covariates

Pre-baseline standard therapy refers to the standard glucocorticoid replacement therapy the subject was receiving for at least 6 months prior to joining the study, namely the strata used for randomisation:

[redacted]

- Hydrocortisone only
- Prednisone or prednisolone, alone or in combination with hydrocortisone
- Dexamethasone only or in combination with any other glucocorticoid

8.5. Examination of subgroups

Additional exploratory and sensitivity analyses of the assessment of the efficacy results in subgroups may be required if appropriate.

9. Data handling conventions

9.1. Premature withdrawal and missing 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). Further details are given in Section 9.3.3. In the event that several values are missing from a single profile, a decision will be made about the validity of the whole profile at the Data Review Meeting on a case-by-case basis.

For efficacy analyses based on the Week 12 and Week 24 visits, subjects who have withdrawn 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.

When calculations must be based upon incomplete dates the following process will be used. If year is missing do not impute. The value should be considered missing. If year is populated but both month and day are missing then the date defaults to 1st July. If day only is missing then the day defaults to the 15th of the month.

For adverse events and concomitant medications, if year is missing do not impute. If start year is populated but both month and day are missing, or if month is missing and day is present, then the date defaults to 1st January. If day only is missing then the day defaults to the 1st of the month. If end year is populated but both month and day are missing, or if month is missing and day is present, then the date defaults to 31st December. If day only is missing then the day defaults to last day of the month. For definition of treatment emergent and ongoing, if partial dates are only available for start and end, then we are conservative and assume treatment emergent/ongoing.

For those subjects with one middle dose then this is considered as “middle 1”, and middle2 is blank for all subjects except those with a second middle dose.

Exploratory and sensitivity analyses will be performed to assess the effect of any missing data on the efficacy conclusions. This will be discussed at the Data Review Meeting and a decision will be made on the appropriate analyses.

9.2. Derived and transformed data

9.2.1. Baseline and demographic derivations

The age of the subject in years will be determined using the date of birth (recorded at screening) and the date of consent. Since year only is being collected for this study, age will be calculated as the difference between the year of the screening visit and date of birth as:

- Year of consent – year of birth + 1.

[redacted]

Time since CAH diagnosis will be determined using the date of CAH diagnosis captured in the electronic case record form (eCRF) and will be calculated as:

- Date of randomisation – date of CAH diagnosis + 1 / 365.25.

In the derivation of age at study entry and time since CAH diagnosis partial dates will be handled as described in Section 9.1.

9.2.2. Derivations of SDS scores

The primary efficacy variable is the natural logarithm of the mean of the 24-hour hormonal profile of the SDS for the natural logarithm of 17-OHP. The primary analysis is focused on the change from baseline to week 24 in the primary efficacy variable.

The SDS is defined as the absolute (unsigned) number of standard deviations above or below the average of the lower and upper limit of normal.

The change from baseline to week 24 in the primary efficacy variable will be calculated in the following way:

- Step 1: **Calculate the SDS profile of log-transformed 17-OHP**

  For each of the 13 concentrations at each visit (baseline, week 24), take the natural logarithm and then calculate the SDS by counting the number of standard deviations (given in Table 3) which are above or below the mean of the log transformed range (given in Table 3).

- Step 2: **Calculate the mean of the SDS profile**

  Calculate the arithmetic mean over all 24-hour SDSs at each visit with the first and last observations weighted one half relative to the intermediate observations, e.g. for 13 observations (n_1, … n_{13}) this is calculated by ($½n_1+n_2+...+n_{12}+ ½n_{13}$)/12. Lower values of the mean of the SDS profile should be interpreted as “better” hormonal control.

- Step 3: **Change from baseline to 24 weeks**

  Take the natural logarithm of the mean of the SDS profile for the week 24 visit and subtract the natural logarithm of the mean of the SDS profile for the baseline visit. Negative values of this result should be interpreted as an improvement in hormonal control compared with baseline.

Table 2: Normal reference ranges for 17-OHP and A4

	Male	**Female**
17 OHP	1.2* – 6.7 nmol/L	1.2* – 8.6 nmol/L
A4	1.4 - 5.2 nmol/L	1.0 – 7 nmol/L

Source: Mayo Clinic.

17-OHP: http://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/9231.

Please note the upper reference range for females is during the Luteal phase.

**There is no lower reference range available for 17-OHP, hence the lower limit of the optimal range (provided in Table 7) will be used in the derivation of the average SDS score. This will enable calculation of an 'unsigned' SDS score which can be used to assess potential overtreatment as well as undertreatment.*

A4: http://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/9709

Table 3: Mean and SD of normal log-transformed range

Analyte	**Sex**	**mean of $\log_e$-transformed range** ***[$\log_e$ (nmol/L)]***	**SD of $\log_e$-transformed range** ***[$\log_e$ (nmol/L)]***
17-OHP	Male	1.042	0.430
	Female	1.167	0.492
A4	Male	0.993	0.328
	Female	0.973	0.486

Source: Mayo Clinic.

17-OHP: http://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/9231.

Please note the upper reference range for females is during the Luteal phase.

A4: http://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/9709

The mean of the "normal" log-transformed range was calculated by taking the natural logarithm of the upper and lower limit given in Table 2, calculating the range of the log-transformed values and finding the midpoint of the range. The SD of the log-transformed range was approximated by dividing the range of the log-transformed values by four.

9.2.3. Conversion factors

For the conversion of standard glucocorticoid replacement therapy to hydrocortisone, the conversion factors (Finkielstain 2012) are given in Table 4.

Table 4: Conversion factors for standard glucocorticoid replacement therapy to hydrocortisone

Standard glucocorticoid replacement therapy	Conversion factor
Prednisone or prednisolone	5
Dexamethasone	80 (up to a maximum starting dose of Chronocort® 30mg, split as 20mg at night and 10mg in the morning)

Note: The conversion factor for Chronocort® is 1.

For example, if a subject was previously taking 6mg daily of prednisone daily, this would be multiplied by a conversion factor of five and the equivalent hydrocortisone daily dose would be 30mg.

If a subject was previously taking prednisone in combination with hydrocortisone, then a conversion factor of five would be applied to the prednisone component of the dose, and a conversion factor of one would be applied to the hydrocortisone component of the dose, and the two added together.

All laboratory results will be reported in SI and conventional units. If for any reason the results are not collected in SI or conventional units, a conversion will be performed. Examples of some conversions to SI units are given in Table 5.

Table 5: SI unit conversions

Quantity	**Conversion to SI units**		
17-OHP	1 ng/dL	= 0.0303	nmol/L
ACTH	1 pg/mL	= 0.22	pmol/L
Androstenedione	1 ng/dL	= 0.0349	nmol/L
Glucose	1 mg/dL	= 0.0555	mmol/L
Insulin	1 µIU/mL	= 6.945	pmol/L
Osteocalcin	1 µg/L	= 0.171	nmol/L
PRA	1 NG/ML/HR	= 0.2778	NG/L/S

9.2.4. Coding of adverse events, concomitant medications, etc.

AEs and medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 18.0 or later (the exact version to be determined when coding is done). Coding will be to the level of the lowest level term (LLT). Concomitant medications and pre-treatment CAH medications will be coded using the World Health Organisation (WHO) Drug Dictionary including Anatomical Therapeutic Chemical (ATC) drug classification.

9.3. Assessment time windows

9.3.1. Definition of permissible time windows

Actual study day will be calculated by:

- Date of assessment - Date of randomisation + 1

Participants will receive their first dose of randomised treatment in the evening of the second baseline visit (Day 2 of Visit 1) after they have been randomised. As such study day 1 will be considered the day of randomisation. All assessments which are performed at the baseline visit (Visit 1, Days 1 and 2) will be considered prior to randomised study treatment.

All assessments that are summarised by visit (endocrine profile, DEXA, ECG, laboratory results, Vitals etc.) will be summarised according to the scheduled visit. Any extreme deviations between the actual study day of the scheduled visit and the target study day (see Table 6) will be discussed at the Data Review Meeting. A deviation will be considered extreme if more than +/- 3 weeks from visit 2, or +/- 4 weeks from visit 3 or 4.

Table 6: Target study day for visit assessments

Visit number	Visit description	Target study day	Target study day range
Visit 0	Screening		<-1
Visit 1	Baseline	-1,1	
Visit 2	Week 4	29,30	>8 to <51
Visit 3	Week 12	85,86	>57 to <114
Visit 4	Week 24	169,170	>141 to <198

Note: There is no study day 0 as per CDISC standards. Study day 1 is first day of dosing.

9.3.2. Baseline Assessment

Baseline, used in calculations for change from baseline summaries, will be defined as the latest pre-dose measurement. This is expected to be the visit 1 assessment, however if a result is missing and there is a suitable result available at the screening visit (taking account of fasting requirements where needed), this will be used in its place.

9.3.3. Methods for handling out-of-window observations

Missing 17-OHP and A4 values will be handled as follows:

- If the Day 1 15:00 sample of a 24-hour profile is completely missing, the result from the 17:00 planned time point will be used.
- If the Day 2 15:00 sample of a 24-hour profile is completely missing, the result from the 13:00 planned time point will be used.

[redacted]

- For all other time points where the result is completely missing, the average of the two closest results will be calculated and used for the missing time point.
- If the result at any time point is below the lower limit of quantification (LLOQ), a value of half the LLOQ will be substituted.
- For the purpose of analysis, a result will be considered to be out-of-window if more than +/-60 minutes from the scheduled time point[1]. For each time point where the result is 'out-of-window':
  - If the out-of-window result is >60 minutes after the scheduled time point then the average of the previous scheduled time point and the out-of-window result will be calculated and used for the scheduled time point with the out-of-window result.
  - If the out-of-window result is >60 minutes before the scheduled time point then the average of the next scheduled time point and the out-of-window result will be calculated and used for the scheduled time point with the out-of-window result.

Subjects with 2 or more of the expected results missing (or outside of a +/-15 minute window) for a particular 24hr period were discussed on a case-by-case basis at the Data Review Meeting which occurred prior to database lock and study unblinding.

9.3.4. Other clinical laboratory values below the lower limit of quantification

If a clinical laboratory result is below the LLOQ at any time point, a value equal to the LLOQ will be substituted.

9.4. Handling outliers

Any extreme values which are considered to have potential to impact the interpretation of results will be discussed at the Data Review Meeting (See 4.1) and sensitivity analyses may be performed as required.

10. Study population

10.1. Disposition of subjects

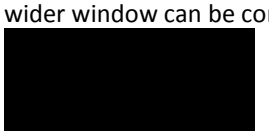
Subject disposition will be listed and summarised by treatment group (including screen failures) and pre-baseline standard therapy. The summary will include reason for withdrawal and whether the subject is continuing into the extension study.

10.2. Protocol deviations

Any deviations from the protocol will be reviewed at the Data Review Meeting following trial completion but prior to database lock. Each protocol deviation will be classified as either 'minor' (unlikely to affect trial outcomes) or 'major' (likely to affect outcomes). Any subject considered to have a major protocol deviation will be excluded from the Efficacy Analysis set (See 6.223). In addition, protocol deviations will be grouped into the following high-level categories:

- Inclusion criteria – subject failed to meet all inclusion criteria,
- Exclusion criteria – subject met at least one exclusion criteria,

[1] This differs from the +/- 10 minute window specified for investigators in the protocol so that results within a wider window can be considered acceptable for analysis.



- Study procedure – site or subject did not follow procedures specified in protocol,
- Titration – site or subject deviated from the titration process,
- Treatment – IMP not taken as per protocol,
- Local sampling – site performed endocrine sampling locally.

Protocol deviations will be listed and summarised by randomised treatment group, classification (major or minor) and protocol deviation category.

10.3. Demographic and baseline characteristics

The following demographic and baseline characteristics will be summarised and listed at the screening visit: age (calculated in whole years), gender, race, ethnicity, height, weight, BMI, waist circumference. Age will be split into four groups and will be included in the demographic and baseline characteristics summary table. The following age groups will be displayed:

- >=18 - <30
- >=30 - <50
- >=50 - <70
- >= 70

Baseline disease characteristics including time since CAH diagnosis, whether the subject was hospitalized in the last year due to CAH, the number of adrenal crises in the past year and prior CAH medications will be summarised and detailed listings will be produced.

Congenital adrenal hyperplasia medical history, other medical history excluding CAH related events and prior medications will each be summarised and detailed listings will be produced. Mutation status will also be listed.

10.4. Treatment compliance

For treatment compliance, overall compliance will be calculated and the overall period will start from the first dose of randomised study treatment up to the last dose taken.

The overall compliance will be calculated as a percentage for each subject by

$$\frac{\text{actual total dose}}{\text{expected total dose}} \times 100.$$

To calculate the expected total dose, dose titrations are to be taken into account. For each dose regimen the expected total dose will be calculated by summing the total daily dose for the duration of the dose regimen. If a subject has their dose changed then the expected total dose will be calculated by summing the total daily dose of all the dosing regimens. If the study end day of a dosing regimen overlaps with the study start day of the next dosing dose regimen then the average total daily dose of the two dosing intervals will be used for the overlapping study day.

The actual total dose will be calculated by subtracting the number and dose of capsules returned from the number and dose of capsules dispensed.

Actual total dose and expected total dose will only be calculated when a subject has a full record of drug accountability.

[redacted]

Summary statistics will be produced for the overall subject compliance. A listing of subject compliance (including flags for when this is <80% or >120%) and a listing of drug accountability will be produced.

A listing of dispensed sick day medication accountability will be produced detailing the quantity dispensed and returned.

10.5. 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. The calculation of the primary efficacy variable is described 9.2.2. The comparison will performed using an ANCOVA linear model as described in 8.2. The unadjusted mean of the primary efficacy variable will be presented along with the least squares (LS) estimated mean. The difference in LS means will be presented with the associated 95% two-sided confidence interval and p-value. Residual plots of scaled residuals will be used to check the fit of the model and assess whether there is any evidence of non-normality.

Summary statistics will be produced for the absolute values and change from baseline at each visit (weeks 4, 12 and 24) for the primary efficacy variable by treatment group and pre-baseline standard therapy. The geometric mean of the 17-OHP concentration will be plotted along with the 95% confidence intervals at each time point over the 24hr sampling period (15:00h to 15:00h) for each treatment group and pre-baseline standard therapy for week 24 for the primary analysis. The plot will be repeated for the baseline, week 4 and week 12 visits as part of the exploratory analyses.

Three subject profile plots will be created for each subject displaying the following results over the 24hr sampling period (15:00h to 15:00h) for week 24: 17-OHP concentration-time (on a logarithmic scale) and absolute (unsigned) deviations from the “normal” mean (SDS score) (See 9.2.2). The two subject profiles will be repeated for the baseline, week 4 and week 12 visits as part of the exploratory analyses.

All summary tables and plots above will be repeated for A4 for the secondary hormonal profile analysis.

The above analyses will be repeated in the full analysis set as part of the secondary analyses.

10.6. Secondary efficacy analyses

10.6.1. Secondary hormonal profile analysis

There will be a comparison of the mean change from baseline to 24 weeks in the natural logarithm of the mean over the 24-hour SDS profile for the natural logarithm of A4 between the Chronocort® treatment group and the standard therapy treatment group within the efficacy evaluable analysis set. The comparison will performed using an ANCOVA linear model as described in 8.2. The same summary statistics will be produced for A4 as the primary efficacy analysis (see 10.5).

This analysis will be repeated for each of the individual baseline treatment strata for both 17-OHP and A4.

A responder analysis to compare the response between the Chronocort® treatment group and the standard therapy treatment group within the efficacy evaluable analysis set will be performed using logistic regression with adjustment for pre-baseline standard therapy. A subject will be considered a responder if their 09:00h result at week 24 is in the optimal and reference ranges as defined in Table 7. The number and percentage of subjects with a response will be presented together with the

[redacted]

adjusted response rate and the odds ratio will be estimated together with two-sided confidence interval and p-value.

Summary Statistics will be produced for the 09:00h result at week 24.

Table 7: Optimal and reference ranges for responder analysis

17-OHP	1.2- 36.4 nmol/L
Androstenedione (A4)	Males: 1.4 – 5.2 nmol/L Females: 1.0 – 7.0 nmol/L

Source:

[#] 17-OHP: Note the Mayo Clinic laboratory normal ranges for 17-OHP were derived from a very small number of volunteers, who did not have CAH and for whom nothing else was known, e.g. time of day, comorbidities. The appropriateness of trying to drive the CAH population into this range is questionable and therefore based on verbal feedback from clinicians who manage these patients, a broader "optimal range" has been used for 17-OHP).

**Mayo Clinic.*

A4: http://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/9709

The above analyses will be repeated in the full analysis set.

10.6.2. DEXA scans

The mean change from baseline to 24 weeks in body composition (DEXA) between the Chronocort® treatment group and the standard therapy treatment group will be compared separately for fat mass, lean mass and total bone density using an ANCOVA linear model as described in 8.2. This will be based on the efficacy evaluable analysis set excluding Germany (as DEXA scans were not performed at sites in Germany).

Summary statistics will be produced for the absolute values and change from baseline in body composition (DEXA) at each visit (weeks 4, 12 and 24).

10.7. Other efficacy analysis

The following analyses described in this section are considered exploratory, in order to aid better understanding of the effect of Chronocort® in CAH. As such, a limited number of analyses are described to cover the key exploratory objectives outlined in the protocol and in section 2.4.

10.7.1. Exploratory hormonal profile analysis

The natural logarithm of the means over the partial profiles of 17-OHP and A4 at 15:00-23:00, 23:00-07:00, and 07:00-15:00 (all refer to actual clock time of sampling) for week 24.

The natural logarithm of the mean SDS profile will be calculated in the same way as described in Section 9.2.2, with the first and last observations weighted half compared with the others.

The primary endpoint measure (natural logarithm of the 24 hour 17-OHP profile) will also be presented for the profiles measured at 4 and 12 weeks for the purposes of titration as described in section 10.5.

[redacted]

The ANCOVA analysis for 8-hour profiles at 24 weeks and the 24-hour profiles at 4 and 12 weeks will be conducted following the method described in Section 10.5. These analyses will be repeated for the separate pre-baseline strata.

10.7.2. Bone markers and laboratory assessments of special interest

Changes relative to standard treatment in:

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

For the assessment of glucose and insulin, the homeostasis model assessment of insulin resistance (HOMA-IR) value (Wallace TM, 2004) will be calculated using fasting values with following formula:

HOMA-IR = [glucose (mmol/L) * insulin (µU/mL)/22.5].

Change from baseline will be calculated at each visit (Week 4, Week 12, and Week 24) and summary statistics will be presented for both absolute values and change from baseline for all bone markers and laboratory assessments of special interest listed above by treatment group, pre-baseline standard therapy and visit. Shift tables of baseline to minimum and maximum on-treatment will be produced for the appropriate parameters displaying the number and percentage of subjects in each of the categories (High, Low and Normal) relative to the category of their baseline assessment. Results considered clinically significant by the investigator will be summarised. Detailed listings will be produced for all bone markers and laboratory assessments of special interest. In addition, boxplots of change from baseline over time for each bone marker or laboratory assessment of special interest will be produced along with a line connecting the mean change through time.

10.7.3. Quality of life (QoL) questionnaires

Changes relative to standard treatment in QoL at 24 weeks, measured using three instruments: SF-36®, MAF, EQ-5D™.

SF-36®

The SF-36® questionnaire is a multipurpose, generic, short-form health survey containing 36 questions (4-week recall) yielding 8 health domain scales and 2 psychometrically based physical and mental component summary measures (Maruish 2011). For each questionnaire, standardised scores will be generated using a validated scoring software package (QualityMetric Health Outcomes™ Scoring Software 4.5) to calculate scores for for the 8 health domain scales and 2 summary measures using algorithms specific to the questionnaire.

The two summary measures are referred to as the physical component score and mental component score.

The 8 health domain scales to be summarised are:

- Physical Functioning (PF)
- Role-Physical (RP)
- Bodily Pain (BP)
- General Health (GH)

[redacted]

- Vitality (VT)
- Social Functioning (SF)
- Role-Emotional (RE)
- Mental Health (MH)

For each summary measure and scale, the change from baseline and percentage change from baseline at week 24 will be calculated. Summary statistics for absolute values at each visit, change and percentage change from baseline at week 24 will be tabulated by treatment group and pre-baseline standard therapy.

Individual question scores, summary measure scores and scale scores will be listed.

Multidimensional Assessment of Fatigue (MAF)

The MAF is a self-administered questionnaire consisting of 16 questions. The Global Fatigue Index (GFI) will be calculated using a standard method specific to the MAF questionnaire. This combines the responses to the questionnaire to give one score ranging from 1 (no fatigue) to 50 (severe fatigue).

To calculate the GFI: Convert item #15 to a 0-10 scale by multiplying each score by 2.5 and then sum items #1, 2, 3, average #4-14, and newly scored item #15.

Scores range from 1 (no fatigue) to 50 (severe fatigue). Do not assign a score to items #4-14 if respondent indicated they "do not do any activity for reasons other than fatigue." If respondents select no fatigue on item #1, assign a zero to items #2-16. Item #16 is not included in the GFI.

The change from baseline and percentage change from baseline in GFI at week 24 will be calculated. Summary statistics for absolute values of GFI, change and percentage change from baseline at week 24 will be tabulated by treatment group and pre-baseline standard therapy.

Individual question scores and Global Fatigue index will be listed.

EQ-5D™

The EQ-5D™ questionnaire consists of two parts, the EQ-5D™ descriptive system and the EQ visual analogue scale (VAS). The descriptive system consists of 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The EQ VAS is a visual scale in which the subject gives a single score between 0 and 100.

The results from the dimensions from will be combined using a standard method specially designed for the EQ-5D™ questionnaire to give a single index value (EuroQol Research Foundation). Two methods will be used to calculate the single index value:

Method 1 will use the directly elicited 5L value set for the EQ-5D™ questionnaire as specified in Devlin 2016.

Method 2 will use mapping approach described in van Hout 2012.

A table showing the frequency and percent of subjects with each score for each of the domains will be produced by treatment group and pre-baseline standard therapy. The change from baseline and percentage change from baseline will be calculated for both the single index value calculated from the 5 dimensions and the VAS score. Summary statistics for the absolute values of these two scores as well as change and percentage change from baseline at week 24 will be tabulated by treatment

group and pre-baseline standard therapy. Shift table of baseline to end of study will be produced by domain, pre-baseline therapy and treatment group.

Individual question scores for the EQ-5D™ descriptive system, the calculated single index value and EQ VAS score will be listed.

10.7.4. Use of glucocorticoids

Use of glucocorticoids at visit 1 (baseline) and visit 4 (week 24) of the study will be presented as individual glucocorticoids used. Change in dose of last glucocorticoid from baseline to each visit will be presented as hydrocortisone equivalents using accepted conversion constants for the calculations (see Section 9.2.3).

A summary of the frequency and percent of subjects with total hydrocortisone dose equivalent increments versus baseline at each visit falling within the following categories:

- Dose increases versus baseline:
  - No increase observed (≤ 0mg),
  - > 0 to ≤ 5mg increase,
  - > 5 to ≤ 10mg increase,
  - > 10 to ≤ 15mg increase,
  - > 15 to ≤ 20 mg increase,
  - > 20 to ≤ 25 mg increase,
  - > 25 to ≤ 30 mg increase and
  - > 30 mg increase.
- Dose decreases versus baseline:
  - No decrease observed (≤ 0mg),
  - > 0 to ≤ 5mg decrease,
  - > 5 to ≤ 10mg decrease
  - > 10 to ≤ 15mg decrease,
  - > 15 to ≤ 20 mg decrease,
  - > 20 to ≤ 25 mg decrease,
  - > 25 to ≤ 30 mg decrease and
  - > 30 mg decrease.

10.7.5. Sensitivity analyses

If the primary analysis demonstrates favourability towards Chronocort®, sensitivity analyses will be performed using different definitions of the SDS to check the robustness of the result.

[redacted]

11. Safety analyses

11.1. Extent of exposure

Summary statistics will be presented for both the total duration and actual duration of exposure in days. Total treatment duration will be calculated as follows:

Date of first dose of study drug – Date of last dose of study drug + 1.

Actual treatment duration will consider dose interruptions and will be the total number of days in which the subject took at least one dose of study medication.

The recommended dose titrations which are made by a central independent blinded physician within 2 weeks of each profiling visit will be summarised by treatment group for week 4 and week 12. The summary will show frequency and percentage of subjects requiring a dose adjustment, as well as the dose adjustment required (for both treatment groups: increase morning dose, increase evening dose, decrease morning dose, decrease evening dose; and additional doses for standard GC therapy: increase middle dose, decrease middle dose). A listing of dose titration decisions which are contrary to those directed by the blinded physician will be produced showing the reason for the deviation.

A summary of unplanned dose changes will be produced showing the number of increases and decreases in dose that were unplanned i.e. not at the scheduled timepoints.

A summary of the number and percentage of subjects with dose increases, reductions and interruptions will be produced also showing the number of dose increases, reductions and interruptions per subject, and summary of reason for dose increases, reductions and interruptions.

All treatment exposure data will be listed in detail. In addition to this, the study drug dosing instructions given to the subject by the investigator will be listed in detail.

11.2. Adverse events

All AEs, in terms of MedDRA system organ class (SOC) and preferred term (PT), will be listed and summarised descriptively by count (n) and percentage (%) for each treatment group. For the purpose of the CSR, only AEs up to the follow up-telephone call after the week 24 visit will be included in summaries. Any AE occurring before randomised Chronocort®/ standard glucocorticoid replacement therapy treatment (i.e. before the first dose of randomised treatment on Day 2 of visit 1) will be included in listings but not summaries, unless there is an increase in severity occurring after the start of treatment. Similarly, any AE occurring after the last day of study treatment for subjects who enter the extension study or the last day of study treatment plus 30 days for subjects who do not enter the extension study will be listed but not summarised.

All reported AEs will be listed along with the study day of onset, resolution, duration, seriousness, severity, action taken with study drug, relationship to study drug, treatments administered and outcome. Frequencies and percentages of subjects reporting each PT will be presented (i.e. multiple events per subject will not be accounted for, apart from on the episode level summaries). Where severity is displayed, if a subject has more than one AE of the same term, the maximum severity will be used.

An overview table of AEs displaying the number of AEs by treatment group as well as the number and percent of subjects with the following categories will be produced:

- Any AE
- Any AE causally related to IMP

[redacted]

- Any AE leading to sick day rules
- Any AE leading to sick day rules causally related to IMP
- Any AE leading to Addisonian crisis
- Any AE leading to Addisonian crisis causally related to IMP
- Any AE leading to unexpected therapeutic benefit
- Any AE leading to unexpected therapeutic benefit causally related to IMP
- Any AE leading to death
- Any AE leading to death causally related to IMP
- Any AE leading to discontinuation
- Any AE leading to discontinuation causally related to IMP
- Any SAE
- Any SAE causally related to IMP
- Any SAE leading to discontinuation
- Any SAE leading to discontinuation causally related to IMP.

The number and percent of subjects experiencing each AE will be summarised by treatment, SOC and PT for the following:

- All AEs
- All serious adverse events (SAEs)
- SAEs with outcome of death
- AEs leading to discontinuation of study treatment
- SAEs leading to discontinuation of study treatment

Separate summaries for AEs and SAEs will be created, split by the following:

- Causality (not related, related to the investigational medicinal product (IMP), related to sick day medication, related to an interaction between IMP and sick day medication, related to either IMP or sick day medication)
- Action taken (dose unchanged, dose increased, dose decreased, drug interrupted, drug withdrawn)
- Outcome (Resolved, resolved with sequelae, resolving, not resolved, unknown, fatal)
- By severity (Mild, moderate, severe)

Additionally, all summaries above have the potential to be repeated to show the number of episodes in each category (using total number of patient-years exposed to IMP as the denominator). This is optional and to be done only if there are differences in exposure between treatment groups. A decision as to whether this is required will be made at the Data Review Meeting.

Tables of most common AEs (frequency of >10%) and common SAEs (>1% of subjects overall), will be summarised by preferred term, by decreasing frequency. These thresholds may be adjusted downwards at the Data Review Meeting if there are relatively few subjects with AEs.

11.3. Adverse events of special interest

11.3.1. Use of "sick days"

As per the protocol each site will have a set of sick day rules where certain AEs will result in emergency hydrocortisone being taken.

All AEs leading to use of "sick day rules" will be summarised (frequency and percentage of subjects) by system organ class, preferred term and treatment group.

In addition, all AEs leading to use of "sick day rules" will also be summarised (frequency and percentage of subjects) by preferred term, route of, and specific sick day medication by treatment group.

There will be a separate listing showing details of all AEs leading to use of sick day rules and specific sick day medication.

11.3.2. Adrenal crises

All AEs leading to adrenal crises as defined in the protocol will be summarised (frequency and percentage of subjects) by SOC, PT and treatment group. There will be a separate listing showing details of all AEs leading to adrenal crises.

11.3.3. Unexpected therapeutic benefit

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

11.4. Routine clinical laboratory evaluations

11.4.1. Naming conventions

The laboratory test names will be displayed using test names consistent with the protocol for all reporting. Study Data Tabulation Model (SDTM) standard names will be derived in the dataset, but not displayed. Where needed, an abbreviated version of the laboratory test names may be displayed.

A full list of laboratory display names (full and an acceptable abbreviation) together with their SDTM laboratory test code and name is given in Appendix B for haematology, clinical biochemistry, bone markers and laboratory parameters of special interest, and urinalysis tests.

11.4.2. Haematology

The following haematology parameters will be collected:

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 (PLT), white blood cell count (WBC), WBC differential count: neutrophils, eosinophils, basophils, lymphocytes, monocytes (absolute).

All laboratory analyses will be carried out by the central laboratory Q^2 Solutions. If laboratory results are needed urgently for safety reasons during the study, these can be processed at the local

[redacted]

laboratory and the results recorded in the electronic case report form (eCRF). For the local lab data, the local reference ranges will be used and if for any reason these are missing, the central ranges will be used, with any such occurrences clearly marked in the listings.

Change from baseline will be calculated at each visit (Week 4, Week 12, and Week 24) and summary statistics will be presented for both absolute values and change from baseline for all haematology parameters by treatment group, pre-baseline standard therapy and visit. Shift tables of baseline to minimum and maximum on-treatment will be produced for the appropriate parameters displaying the number and percentage of subjects in each of the categories (High, Low and Normal) relative to the category of their baseline assessment. Haematology results considered clinically significant by the investigator will be summarised at each visit. Detailed listings will be produced for all haematology parameters. In addition, boxplots of change from baseline in haematology parameters over time will be produced along with a line connecting the mean change through time.

For the purpose of both Listings and Summary Tables, the haematology results will be divided into the following groups of related items:

Haematology (1)

- Red blood cell count (RBCs)
- haemoglobin (Hb)
- haematocrit (Hct)

Haematology (2)

- red cell distribution width (RDW)
- mean corpuscular volume (MCV)
- mean cell haemoglobin (MCH)
- mean cell haemoglobin concentration (MCHC)
- platelet count (PLTs)

RDW-CV(%) will be provided by the central laboratory. In any local laboratories provide RDW-SD (fL) measurements, RDW-CV(%) will be calculated from the RDW-SD (fl) and MCV measurements using the formula:

- RDW-CV(%) = (RDW-SD(fL)/MCV)*100.

Haematology (3)

- total white blood cell count (WBCs)
- lymphocyte count
- monocyte count
- neutrophil count
- basophil count
- eosinophil count

White blood cells (Leukocytes) are made up of Neutrophils + Eosinophils + Basophils +Lymphocyte + Monocyte.

Therefore, to express any of the components as a percentage of Leukocytes, the formula is:

- Components cell count/Leukocytes counts*100, (e.g. Neutrophils count/Leukocytes counts*100)

However, if the percentage is given and to derive the cell count, the formula is:

- (Components percentage/100)*Leukocytes counts, (e.g. (Neutrophils % /100)*Leukocytes counts)
- Note it is important that the component cell count and white blood cell count (Leukocytes) are expressed in the same units when applying these derivations.

11.4.3. Clinical biochemistry

The following routine biochemistry parameters will be collected:

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

All laboratory analyses will be carried out by the central laboratory Q^2 Solutions. If laboratory results are needed urgently for safety reasons during the study, these can be processed at the local laboratory and the results recorded in the electronic case report form (eCRF). For the local lab data, the local reference ranges will be used and if for any reason these are missing, the central ranges will be used, with any such occurrences clearly marked in the listings.

Change from baseline will be calculated at each visit (Week 4, Week 12, and Week 24) and summary statistics will be presented for both absolute values and change from baseline for all clinical biochemistry parameters by treatment group, pre-baseline standard therapy and visit. Shift tables of baseline to minimum and maximum on-treatment will be produced for the appropriate parameters displaying the number and percentage of subjects in each of the categories (High, Low and Normal) relative to the category of their baseline assessment. Biochemistry results considered clinically significant by the investigator will be summarised. Detailed listings will be produced for all routine biochemistry parameters. In addition, boxplots of change from baseline in clinical biochemistry parameters over time will be produced along with a line connecting the mean change through time.

For the purpose of both Listings and Summary Tables, the clinical biochemistry results will be divided into the following groups of related items:

Biochemistry (1)

- Sodium
- potassium
- chloride
- total CO_2
- total calcium
- total magnesium
- inorganic phosphorus

Biochemistry (2)

- creatinine
- blood urea nitrogen (BUN)
- glucose

[redacted]

- uric acid
- total protein
- albumin

Biochemistry (3)

- alkaline phosphatase
- ALT/GPT
- AST/GOT
- total creatinine kinase
- lactate dehydrogenase
- total bilirubin
- direct bilirubin

Biochemistry (4)

- total cholesterol
- high density lipoprotein (HDL) cholesterol
- low density lipoprotein (LDL) cholesterol
- triglycerides

11.4.4. Urinalysis

The following urinalysis parameters will be collected: protein, specific gravity, ketones, urobilinogen, bilirubin, pH, blood.

For the continuous results (pH and specific gravity), change from baseline will be calculated at each visit (Week 4, Week 12, and Week 24) and summary statistics will be presented for both absolute values and change from baseline by treatment group, pre-baseline standard therapy and visit. In addition, boxplots of change from baseline in continuous urinalysis parameters over time will be produced along with a line connecting the mean change through time.

For all other urinalysis parameters, the frequency and percentage of subjects with results in each category, and shift table of baseline to worst on-treatment will be presented by treatment group, pre-baseline standard therapy and visit. 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.

Urinalysis results considered clinically significant by the investigator will be summarised.

A pregnancy test will also be carried out in female subjects of child bearing potential and the results will be listed.

11.5. Vital signs

The following vital signs will be collected: systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate, respiratory rate, temperature, height, waist circumference, weight, BMI.

The change from baseline will be calculated and summary statistics will be tabulated for both absolute values and change from baseline by treatment group, pre-baseline standard therapy, and visit. Shift tables of baseline to minimum and maximum on-treatment will be created for the following vital signs: SBP and DBP. In addition, boxplots of change from baseline in vital signs over time will be produced along with a line connecting the mean change through time.

[redacted]

Vital signs will be listed and abnormal findings will be marked.

The following reference ranges will be used to determine the categories for the vital signs shift table, and to mark the abnormal (high/low) findings in the vital signs listing:

- Systolic blood pressure: Low < 100 mmHg; Normal ≥ 100 mmHg to ≤ 150 mmHg; High > 150 mmHg
- Diastolic blood pressure: Low < 60 mmHg; Normal ≥ 60 mmHg to ≤ 95 mmHg; High > 95 mmHg

11.6. Electrocardiogram (ECG)

The following ECG data will be collected*:* heart rate, PR interval, QRS width, QT interval and Bazett's and Fridericia QTc interval (QTcB and QTcF).

The change from baseline will be calculated and summary statistics will be tabulated for both absolute values and change from baseline by treatment group, visit and dose level. Abnormal findings will be tabulated by visit showing a frequency count and percentage of subjects with at least one abnormal finding.

ECG results will be listed and abnormal findings will be marked, together with an indication of whether or not that finding was clinically significant. Values with a change from baseline > 30 msec in QT interval, QTcB and QTcF will be flagged in the listing.

The following reference ranges will be used to determine the categories for the ECG shift table, and to mark the abnormal (high/low) findings in the ECG listing:

- Heart rate: Low < 40 msec; Normal ≥ 40 msec to ≤ 110 msec; High > 110 msec
- PR interval: Low < 120 msec; Normal ≥ 120 msec to ≤ 220 msec; High > 220 msec
- QRS width: Low < 70 msec; Normal ≥ 70 msec to ≤ 120 msec; High > 120 msec
- QT interval: Low < 330 msec; Normal ≥ 330 msec to ≤ 450 msec; High > 450 msec
- QTcB: Low < 350 msec; Normal ≥ 350 msec to ≤ 450 msec; High > 450 msec
- QTcF: Low < 350 msec; Normal ≥ 350 msec to ≤ 450 msec; High > 450 msec

11.7. Other safety evaluations

11.7.1. Physical examination

A shift table of baseline assessment of full physical examination to week 24/End of Study (EOS) by category, pre-baseline therapy and treatment group will be produced. At screening and week 24/EOS, if the eCRF confirms the physical examination has been performed and there are no abnormalities, a 'Normal' status will be imputed for each of the physical examination categories:

- General
- Cardiovascular
- Neurological
- Gastrointestinal
- Respiratory
- Skin
- Head, eyes, ears, nose & throat

[redacted]

- Musculoskeletal including extremities
- Genitourinary
- Other

Abnormal physical examination status categories are captured in the eCRF, together whether the finding was clinically significant.

Physical examination results will be listed and abnormal findings will be marked, together with an indication of whether or not that finding was clinically significant.

11.7.2. Concomitant medications excluding glucocorticoid steroids

Concomitant medications excluding glucocorticoid steroids[a], which include medications that began prior to date of randomisation but were ongoing after first dose of randomised treatment or started after the start of randomised treatment, will be summarised descriptively by ATC text, generic term, and treatment group using counts and percentages as appropriate.

A detailed listing of all concomitant medications excluding glucocorticoid steroids will be listed.

[a] The following list of steroids will be excluded from the summaries and listings of concomitant medications and instead will be reported under *sick day medications and steroids taken in addition to IMP* (see section 11.7.3).

ATCCODE	LEVEL	ATC Text
D07AC	4	Corticosteroids, potent (group III)
D07AD	4	Corticosteroids, very potent (group IV)
H02	2	CORTICOSTEROIDS FOR SYSTEMIC USE
H02A	3	CORTICOSTEROIDS FOR SYSTEMIC USE, PLAIN
H02AA	4	Mineralocorticoids
H02AB	4	Glucocorticoids[b]
H02B	3	CORTICOSTEROIDS FOR SYSTEMIC USE, COMBINATIONS
H02BX	4	Corticosteroids for systemic use, combinations
R01AD	4	Corticosteroids
R03BA	4	Glucocorticoids
S01BA	4	Corticosteroids, plain
S02B	3	CORTICOSTEROIDS
S02BA	4	Corticosteroids
S03B	3	CORTICOSTEROIDS
S03BA	4	Corticosteroids

[b] Excluding Fludrocortisone, which will be summarised alongside concomitant medication.

11.7.3. Use of dispensed sick day medications and steroids taken in addition to IMP

Use of dispensed sick day medications by route and drug name and steroids taken in addition to IMP (which includes medications that began prior to the date of randomisation but were ongoing after first dose of randomised treatment or started after randomised treatment) by ATC text and generic term will be summarised by treatment group.

A detailed listing of all dispensed sick day medications and steroids taken in addition to IMP will be produced.

11.7.4. Adrenal insufficiency

Signs and symptoms of adrenal insufficiency will be summarised by treatment group and visit. A listing of all signs and symptoms of adrenal insufficiency will be produced flagging any significant findings and significant findings related to under/over replacement of steroid.

12. Changes from the planned analyses

At the time of finalising the SAP version 2.0, there are minor changes from the planned analyses specified in the protocol. For routine clinical laboratory variables (haematology and clinical biochemistry) shift tables to each visit relative to baseline have been replaced with shift tables to minimum on-treatment versus baseline and to maximum on-treatment versus baseline. This is judged to be a more conservative approach to detecting potential safety signals from clinical laboratory data. For vital signs, the split by dose level has been removed from the summaries of absolute values and change from baseline over time, due to the low number of subjects per category. Instead this will be assessed via listings. For a similar reason, the split by dose level has been removed from the summary of abnormal ECG results.

13. References

Arlt W, Willis DS, Wild SH, et al. Health status of adults with congenital adrenal hyperplasia: a cohort study of 203 patients. J Clin Endocrinol Metab. 2010;95(11):5110-5121.

Han TS, Walker BR, Arlt W, Ross RJ. Treatment and health outcomes in adults with congenital adrenal hyperplasia. Nat Rev Endocrinol. 2014;10(2):115-124.

Devlin, N., Shah, K., Feng, Y., Mulhern, B. and Van Hout, B. Valuing Health-Related Quality of Life: An EQ-5D-5L Value Set for England. Office of Health Economics Research Paper 2016.

EuroQol Research Foundation. *euroqol.org*. Retrieved (Sept 2015) from http://www.euroqol.org/fileadmin/user_upload/Documenten/PDF/Folders_Flyers/EQ-5D-5L_UserGuide_2015.pdf

EuroQol Research Foundation. *euroqol.org*. Retrieved (Sept 2017) from https://euroqol.org/wp-content/uploads/2016/09/EQ-5D-5L_UserGuide_2015.pdf

Finkielstain GP, Kim MS, Sinaii N, Nishitani M, Van Ryzin C, Hill SC, et al. Clinical characteristics of a cohort of 244 patients with congenital adrenal hyperplasia. Journal of Clinical Endocrinology & Metabolism 2012;97(12): 4429-38.

Maruish, M.E. (Ed.). User's manual for the SF-36v2 Health Survey (3rd ed, 2011). Lincoln, RI: QualityMetric Incorporated.

Merke DP, Bornstein SR. Congenital adrenal hyperplasia. Lancet. 2005;365(9477):2125-2136.

New MI. Extensive clinical experience: nonclassical 21-hydroxylase deficiency. J Clin Endocrinol Metab. 2006;91(11):4205-4214.

Pang S, Clark A, Neto EC, et al. Congenital adrenal hyperplasia due to 21-hydroxylase deficiency: Newborn screening and its relationship to the diagnosis and treatment of the disorder. Screening. 1993;2(2-3);105-139

Therrell BL. Newborn screening for congenital adrenal hyperplasia. Endocrinol Metab Clin North Am. 2001;30(1):15-30.

van Hout B, Janssen MF, Feng Y, Kohlmann T, Busschbach J, Golicki D, Lloyd A, Scalone L, Kind P, Pickard S. Interim Scoring for the EQ-5D-5L: Mapping the EQ-5D-5L to EQ-5D-3L Value Sets. Value in Health. 2012; 15: 708-715.Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modelling. Diabetes Care. 2004 Jun;27(6):1487-95.

14. Appendix A – List of tables, listings and figures

14.1. List of planned tables

Study population
Subject disposition (All subjects)
Protocol deviations (All subjects)
Analysis sets (All subjects)
Demographic characteristics (Safety analysis set)
Baseline disease characteristics (Safety analysis set)
CAH medical history (Safety analysis set)
Other medical history excluding CAH events (Safety analysis set)
Prior medications (Safety analysis set)
Concomitant medications excluding steroids (Safety analysis set)
Use of sick day medication and steroids taken in addition to IMP (Safety analysis set)
Subject compliance (Safety analysis set)
Use of glucocorticoids: last dose prior to each visit (Safety analysis set)
Table of change from baseline to each visit in dose (hydrocortisone equivalent) of last glucocorticoid (Safety analysis set)
Categories of hydrocortisone dose equivalent increments versus baseline (Safety analysis set)
Safety
Duration of exposure (Safety analysis set)
Dose titrations recommended by the independent blinded physician (Safety analysis set)
Reasons for dose increases and reductions recommeded by the independent blinded physician (Safety analysis set)
Table of dose titrations instructed by the Investigator (Safety analysis set)
Reasons for dose changes instructed by the Investigator (Safety analysis set)
Adverse event in any category - subject level (Safety analysis set)
Adverse event in any category - episode level (Safety analysis set)
Listing of deaths (Safety analysis set)
Adverse events leading to death (Safety analysis set)
Listing of adverse events leading to death (safety analysis set)
All adverse events (Safety analysis set)
All serious adverse events (Safety analysis set)
Listing of all serious adverse events (Safety analysis set)
Adverse events leading to discontinuation of study treatment (Safety analysis set)
Listing of adverse events leading to discontinuation of study treatment (Safety analysis set)
Adverse events by causality (Safety analysis set)
Adverse events by action taken (Safety analysis set)
Adverse events by outcome (Safety analysis set)
Adverse events by severity (Safety analysis set)
Repeat above 6 tables for SAEs
Most common (frequency of >10%) adverse events (Safety analysis set)
Most common (frequency of >1%) SAEs (Safety analysis set)
Adverse events leading to use of "sick day rules" (Safety analysis set)

[redacted]

Adverse events leading to use of “sick day rules” by sick day medication (Safety analysis set)
Adverse events leading to Adrenal crises (Safety analysis set)
Adverse events of unexpected therapeutic benefit (Safety analysis set)
Repeat of AE Tables at episode level to be decided at Data Review meeting
Signs and symptoms of adrenal insufficiency and over treatment (Safety analysis set)
Haematology (1) laboratory variables (Safety analysis set)
Change from baseline in Haematology (1) laboratory variables (Safety analysis set)
Shift table of baseline to minimum on-treatment for Haematology (1) laboratory variables (Safety analysis set)
Shift table of baseline to maximum on-treatment for Haematology (1) laboratory variables (Safety analysis set)
Haematology (1) results considered clinically significant by the investigator (Safety analysis set)
Repeat above 5 tables for Haematology (2), Haematology (3)
Biochemistry (1) laboratory variables (Safety analysis set)
Change from baseline in Biochemistry (1) laboratory variables (Safety analysis set)
Shift table of baseline to minimum on-treatment for Biochemistry (1) laboratory variables (Safety analysis set)
Shift table of baseline to maximum on-treatment for biochemistry (1) laboratory variables (Safety analysis set)
Biochemistry (1) results considered clinically significant by the investigator (Safety analysis set)
Repeat above 5 tables for Biochemistry (2), Biochemistry (3), Biochemistry (4)
Urinalysis results - continuous parameters (Safety analysis set)
Change from baseline for urinalysis results - continuous parameters (Safety analysis set)
Categorical urinalysis parameters (Safety analysis set)
Shift table of baseline to worst on-treatment for categorical urinalysis laboratory variables (Safety analysis set)
Continuous urinalysis parameters - results considered clinically significant by the investigator (Safety analysis set)
Categorical urinalysis parameters - results considered clinically significant by the investigator (Safety analysis set)
Vital signs variables (Safety analysis set)
Vital signs variables, change from baseline (Safety analysis set)
Vital signs shift table for SBP and DBP, baseline to minimum on-treatment (Safety analysis set)
Vital signs shift table for SBP and DBP, baseline to maximum on-treatment (Safety analysis set)
Electrocardiogram variables over time (Safety analysis set)
Electrocardiogram variables, change from baseline (Safety analysis set)
Abnormal electrocardiogram findings (Safety analysis set)
Physical examination - baseline versus end of study assessment (Safety analysis set)
Efficacy
Primary efficacy analysis for 17-OHP, change from baseline to 24 weeks in primary efficacy variable, analysis of covariance model (Efficacy evaluable analysis set)
Repeat above 1 table for weeks 4 and 12

[redacted]

Secondary efficacy analysis of 17-OHP by pre-treatment strata, change from baseline to 24 weeks in primary efficacy variable, analysis of covariance model (Efficacy evaluable analysis set))
Repeat above 1 table weeks 4 and 12
Summary of absolute values of primary efficacy variable for 17-OHP, by visit (Efficacy evaluable analysis set)
Summary of change in baseline in primary efficacy variable for 17-OHP, by visit (Efficacy evaluable analysis set)
Secondary efficacy analysis of responders at 09:00h week 24 for 17-OHP, logistic regression model (Efficacy evaluable analysis set)
Summary of the 17-OHP results at 09:00h week 24 (Efficacy evaluable analysis set)
Repeat all 17-OHP only Efficacy outputs above for the A4 hormone (including repeats)
Repeat all Efficacy outputs above in the Full analysis set (including repeats)
Secondary efficacy analysis of change from baseline to 24 weeks in body composition - Dual Energy X-ray Absorptiometry, analysis of covariance model (Efficacy evaluable analysis set)
Summary of absolute values of body composition - Dual Energy X-ray Absorptiometry (Efficacy evaluable analysis set)
Summary of change from baseline in body composition - Dual Energy X-ray Absorptiometry (Efficacy evaluable analysis set)
Exploratory analysis of 17-OHP 8-hour profiles: change from baseline to 24 weeks in primary efficacy variable, analysis of covariance model (Efficacy evaluable analysis set)
Above partial profile ANCOVA table to be repeated for separate pre-baseline strata
All partial profile outputs above to be repeated for A4 hormone (total of 2 tables)
Summary of change from baseline for bone markers and laboratory assessments of special interest (Efficacy evaluable analysis set)
Summary of absolute values for bone markers and laboratory assessments of special interest (Efficacy evaluable analysis set)
Shift table of baseline to minimum on-treatment for bone markers and laboratory assessments of special interest (Efficacy evaluable analysis set)
Shift table of baseline to maximum on-treatment for bone markers and laboratory assessments of special interest (Efficacy evaluable analysis set)
Summary of clinically significant results for bone markers and laboratory assessments of special interest (Efficacy evaluable analysis set)
Summary of SF-36 scores (Efficacy evaluable analysis set)
Summary of SF-36 change from baseline (Efficacy evaluable analysis set)
Summary of SF-36 percentage change from baseline (Efficacy evaluable analysis set)
Repeat above 3 tables for GFI, MAF and EQ-5D™

14.2. List of planned listings

Study population
Subject disposition (All subjects)
Protocol deviations (All subjects)
Listing of subjects with extreme visit deviations (All randomised subjects)

Subjects excluded from the safety analysis set
Subjects excluded from the full analysis set
Subjects excluded from the efficacy evaluable analysis set
Demographic characteristics (Safety analysis set)
Congenital adrenal hyperplasia medical history (Safety analysis set)
Mutation status
Other medical history excluding CAH related events (Safety analysis set)
Pre-baseline therapy strata (Safety analysis set)
Prior medications (Safety analysis set)
Safety
Sick day pack accountability (Safety analysis set)
Steroids and other glucocorticoids taken in addition to IMP (Safety analysis set)
Sick day medication administration (Safety analysis set)
Treatment exposure (Safety analysis set)
Dose titrations recommended by the independent blinded physician (Safety analysis set)
Study drug accountability (Safety analysis set)
Unscheduled dose changes (Safety analysis set)
Investigator adherence to protocol defined dose titrations (Safety analysis set)
Dosing instructions provided to subjects from investigator (Safety analysis set)
Subject compliance (Safety analysis set)
All Adverse events (Safety analysis set)
Serious adverse events leading to death (Safety analysis set)
Adverse events leading to use of sick day rules (Safety analysis set)
Adverse events leading to adrenal crises (Safety analysis set)
Adverse events of unexpected therapeutic benefit (Safety analysis set)
Signs and symptoms of adrenal insufficiency and over treatment (Safety analysis set)
Haematology (1) laboratory variables (Safety analysis set)
Repeat for Haematology (2), Haematology (3)
Biochemistry (1) laboratory variables (Safety analysis set)
Repeat for Biochemistry (2), Biochemistry (3), Biochemistry (4)
Urinalysis laboratory variables (Safety analysis set)
Pregnancy test results (Safety analysis set)
Vital signs (Safety analysis set)
Electrocardiogram parameters (Safety analysis set)
Physical examination (Safety analysis set)
Concomitant medications excluding steroids (Safety analysis set)
Efficacy
Bone markers and laboratory assessments of special interest (Efficacy evaluable analysis set)
DEXA scan parameters (Efficacy evaluable analysis set)
17-OHP and A4 (Full analysis set)
SF-36 scores (Efficacy evaluable analysis set)
MAF scores and GFI (Efficacy evaluable analysis set)
EQ-5D scores (Efficacy evaluable analysis set)

14.3. List of planned figures

14.3.1. Summary figures

Safety
Boxplot of change from baseline over time for red blood cell count (Safety analysis set)
Repeat above figure for all remaining haematology (1), haematology (2) and haematology (3) parameters
Boxplot of change from baseline over time for sodium (Safety analysis set)
Repeat above figure for all remaining biochemistry (1), biochemistry (2), biochemistry (3) and biochemistry (4) parameters
Boxplot of change from baseline over time for pH (Safety analysis set)
Repeat above figure for specific gravity
Boxplot of change from baseline over time for systolic blood pressure (Safety analysis set)
Repeat above figure for the following vital signs parameters: diastolic blood pressure, pulse rate, respiratory rate, temperature, weight, waist circumference and BMI
Efficacy
Geometric mean +/- 95% CI for 17-OHP week 24 profile (Efficacy evaluable analysis set)
Repeat above figure for weeks 4 and 12
Repeat all 17-OHP only Efficacy figures above for the A4 hormone (including repeats)
Repeat all 17-OHP and A4 hormone figures for separate pre-baseline strata (including repeats)
Repeat all 17-OHP and A4 hormone figures for SDS score (including repeats)
Boxplot of change from baseline over time for serum CTX (Efficacy evaluable analysis set)
Repeat boxplot of change from baseline over time for the following bone markers and laboratory assessments of special interest parameters: osteocalcin, total testosterone, fasting insulin, fasting glucose, HOMA-IR, HbA1c, hsCRP and plasma renin activity

14.3.2. Individual patient figures

Efficacy
Concentration-time plot for 17-OHP over 24 hours at week 24 (Efficacy evaluable analysis set)
SDS profile showing unsigned deviations from the "normal" mean at week 24 of 17-OHP (Efficacy evaluable analysis set)
Repeat above 2 figures for weeks 4 and 12 *Note: Additional figures may be required, depending on the final decision on the grouping of reference ranges*
Repeat all 17-OHP only Efficacy figures above for the A4 hormone (including repeats)

15. Appendix B – Laboratory test display names and SDTM standard nomenclature

The preferred display names and SDTM standard names for all laboratory tests to be conducted in this study are given in Table 8. The protocol lab name is preferred for display in all outputs, however the abbreviated display name may be used instead if space is limited on the page. SDTM lab test codes and names are to be included in SDTM-compliant datasets, but will not be displayed in the tables, figures and listings. Note: British English is used for the protocol lab names; American English is used for the SDTM standard names.

Table 8: Lab parameter SDTM test codes and abbreviated display names

Protocol lab name (for display)	Abbreviated display name	SDTM lab test code	SDTM lab test name
	Haematology		
Red blood cell count	RBC	RBC	Erythrocytes
Haemoglobin	Hb	HGB	Hemoglobin
Haematocrit	Hct	HCT	Hematocrit
Red cell distribution width	RDW	RDW	Erythrocytes Distribution Width
Mean corpuscular volume	MCV	MCV	Ery. Mean Corpuscular Volume
Mean cell haemoglobin	MCH	MCH	Ery. Mean Corpuscular Hemoglobin
Mean cell haemoglobin concentration	MCHC	MCHC	Ery. Mean Corpuscular HGB Concentration
Platelet count	PLT	PLAT	Platelets
Total white blood cell count	WBC	WBC	Leukocytes
Lymphocyte count	Lymph.	LYM	Lymphocytes
Monocyte count	Mono.	MONO	Monocytes
Neutrophil count	Neut.	NEUT	Neutrophils
Basophil count	Baso.	BASO	Basophils
Eosinophil count	Eosi.	EOS	Eosinophils
	Chemistry		
Sodium	Sodium	SODIUM	Sodium
Potassium	K	K	Potassium
Chloride	Cl	CL	Chloride
Total CO2	CO2	CO2	Carbon Dioxide
Total calcium	Ca	CA	Calcium
Total magnesium	Mg	MG	Magnesium
Inorganic phosphorus	Phos.	PHOS	Phosphate
Creatinine	Creat.	CREAT	Creatinine
Blood urea nitrogen	BUN	BUN	Blood Urea Nitrogen
Glucose	Gluc.	GLUC	Glucose
Insulin	Insulin	INSULIN	Insulin
Uric acid	Urate	URATE	Urate
Total protein	Prot.	PROT	Protein
Albumin	ALB	ALB	Albumin
Alkaline phosphatase	ALP	ALP	Alkaline Phosphatase
ALT/GPT	ALT	ALT	Alanine Aminotransferase
AST/GOT	AST	AST	Aspartate Aminotransferase
Total creatine kinase	CK	CK	Creatine Kinase
Lactate dehydrogenase	LDH	LDH	Lactate Dehydrogenase

Total bilirubin	Bili.	BILI	Bilirubin
Direct bilirubin	Bili. Dir.	BILDIR	Direct Bilirubin
Total cholesterol	Chol.	CHOL	Cholesterol
High density lipoprotein cholesterol	HDL	HDL	HDL Cholesterol
Low density lipoprotein cholesterol	LDL	LDL	LDL Cholesterol
Triglycerides	Trig.	TRIG	Triglycerides
Special interest			
HbA1c	HbA1c	HBA1C	Hemoglobin A1C
Total testosterone	Testos.	TESTOS	Testosterone
Plasma renin activity	PRA	RENIN	Renin
hsCRP	hsCRP	CRP	C Reactive Protein
C-terminal cross-linked telopeptide	CTX	CTXI	Type I Collagen C-Telopeptides
Osteocalcin	Osteoc.	OSTEOC	Osteocalcin
Urinalysis			
Protein	Prot.	PROT	Protein
Specific gravity	Spec. grav.	SPGRAV	Specific Gravity
Ketones	Ketones	KETONES	Ketones
Urobilinogen	Urobil.	UROBIL	Urobilinogen
Bilirubin	Bili.	BILI	Bilirubin
pH	pH	PH	pH
Blood	Blood	OCCBLD	Occult Blood