Title: Statistical Analysis Plan for DIUR-006: A Phase III extension study of efficacy, safety and tolerability of Chronocort® in the treatment of congenital adrenal hyperplasia

Compound Name/Number: Chronocort®

Effective Date: 12 July 2022

Subject: Congenital Adrenal Hyperplasia

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Signature pages

The signatories on the following pages have all read and approved this present version of the document.

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Abbreviations

17-OHP	17-hydroxyprogesterone
A4	Androstenedione
AE	Adverse event
ALT/GPT	Alanine aminotransferase
AST/GOT	Aspartate aminotransferase
ATC	'Anatomical Therapeutic Chemical' drug classification (WHO)
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
CAH	Congenital adrenal hyperplasia
CK	Creatine kinase
CO_2	Carbon dioxide
CTX	C-terminal cross-linked telopeptide
DBP	Diastolic blood pressure
DEXA	Dual Energy X-ray Absorptiometry
eCRF	Electronic case report form
EQ-5D™	EQ-5D™ Standardised Health Questionnaire (5-level)
GC	Glucocorticoid
GFI	Global Fatigue Index
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
LLT	Lowest Level Term (MedDRA®)
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
PLT	Platelet count
PRA	Plasma renin activity
PT	Preferred term
QoL	Quality of life
RBC	Red blood cell
RDW	Red cell distribution width

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-36®	Medical Outcome Short Form (4-week recall) Health Survey Form 36 (Subject Questionnaire)
SI	International system of units
SOC	System Organ Class
VAS	Visual analogue scale
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

Revision history

Version	Date	Summary of revisions
1.0	27 July 2016	Initial version
2.0	28 June 2018	**Section 1 Introduction:** Clarified that SAP Version 1.0 was written using Protocol Version 3.0 dated 26 July 2016 and that at the time of writing SAP Version 2.0 the most recent version of the Protocol was Protocol Version 9.0 dated 08 November 2017.
		Section 2.2.2 Secondary endpoints: Definition of pre-Chronocort® baseline updated to include handling of DIUR-005 gap subjects as a result of substantial protocol amendment 6.0 incorporated into Protocol Version 7.0 dated 21 June 2017.
		Section 3 Study design: Section updated to include handling of DIUR-005 gap subjects as a result of substantial protocol amendment 6.0 incorporated into Protocol Version 7.0 dated 21 June 2017.
		Section 4.2 Interim analyses: Minor updates have been made to the wording of this section to reflect the wording in Section 13 of the protocol (added during protocol amendment 6.0 incorporated into Protocol Version 7.0 dated 21 June 2017.)
		Section 5 Sample size considerations: Section updated to reflect increase in sample size as a result of substantial protocol amendment 6.0 incorporated into Protocol Version 7.0 dated 21 June 2017.
		Section 6.2 Interim analysis set: New section added to provide the definition of the Interim Analysis Set which will be used for any interim analyses performed for this study, as per protocol amendment 8.0 incorporated into Protocol Version 9.0 dated 08 November 2017.
		Section 7.2 Data display (feeder study and previous treatment) descriptors: Previous treatment label updated to 'Non-Study GC Therapy' for subjects from DIUR-003 and DIUR-005 gap subjects. This update was implemented to make it clearer that the GC therapy these subjects were receiving immediately prior to entering DIUR-006 was per local practice.

	Section 9.1 Premature withdrawal and missing data: Text has been added for imputation/handling of missing or partial dates.
	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.'*
	Section 9.2.3 Conversion factors: Included Finkielstain 2012 reference for conversion factors used. 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: Updated clarification 1) so it only applies to subjects entering immediately from DIUR-005. Target study day ranges added to Table 6. Target study days corrected to account for the fact that visits are performed on 1 day in DIUR-006. 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 to 1).
	Section 9.3.2 Baseline assessment: Definition of pre-Chronocort® baseline updated to include handling of DIUR-005 gap subjects as a result of substantial protocol amendment 6.0 incorporated into Protocol Version 7.0 dated 21 June 2017.

	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: Listing of demographic information added. Summary and listing of baseline disease characteristics added. 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: Additional detail added specifying how each interval will be split to take account of dose titrations. Clarification provided that actual and expected dose will only be calculated using time periods where subjects have an opportunity to return IMP. Summaries of sick day medications moved to new section - Section 12.3 Use of dispensed sick day medications and steroids taken in addition to IMP. Listing of dispensed sick day medication pack accountability added.
	Section 11.1 Adrenal insufficiency Section updated to include 'and over treatment' where appropriate, to reflect text used in protocol.
	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 day 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 11.3.2 Adrenal crises: Section title updated to '**Adrenal** crises'. Section text updated to replace 'Addisonian' with 'adrenal'.

	Section 11.3.3 Unexpected therapeutic benefit: New Section added describing the additional summary table and listing that will be produced for these events.
	Section 11.4.1 Naming conventions: Biomarkers revised to bone biomarkers.
	Section 11.4.2 Haematology: Clarification added regarding central and local laboratory results and reference ranges. Shift tables for 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. Boxplots of change from pre-Chronocort® baseline over time added for all haematology parameters.
	Section 11.4.3 Clinical biochemistry: Clarification added regarding central and local laboratory results and reference ranges. Shift tables for each visit relative to baseline replaced with shift tables to minimum on-treatment versus baseline and to maximum on-treatment versus baseline. Boxplots of change from pre-Chronocort® baseline over time added for all biochemistry parameters.
	Section 11.5 Vital signs: Text updated to specify that boxplots of change from pre-Chronocort® baseline will be produced for vital signs.
	Section 12.1 Physical examination: Text updated to specify that abnormal physical examination will be listed as this is what is being captured in the Electronic case report form (eCRF).

	Section 12.2 Concomitant medication 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 12.3 Use of dispensed sick day medications and steroids taken in addition to IMP: New section added specifying which concomitant steroids will be summarised alongside dispensed sick day medications.
	Section 13.1 Extent of exposure: Section updated to include handling of DIUR-005 gap subjects as a result of substantial protocol amendment 6.0 incorporated into Protocol Version 7.0 dated 21 June 2017. Clarified that cumulative exposure will only be derived for subjects from DIUR-005 who continuously receive Chronocort® (i.e. DIUR-005 subject who immediately enter DIUR-006 who were randomised to Chronocort®). Formulae for calculation of Total Daily Dose of Chronocort® which takes account of dose titrations added.
	Section 13.2.1 Disease Control: Table 7 added showing optimal (17-OHP) and reference (A4) ranges that will be used to define whether a subject has achieved disease control. Extra proportion of daily dose given at night category (>50% - <=70%) which was erroneously missing from SAP v1.0 added.
	Section 13.3 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 for each visit relative to baseline replaced with shift tables to minimum on-treatment versus baseline and to maximum on-treatment versus baseline. Text updated to specify that boxplots of change from pre-Chronocort® baseline will be produced for all bone marker and laboratory assessments of special interest.

[redacted]

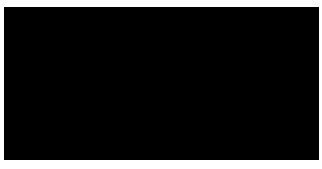
		Section 13.4 DEXA scans T scores and Z scores added to list of DEXA parameters that will be summarised.
		Section 13.5 Quality of Life Questionnaires References have been added for EQ-5D™ (derivation of single index score). Shift table added for EQ-5D™ domains.
		Section 14 Changes from the planned analyses: Text updated to '**At the time of finalising the SAP** there are currently no changes from the planned analyses **specified in the protocol**.'
		Section 16 Appendix A – List of tables, listings and figures: Minor addition/removal of tables/listings following review of mock shells and SAP updates. Inclusion of <Interim> in titles to clarify what population will be used for each output at the time of any interim analyses.
3.0	21JUN2019	**Section 1 Introduction:** Added that at the time of writing SAP Version 3.0 the most recent version of the Protocol was Version 11.0 dated 25 January 2019.
		Section 2.4 Exploratory objective and endpoint Added objectives and endpoints for Total daily dose of Chronocort® per body surface area (mg/day/m^2).
		Section 3 Study Design Length of study updated to 3.5 years.
		Section 4.2 Interim Analyses Text stating that no changes to statistical analyses are anticipated has been removed as analysis of Total daily dose of Chronocort® per body surface area has been added.
		Section 9.1 Missing data Text updated as samples taken outside of the time window will not be considered missing.
		Section 9.2.1 Baseline and demographic derivations Derivation of body surface area (m^2) added and derivation of age updated.

[redacted]

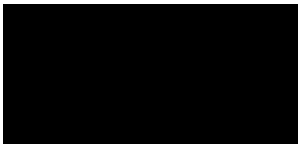
		Section 10.3 Demographic and baseline characteristics Added summary of body surface area (m^2).
		Section 11.1 Adrenal insufficiency Added summary of signs and symptoms across the study treatment period.
		Section 11.2 Adverse events Added additional summaries of AEs in the top-line AE table.
		Section 13.1 Extent of exposure Added the summary of total daily dose of Chronocort® per body surface area endpoint derivation.
		Section 13.5 Quality of life questionnaires – ED-5D Clarified that the denominators for percentage calculations for the frequency summaries will be based on the number of patients with an evaluable EQ-5D assessment.
		Section 14 Changes from the planned analyses Added total daily dose of Chronocort® per body surface area analysis, which is not specified in protocol version 11.0 dated 25th January 2019.
4.0	13JUL2020	**Signature Page** Added [redacted] as the [redacted] Lead Statistician, taking over from [redacted].
		Section 1 Introduction: Added that at the time of writing SAP Version 4.0 the most recent version of the Protocol was Version 14.0 dated 17th April 2020**.**
		Section 3 Study design Study length was updated from 3.5 to 5.5 years. Text describing re-entry of subjects' post-pregnancy added to reflect the change in study design per Protocol Amendment 13.
		Section 7.1 General Text added describing handling of data collected during re-entry phase post-pregnancy in summary tables, figures and listings.
		Section 9.1 Missing data The window around 17-OHP and A4 samples has been widened to +/- one hour so that missing data due to COVID-19 disruptions is minimized.

[redacted]

	Section 9.3 Assessment time windows Analysis visit windows up to 5.5 years and End of Study/Early discontinuation analysis visit added.
	Section 10.1 Disposition of subjects Text added describing handling of subjects who re-enter post-pregnancy in disposition summaries.
	Section 10.2 Protocol deviations New categories of protocol deviation (which were created on 29 October 2019 after the addition of the process deviation log to the protocol deviation log) have been added. These are: 'NIMP', 'Drug Accountability', 'Safety Reporting', 'Informed Consent' and 'Other'. The category of 'Last dose pre visit' was removed.
	Section 10.3.1 Disruptions due to COVID-19 pandemic New section added describing summaries of disruptions due to COVID-19 pandemic.
	Section 10.4 Treatment compliance Text updated to remove references to dose titrations as these were not used to construct treatment compliance. Text updated to remove references to the interval-level analyses of treatment compliance, as this analysis was only conducted on an overall level.
	Section 11.3.3 Unexpected therapeutic benefit Text updated to specify that the summaries of unexpected therapeutic benefit will be by PT and LLT.
	Section 13.4 Extra summaries excluding any data post scanner changes included. Extra analysis assessing impact of scanner changes added.
	Section 14 Text updated to state that there are no planned changes versus Protocol Version 14.0
	Section 16 List of tables and listings updated to include disruption due to COVID-19 pandemic and new DEXA summaries. New section added outlining content of subject profiles for those who re-enter the study post-pregnancy.



5.0	09NOV2020	**Section 9.1 Missing data** **Text added to describe that some missing data may result from the domiciliary visits to US subjects as a result of COVID-19, since only one of the protocol-scheduled 09:00 and 13:00 hours blood samples for analysis of 17-OHP and A4 may be collected.** **Section 9.3.3 'End of Study Assessment'** **Section added to detail the handling of the assessments collected at the EOS visit, as only safety assessments will be performed if the EOS visit is within 3 months of a scheduled visit and other results will be carried forward.** **Section 11.2 Adverse events** **Note added to state the AE listings should display a flag noting if the AE occurred within the 28-day period following COVID-19 vaccination.** **Section 11.3.2 Adrenal crises** **Text updated to describe the adrenal crisis table and listing.** **Section 11.5 Vital Signs** **Text updated to describe the intra-subject/within-subject table and spaghetti plot showing the change from baseline in subject weight at each visit.** **Section 13.1 Extent of exposure** **Text updated to describe the dose distribution table.** **Section 13.2.1 Disease control** **Text updated to describe the summary table of number of subjects achieving <36.4 nmol/L in 17-OHP, and the table and spaghetti plot of by-visit changes from baseline in 17-OHP and A4 levels. Note added to explain that the subjects are presented in ascending order of initial daily dose of Chronocort®.** **Section 13.3 Bone markers and laboratory assessments of special interest**



		Text updated to advise that all testosterone tables and figures shall report on the testosterone results overall and then by both sexes individually. **Section 14 Changes from the planned analysis** **Text included to explain some US subjects may receive domiciliary visits for blood sample analysis of 17-OHP and A4 at only one of the protocol-scheduled 09:00 and 13:00 hours visits due to COVID-19. Text also updated to note the separate French subset analysis required for the third interim analysis and final analysis.** **Section 16** **Six new TLFs added in (dose distribution table for Chronocort®; table and spaghetti plot for Intra-subject/within-subject change from baseline in 17-OHP, A4 and weight; adrenal crisis per 100 patient years table and listing of all adrenal crises; and summary table showing by-visit number and percentage of subjects achieving <36.4 nmol/L in 17-OHP at 09:00)**
6.0	04MAR2022	**Signature Page** Replaced author signatory with [redacted] as the [redacted] Lead Statistician, taking over from [redacted]. **General** Replaced double spaces following periods with single space so as to retain consistent format throughout the document. **Section 2.1.2** Added T and Z scores as secondary endpoints of DEXA scan parameters. **Section 2.2.2** Added bullet c. in the definition of pre-Chronocort® baseline to align with wording in protocol. **Section 7.1** Added text to clarify that data from subjects who re-enter study post-pregnancy will be included in AE summaries and listings only.

[redacted]

Section 8.3

Added text for sensitivity analyses on A4 and 17-OHP summaries excluding extreme cases.

Section 9.2.4

Added section for normal reference ranges of DEXA scan results.

Section 9.3.1

Added clarifying rule for when 2 visits fall within the same analysis window. Also account for unscheduled visits.

Section 9.3.3

Added section to describe the End of Study data handling.

Section 10.2

Added wording to reference the COVID-19 related flag in the PD listing and a separate summary.

Section 11.2

Added wording to reference post COVID-19 vaccination flag in the AE listings and a separate COVID-19 related AE listing.

Section 12.2

Updated text to clarify that the listing of concomitant medications excludes glucocorticoid steroids.

Section 13.1

Updated visit format of dose titration summary so that it reflects the scheduled assessments more accurately

Section 13.2.1

Updated section to group spaghetti plots of intra-subject/within-subject change from baseline in 09:00 hours levels of 17-OHP and A4 by feeder study if needed and additionally display the arithmetic mean. This text has also been moved to section 13.2.2 so it is described along other change from baseline assessments of 17-OHP and A4 levels.

Section 13.2.2

Added text to clarify that the analyses will be produced under both baselines (pre-Chronocort® and Visit 1).

Section 13.3

Specified that total testosterone will only be summarised by gender separately.

Section 13.4

Added text to clarify that the ANOVA will be conducted separately and exclusively on the T score and Z score results. Also clarified that only T score and Z score summaries may be reproduced with a shift up or down in the values post scanner change in the scenario of a statistically significant difference at 5% in the corresponding ANOVA.

Section 14

French subset analyses not required.

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 2014).

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

The proposed study aims to build on the results of studies DIUR-003 and DIUR-005 and evaluate the long-term safety of Chronocort® and also its long-term efficacy in improving control of serum

androgen levels (using 17-OHP and A4 as markers). The purpose of this document is to formally set out the primary and secondary analyses to be conducted for this study. SAP version 1.0 was written using protocol version 3.0 dated 26 July 2016. At the time of writing SAP version 2.0, the most recent version of the protocol is version 9.0 dated 08 November 2017. At the time of writing SAP version 3.0, the most recent version of the protocol is Version 11.0 dated 25 January 2019. At the time of writing SAP version 4.0, the most recent version of the protocol is version 14.0 dated 17 April 2020. At the time of writing SAP version 5.0, the most recent version of the protocol is version 15.0 dated 17 August 2020. At the time of writing SAP version 6.0, the most recent version of the protocol is version 20.0 dated 16 June 2022.

2. Study objectives and endpoints

2.1. Study objectives

2.1.1. Primary objective

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

2.1.2. Secondary objectives

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

1. Total daily dose of Chronocort® in milligram (mg)/day of hydrocortisone during the study and the incidence of dose titrations.
2. 17-OHP and A4, measured at two time points (at 09:00 and 13:00 hours) for:
    a. Disease control at each visit as assessed by both 17-OHP and A4 levels in the optimal and normal range, respectively, at both time points.
    b. 17-OHP and A4 standard deviation scores (SDS).
    c. Change in absolute values compared to pre-Chronocort® baseline values.
3. Changes compared to pre-Chronocort® baseline in:
    a. Bone turnover markers - serum C-terminal cross-linked telopeptide (CTX), osteocalcin
    b. Testosterone (total)
    c. Fasting insulin and blood glucose levels, and glycated haemoglobin (HbA1c)
    d. High sensitivity c-reactive protein (hsCRP) and plasma renin activity (PRA)
    e. Body composition (dual energy X-ray absorptiometry [DEXA])(fat mass, lean mass, total bone density, T score and Z score) (except in Germany)
    f. Quality of life (QoL) – Medical Outcome Short Form (4-week recall) Health Survey Form 36 (Subject Questionnaire) (SF-36®), Multidimensional Assessment of Fatigue (MAF), EQ-5D™ Standardised Health Questionnaire (5-level) (EQ-5D™)

2.2. Study endpoints

2.2.1. Primary endpoints

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

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

2.2.2. Secondary endpoints

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

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

e. Body composition (DEXA) (fat mass, lean mass, total bone density, T score and Z score) (except in Germany)

f. QoL - SF-36®, MAF, EQ-5D™

- Incidence of dose titrations

2.3. Statistical hypotheses

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

2.4. Exploratory objective and endpoint

2.4.1. Exploratory objective

To assess the relationship between disease control and the proportion of daily dose given at night.

To assess the relationship between total daily dose of Chronocort® per body surface area (mg/day/m^2)

2.4.2. Exploratory endpoints

Disease control will be assessed by both 17-OHP and A4, in the optimal and normal range respectively. The proportion of daily dose given at night is the dose given at 23:00hrs divided by the total daily dose (sum of dose given at 07:00hrs and 23:00hrs).

The secondary endpoint of total dose of Chronocort® (mg/day) of hydrocortisone will be further described proportionally to patient body surface area (m^2).

3. Study design

Subjects completing study DIUR-005 and those who have already completed study DIUR-003 will be offered the opportunity to either continue Chronocort® therapy or to switch from their current glucocorticoid therapy to Chronocort® in this open label extension study. An overview of the study plan is illustrated in Figure 1.

The intention is that subjects will transition straight from study DIUR-005 into DIUR-006 without a gap. However, during the conduct of the study, logistical issues arose precluding this for some subjects and so the protocol has been amended to allow these subjects who have been unable to transition immediately into DIUR-006 to be able to participate in the study (protocol amendment 6 incorporated into Protocol version 7.0 dated 21 June 2017). In general, subjects who complete study DIUR-005 should **not** have an interruption in treatment; if this does occur prior approval should be sought from the Sponsor before entering them into study DIUR-006.

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

All subjects will then return for the baseline visit. For subjects entering from study DIUR-003 and any subjects from DIUR-005 who had a gap between completing study DIUR-005 and starting study DIUR-006 during which they received standard glucocorticoid therapy, the full set of baseline

assessments will be completed, including 2 blood samples (one at 09:00 and one at 13:00 hours) for 17-OHP and A4 (note: baseline DEXA scan only needed for subjects entering from study DIUR-003). For subjects entering immediately from study DIUR-005 test results from their last visit in the feeder study (Visit 4) will be used for this baseline assessment, with the 09:00 and 13:00 hour results taken from the 24-hour hormone profiles conducted at the visit. Any subjects not meeting the inclusion/exclusion criteria following these blood tests will be withdrawn from this study (see section 9.3.2).

Once the baseline assessments are completed, the subjects will be given sufficient Chronocort® to use until Visit 2 (Week 4). Subjects entering immediately from study DIUR-005 who were previously on Chronocort® will continue on the same dose of Chronocort® as they were receiving at the end of the feeder study. Subjects from DIUR-005 on standard therapy, subjects from DIUR-005 who had a gap between completing study DIUR-005 and starting study DIUR-006 during which they received standard glucocorticoid therapy, and subjects from study DIUR-003 will have their initial dose of Chronocort® determined using the hydrocortisone equivalent of their previous treatment (immediately prior to the baseline visit. Note: conversion factors described in Section 9.2.3).

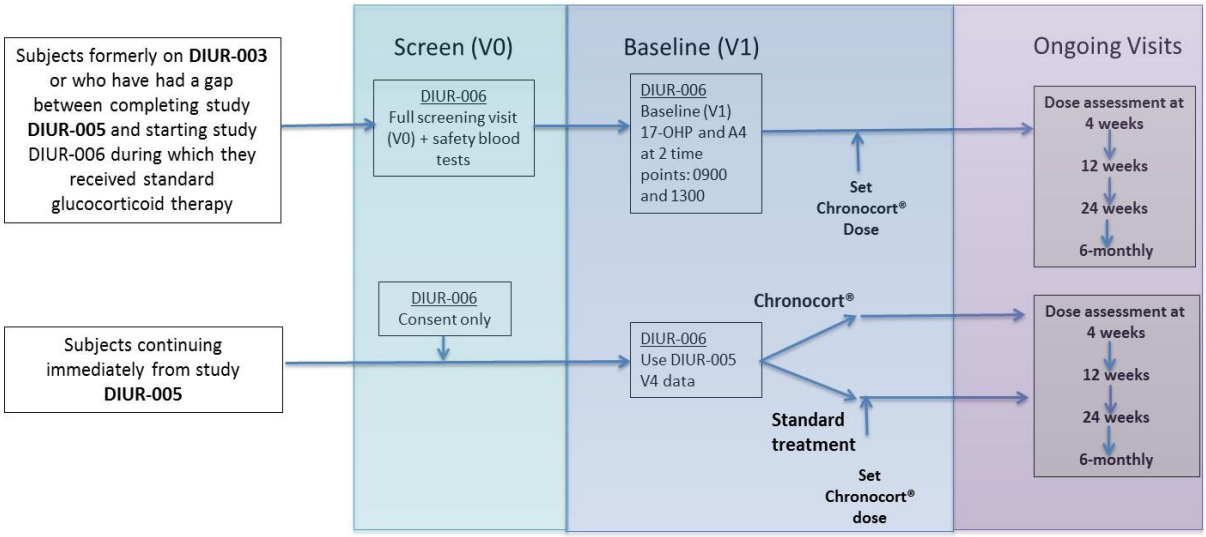
All subjects will return to the study centre at 4, 12 and 24 weeks after starting study DIUR-006 for additional blood tests and dose titration, if necessary. Dose adjustments will be decided by the investigating physician based on the "signs and symptoms of adrenal insufficiency questionnaire" and the measurement of 17-OHP and A4 (see CSP Section 8.1 for further detail). Subjects will receive a telephone call within two weeks of each visit to tell them the outcome of the dose adjustment process – either to tell them the new dose, or if no change in dose (which will also be followed up in writing). Visits thereafter will take place at 6-monthly intervals. However, if the investigator thinks that the Chronocort® dose needs to be changed at any point, then the subject should undergo a visit 4 weeks after the dose has been changed and the assessments specified for Week 4 (Visit 2) and the following telephone call should be conducted. The subject should then continue with the 6-monthly visit schedule as determined before this visit (i.e. the original timings will be maintained with this extra visit added in-between).

All subjects will receive telephone calls at 3 monthly intervals from Week 18, and unscheduled visits will be arranged if necessary. Subjects will also be provided with Chronocort® supplies from the study pharmacy at 3- or 6-monthly intervals.

Subjects who become pregnant whilst on-study must still be withdrawn from the study, however per protocol amendment 13 are allowed to re-enter the DIUR-006 study 6 weeks after the pregnancy is complete or 6 weeks after they finish breastfeeding (whichever is the later date). At the point of study re-entry, post-pregnancy subjects will have secondary baseline measurements taken for all the original baseline tests, including 2 blood samples (one at 09:00 and one at 13:00 hours) for 17-OHP and A4. Post-pregnancy subjects who re-enter will continue on their pre-determined visit scheduling based on the original baseline visit date, following completion of the mandatory secondary baseline visit and a Post Pregnancy Week 4 visit to enable the post-pregnancy dose levels to be checked.

The length of the study will be 5.5 years from the date of the first subject entering the study, so subjects will be treated for a maximum of 5.5 years.

Figure 1: Overview of DIUR-006 Study Schema



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

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 terms of reference for the Data Review Meeting are outlined in Section 13.8 of the protocol.

4.2. Interim analyses

Interim data analyses are expected to be required for regulatory review as part of any marketing authorisation applications. Prior to any interim data analyses a Data Review Meeting will take place as described in Section 4.1. No changes to overall study conduct are anticipated as a result.

4.3. Final analysis

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

5. Sample size considerations

Since this is an open label extension study to gather long term safety and efficacy data on Chronocort®, no formal power or sample size calculations have been performed. All eligible subjects from study DIUR-003 (16 subjects) and DIUR-005 (120 subjects) may enter this study, giving a maximum of 136 subjects. Subjects from study DIUR-003 can be enrolled at any time (since this study has been completed), but subjects from study DIUR-005 will be enrolled when they complete Visit 4 of study DIUR-005. However, in some cases there may be a delay between a subject completing study DIUR-005 and starting study DIUR-006 during which the subject receives standard glucocorticoid therapy. In this case the subject should be entered into study DIUR-006 as soon as possible.

[redacted]

6. Analysis populations

6.1. Full analysis set

The full analysis set comprises all subjects who entered the extension study and who subsequently received at least one dose of Chronocort®. All primary, secondary and exploratory endpoints will be summarised using the full analysis set. Subjects in the full analysis set will be analysed according to the actual treatment received.

6.2. Interim analysis set

The interim analysis set is a subset of the full analysis set. In addition to entering the study and receiving at least one dose of Chronocort®, subjects must have also completed the Week 24 (Visit 4) assessment or discontinued early from treatment and withdrawn from the study at the specified data cut-off requested for the interim analysis.

At the time of interim analyses all primary, secondary and exploratory endpoints will be summarised using the interim analysis set. Subjects in the interim analysis set will be analysed according to the actual treatment received. The interim analysis set will be used for all interim analyses carried out in this study.

7. Treatment comparisons

7.1. General

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

For subjects who re-enter the study post-pregnancy, all data collected at following re-entry will be included in the summaries and analyses. For these patients, the original date of first dose of randomized treatment will be used as the date of origin for the assignment of visit windows and the calculation of relative date/time information.

7.2. Data display (feeder study and previous treatment) descriptors

The feeder study and previous treatment group (immediately prior to entering the extension study DIUR-006) 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.

Table 1: Feeder study and previous treatment descriptors

Feeder study/previous treatment	**Full data display descriptor**	**Abbreviated data display descriptor**
Feeder study		
DIUR-003	DIUR-003	DIUR-003
DIUR-005	DIUR-005	DIUR-005
Chronocort® with previous treatment (immediately prior to baseline visit)		

[redacted]

Chronocort® (subjects entering immediately from DIUR-005 Chronocort® arm)	Chronocort	Cct
Chronocort® with Standard glucocorticoid replacement therapy (subjects entering immediately from DIUR-005 Standard GC arm)	Standard GC therapy	SGC
Chronocort® with non-study glucocorticoid replacement therapy (subjects from DIUR-003 and DIUR-005 gap subject)*	Non-Study GC therapy	NGC

**Note: For subjects from study DIUR-005 who had a gap between completing study DIUR-005 and starting study DIUR-006 and subjects from study DIUR-003, non-study GC therapy immediately prior to entering DIUR-006 will be per local clinical practice.*

8. General considerations for data analyses

All statistical analyses will be performed using the software package SAS® version 9.2 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. Statistical significance and multiple testing strategy

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

8.3. Sensitivity analyses

8.3.1. Repeat efficacy analysis excluding extreme cases

Sensitivity analyses will be carried out by excluding extreme cases on the following summaries:

- Total daily dose of Chronocort
- 17-OHP and A4 disease control
- 17-OHP and A4 absolute values and change from baseline over time
- Adrenal crises per 100 patient years

The identified extreme cases include subject D605/401/001 who developed Lichen Planus which lead to chronic use of additional GC, subject D605/402/003 who had a large number of adrenal crises and subject D605/301/005 who deviated from the protocol by taking additional doses of GC during their seasonal training.

9. Data handling conventions

9.1. Missing data

Blood samples for analysis of 17-OHP and A4 values are to be taken at the baseline, Week 4, Week 12, Week 24 and 6-monthly visits at both 09:00 and 13:00 hours, with a window of +/- one hour allowed. Missing 17-OHP and A4 values will not be imputed. In calculating the mean of the 09:00 and 13:00 SDS, if one value is missing, then only the non-missing value will be used. If both values are missing, the mean value will be missing.

For subjects based in the US receiving domiciliary visits, only one blood sample for analysis of 17-OHP and A4 will be taken, at either 09:00 or 13:00 hours.

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, the following date imputation methods will be used:

Partial start date

- If the day part is missing then impute as the latest of [1st of the month, date of first dose of Chronocort®[1]].
- if the month part is missing then impute as the latest of [1st of January, date of first dose of Chronocort®[1]].
- if the year is missing then do not impute.

[1] Consider first dose date of Chronocort® unless can be unequivocally determined that the event did not occur on or after the first dose of Chronocort®, based on available information for the partial date.

Partial end date

- if the day part is missing then impute as the earliest of [last date applicable to the respective month part, date of last study contact or interim data cut-off date].
- If the month part is missing then impute as the earliest of [31st of December, date of last study contact or interim data cut-off date].
- If year part is missing then do not impute.

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.

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 in whole years will be calculated as:

- Year of consent into study DIUR-006 - year of birth.

[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 DIUR-006 baseline visit - date of CAH diagnosis + 1.

The derivation of time since CAH diagnosis partial dates will be handled as described in Section 9.1

Body surface area (m^2) will be calculated using the Dubois formula,

$$Weight\ (kg)^{0.425} \times Height\ (cm)^{0.725} \times 0.007184.$$

9.2.2. Derivations of SDS scores

As part of the secondary objectives, the change from pre-Chronocort® baseline (see Section 9.3.2) in SDS of 17-OHP and A4 will be calculated. The SDS is defined as the absolute (unsigned) number of standard deviations above or below the average of the lower and upper limit of normal.

For each of the 17-OHP and A4 concentrations at each visit at each time point (09:00, 13:00), the natural logarithm will be taken and the SDS will be calculated by counting the number of standard deviations which are above or below the mean of the log transformed range (given in Table 3). The mean of the SDS scores for each androgen will be calculated over the two timepoints. Missing values will be handled as described in Section 9.1.

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 8) 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

[redacted]

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 averaging the natural logarithm of the upper and lower limit given in Table 2. 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

Note: The conversion factor for Chronocort® is 1.

** up to a maximum starting dose of Chronocort® 30mg, split as 20mg at night 10mg in the morning*

For example, if a subject was previously taking 6mg 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 using the International System (SI) of units and conventional units. If for any reason the results are not collected in SI units, a conversion to SI units will be performed. Examples of some conversions to SI units are given in Table 5.

[redacted]

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

9.2.4. Derivation of reference flag for DEXA scan results

A reference flag will be derived for DEXA scan results, which will be assigning Low, Normal or High values to the measurements according to Table 6.

Table 6: Normal reference ranges of DEXA scan results

Parameter	**Normal range *(unit)***	
Total fat mass	6.3 to 50	kg
Total lean mass	29 to 63.5	kg
Total bone mineral density	0.9 to 1.3	g/cm2
T score	-1 to +2	
Z score	-1.5 to +2	

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

Adverse events (AEs) and medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 19.0 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 first dose + 1* (or *Date of assessment - Date of first dose* if the assessment is before the date of first dose).

[redacted]

However, due to the first dose being scheduled at 23:00h on the evening of the baseline assessment[1] (Visit 1), a window of +4 hours will be used so that if the time of first dose falls within the window, the date of first dose will be considered to be the planned date of first dose. For example, if a subject takes their first dose at 01:00h the day after the baseline assessment, the date used for the calculation of study day will still be the day of the baseline assessment.

Vital signs, laboratory data, bone turnover markers, physical examinations (including weight, BMI and waist circumference), endocrine profile (17-OHP and A4), signs and symptoms of adrenal insufficiency, DEXA scans and QoL data will be summarised according to scheduled visit.

Please note that visits 2 and 3 are when specific assessments of 17-OHP, A4 and signs and symptoms of adrenal insufficiency are performed. Any extreme deviations between the actual study day of the scheduled visit and the target study day (see Table 7) will be discussed at the Data Review Meeting. A deviation will be considered extreme if more than +/- 3 weeks (+/- 21 days) from visit 2, +/- 4 weeks (+/- 28 days) from visit 3 and 4, or +/- 3 months (+/- 84 days) for visit 5 and onwards. If 2 or more visits (including unscheduled visits) occur within the same analysis window, then the visit closest to the target study day will be used in the descriptive summaries. In case of equidistant visits to the target study day, then the earliest visit will be used in the analyses. All visits will be displayed in the listings.

Table 7: Target study day for visit assessments

Visit number	**Visit description**	**Target study day**	**Target study day range**
Visit 0	Visit 0/Screening	-14 to -1	
Visit 1	Visit 1/Baseline	1	
Visit 2	Visit 2/Week 4	29	8-50
Visit 3	Visit 3/Week 12	85	57-113
Visit 4	Visit 4/Week 24	169	141-197
6-monthly visits from visit 5 onwards			
Visit 5	Visit 5/Month 12	365	281-449
Visit 6	Visit 6/Month 18	548	464-632
Visit 7	Visit 7/Month 24	730	646-814
Visit 8	Visit 8/Month 30	913	829-997
Visit 9	Visit 9/Month 36	1095	1011-1179

[1] For subjects entering immediately from the DIUR-005 feeder study this will be the evening of the second day of Visit 4 (Week 24) of the DIUR-005 study.

[redacted]

Visit 10	Visit 10/Month 42	1278	1194-1362
Visit 11	Visit 11/Month 48	1460	1376-1544
Visit 12	Visit 12/Month 54	1643	1559-1727
Visit 13	Visit 13/Month 60	1825	1741-1909
Visit 14	Visit 14/Month 66	2008	1924-2092
End of Study/Early Discontinuation	End of Study	Last non-missing assessment within 48 hours of last dose of Chronocort®	

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

9.3.2. Baseline Assessment

Pre-Chronocort® baseline, used in calculations for all change from baseline summaries, will be defined as the latest pre-Chronocort® measurement. This will depend on which feeder study and treatment the subject was receiving immediately prior to entering DIUR-006:

- For subjects entering from study DIUR-003, baseline values are defined as those taken at Visit 1 of this DIUR-006 study, 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.
- For subjects entering immediately from study DIUR-005 who received standard glucocorticoid replacement therapy, baseline values are defined as those taken at the last visit in the feeder study i.e. Visit 4 (week 24) in study DIUR-005. However, if a result is missing and there is a suitable result available (within 14 days prior to the first dose of Chronocort® and taking account of fasting requirements where needed), this will be used in its place.
- For subjects entering immediately from study DIUR-005 who received Chronocort®, baseline values are defined as the pre-Chronocort® values recorded in Visit 1 in study DIUR-005, however if a result is missing and there is a suitable result available at the DIUR-005 screening visit (taking account of fasting requirements where needed), this will be used in its place.
- For subjects who delayed entering study DIUR-006 and received standard glucocorticoid therapy in the gap between DIUR-005 and DIUR-006 studies, baseline values are defined as those taken at Visit 1 of this DIUR-006 study, 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. End of Study Assessment

With commercialisation, some patients may withdraw early from study. This End of Study (EOS) data should be handled in the following way:

- If the EOS visit date falls within the three months immediately following a 6-monthly scheduled visit, then only safety assessments will be performed at the visit. All other subject records should be imputed for EOS by carrying forward the previously collected record to the EOS visit.
- If the EOS visit date is more than three months following a 6-monthly scheduled visit, then a full assessment should be performed at this visit.

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 Section 4.1) and sensitivity analyses may be performed as required.

10. Study population

10.1. Disposition of subjects

Subject disposition, including subjects from the feeder studies who don't meet the inclusion/exclusion criteria for DIUR-006, will be listed and summarised by overall DIUR-006 study, feeder study, previous treatment and will include reason for withdrawal from DIUR-006. For subjects who withdraw due to pregnancy an extra row will be included to show the number who re-entered the study.

10.2. Protocol deviations

Any deviations from the protocol will be reviewed at the Data Review Meeting 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). Subjects with major protocol deviations will not lead to exclusion from the full analysis set. 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,
- Study procedure – site or subject did not follow procedures specified in protocol,
- Titration – site or subject deviated from the titration process,
- Treatment – Chronocort® not taken as per protocol,
- NIMP – subject used an unauthorised Non Investigational Medicinal Product,
- Drug Accountability – subject or site failed to account for all Investigation Medicinal Product,
- Safety Reporting - site or subject did not follow safety reporting procedures,
- Informed Consent – site or subject did not correctly document informed consent,
- Other – any other protocol deviations not fitting into the categories outlined above.

Protocol deviations will be listed and summarised by overall DIUR-006 study, feeder study, previous treatment, by classification (major or minor) and protocol deviation category. The listing will also show whether protocol deviations were related to COVID-19 or not. Additionally, a separate summary of COVID-19 related protocol deviations will be produced.

10.3. Demographic and baseline characteristics

For subjects from the DIUR-003 feeder study, demographic data, medical history and any current medical conditions will be collected at the baseline visit of this DIUR-006 study. For subjects from DIUR-005, demography data collected at the start of the DIUR-005 feeder study will be used, with any changes that occurred during or after the feeder study and prior to entry into DIUR-006 being noted.

The following demographic and baseline characteristics will be summarised and listed: age (calculated in whole years), gender, race, height, weight, BMI, waist circumference and body surface area.

Baseline disease characteristics including time since CAH diagnosis, whether the subject was hospitalised 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.

10.3.1. Disruptions due to COVID-19 pandemic

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

10.4. Treatment compliance

For treatment compliance to Chronocort®, the study will be split into the following interval:

- Overall: The overall period will start from the first dose taken in the evening of visit 1 up to the morning dose of the last planned 6-monthly visit prior to the data cut-off).

Compliance will be calculated as a percentage for each subject, for the interval by

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

The actual total dose for each interval will be calculated by subtracting the number and dose of capsules returned at the next visit from the number and dose of capsules dispensed. The actual total dose for the overall period will be a summation of the actual total dose over all visits.

Actual total dose and expected total dose will only be calculated where a subject has the opportunity to return capsules prior to the data cut off. If the subject is dispensed capsules but hasn't yet had the opportunity to return capsules they will be excluded from the calculation of subject compliance.

Summary statistics will be produced for the overall subject compliance, by feeder study and previous treatment. A listing of subject compliance (including flags for when this is <80% or >120%) and Chronocort® drug accountability will also be produced.

Use of "sick day" medication will be considered separately to compliance to Chronocort® (see Section 11.3.1).

11. Primary safety analyses

11.1. Adrenal insufficiency

Signs and symptoms of adrenal insufficiency and over treatment will be summarised by feeder study and previous treatment, including total column, and visit (including an overall summary over the study treatment period). A listing of all signs and symptoms of adrenal insufficiency and over treatment will be produced flagging any significant findings and significant findings related to under/over replacement of steroid.

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 (%) by overall DIUR-006 study, feeder study and previous treatment. For the purpose of the clinical study report, only AEs up to 30 days after the end of the study or early withdrawal visit will be included in summaries. Any AE occurring before the first dose of Chronocort® (in the evening of the baseline visit) will be included in listings but not summaries, unless there is an increase in severity occurring after the start of treatment. Similarly, any AE with a start date after 30 days following the end of the study or early withdrawal 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. Any AE occurring within 28 days post COVID-19 vaccination shall be flagged on the listing as occurring within the immediate period post-vaccination.

A separate listing will be produced, including all the COVID-19 related AEs with an onset date on or after 11th March 2020 (start date of the pandemic according to WHO), based on the MedDRA COVID-19 related new terms spreadsheet.

Frequencies and percentages of subjects reporting each PT will be presented (i.e. multiple events per subject will not be accounted for). 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 overall DIUR-006 study, feeder study and previous treatment as well as the number and percent of subjects with the following categories will be produced:

- Any AE
- Any AE causally related to IMP
- Any AE leading to sick day rules
- Any AE leading to sick day rules causally related to IMP
- Any AE leading to adrenal crisis
- Any AE leading to adrenal crisis causally related to IMP
- Any AE of unexpected therapeutic benefit
- Any AE of unexpected therapeutic benefit causally related to IMP
- Any AE leading to death
- Any AE leading to death causally related to IMP

[redacted]

- 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
- Any severe AE
- Any severe AE that is causally related to Chronocort
- Any AE associated with a dose increase
- Any AE associated with a dose increase and causally related to Chronocort
- Any AE associated with a dose decrease
- Any AE associated with a dose decrease and causally related to Chronocort
- Any AE associated with a dose interruption
- Any AE associated with a dose interruption and causally related to Chronocort.

The number and percent of subjects experiencing each AE will be summarised by overall DIUR-006 study, feeder study, previous 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)

Tables of most common AEs (>10% of subjects overall) and common SAEs (>1% of subjects overall), will be summarised by PT, by decreasing frequency. These thresholds may be adjusted either upwards or downwards at the Data Review Meeting, depending on the actual number of 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 SOC, PT, previous treatment, feeder study and overall DIUR-006 study.

In addition, all AEs leading to use of "sick day rules" will also be summarised (frequency and percentage of subjects) by preferred term, route, 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, previous treatment, feeder study and overall DIUR-006 study. There will be a separate listing showing details of all AEs leading to adrenal crises.

The adrenal crisis rate per 100 subject years will be presented for overall subjects and by feeder study and previous treatment. This table shall display the total number of adrenal crises on study, the number of subject years on study, and the number of subjects who have experienced at least one adrenal crisis on study.

A separate listing will display all subjects who have experienced at least one adrenal crisis, along with the number of adrenal crisis events experienced on study, the number of days on study, the subject's number of adrenal crises per 100 subject years and the mean number of adrenal crises per 100 patient years in this study for the subject's feeder study group.

11.3.3. Unexpected therapeutic benefit

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

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 [redacted]. 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 pre-Chronocort® baseline (see Section 9.3.2) will be calculated at each visit (every 6 months from baseline) and summary statistics will be presented for both absolute values and change from baseline for all haematology parameters by previous treatment group, scheduled visit, feeder study and overall DIUR-006 study. 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. Detailed listings will be produced for all haematology parameters. In addition, boxplots of change from pre-Chronocort® 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. If 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:

[redacted]

- 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 creatine 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 [redacted]. If laboratory results are needed urgently for safety reasons during the study, these can be processed at the local laboratory and the results will be recorded in the 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 (every 6 months from baseline) and summary statistics will be presented for both absolute values and change from baseline for all clinical biochemistry parameters by previous treatment, scheduled visit, feeder study and overall DIUR-006 study. 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 pre-Chronocort® 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

[redacted]

- blood urea nitrogen (BUN)
- glucose
- uric acid
- total protein
- albumin

Biochemistry (3)

- alkaline phosphatase
- ALT/GPT
- AST/GOT
- total creatine 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

A pregnancy test will be carried out in female subjects of child bearing potential at each visit (Week 4, Week 12, Week 24, and then every 6 months) and the results will be listed.

11.5. Vital signs

The following vital signs will be collected at baseline and every 6 months: systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate, respiratory rate, temperature, 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 previous treatment, scheduled visit, feeder study and overall DIUR-006 study. Shift tables will be created for the following vital signs: SBP and DBP. In addition, boxplots of change from pre-Chronocort® baseline in vital signs over time will be produced along with a line connecting the mean change through time.

The intra-subject/within-subject change from baseline in subject weight shall also be presented at each visit and this subject-level change from baseline shall also be displayed visually in a spaghetti plot for this parameter.

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

12. Other safety analyses

12.1. Physical examination

Abnormal findings from the full physical examination at baseline and every 6 months will be tabulated by body system, previous treatment, feeder study, overall DIUR-006 study and visit

showing the frequency and percentage of subjects with an abnormal finding. Abnormal physical examination results will be listed, together with an indication of whether or not that finding was clinically significant.

12.2. Concomitant medications excluding glucocorticoid steroids

Concomitant medications excluding glucocorticoid steroids[a], which include medications that began prior to entering Study DIUR-006 but were ongoing after the first dose of Chronocort® in Study DIUR-006, will be summarised descriptively by ATC text, previous treatment, feeder study and overall DIUR-006 study using counts and percentages as appropriate. A detailed listing of concomitant medications excluding steroids will be produced.

[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 12.3).

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.

12.3. 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.

13. Secondary efficacy analyses

13.1. Extent of exposure

Summary statistics will be presented for both the total duration and actual duration of exposure to Chronocort® in days. For subjects randomised to Chronocort® in DIUR-005 who immediately enter DIUR-006, exposure to Chronocort® during the DIUR-006 study period and continuous cumulative exposure including any immediate exposure prior to DIUR-006 will be considered. Whereas for subjects from DIUR-003 and DIUR-005 gap subjects, exposure during the DIUR-006 will only be derived as this is the only period of time where Chronocort® is taken continuously.

Total treatment duration in DIUR-006 only will be calculated as follows:

- Date of last dose of Chronocort® in DIUR-006 – Date of first dose of Chronocort® in DIUR-006 + 1.

Actual treatment duration in DIUR-006 only will consider dose interruptions and will be:

- The total number of days in which the subject took at least one dose of Chronocort® in DIUR-006.

Cumulative total treatment duration, which includes the exposure prior to DIUR-006 for those subjects who received Chronocort® in DIUR-005 and immediately entered DIUR-006, will be calculated as follows:

- Date of last dose of Chronocort® in DIUR-006 - Date of first dose of Chronocort® in either DIUR-005 or DIUR-006 + 1.

Cumulative actual duration will consider dose interruptions during DIUR-005 and DIUR-006, for subjects who received Chronocort® in DIUR-005 and immediately entered DIUR-006 only. It will be calculated as:

- The total number of days in which the subject took at least one dose of Chronocort® in either DIUR-005 or DIUR-006.

Any planned or unplanned dose titration decisions which are made by the investigating physician will be summarised by overall DIUR-006 study, feeder study and previous treatment and visit (e.g. planned dose titration Visit 1-2/ Baseline-Week4; planned dose titration Visit 2/Week 4; planned dose titration Visit 2-3/ Week4-Week12; planned dose titration Visit 3/Week 12 and so on). A separate category will be used to summarise any unplanned dose titrations at any timepoint during the study. The summary will show frequency and percentage of subjects requiring a dose adjustment, as well as the dose adjustment required (increase morning dose, increase evening dose, increase morning and evening dose, decrease morning dose, decrease evening dose, decrease morning and evening dose.

A summary of the number and percentage of subjects with dose increases, reductions and interruptions will be produced and will be broken down by the reason for dose increases, reductions and interruptions. It will also show the number of dose increases, reductions and interruptions per subject as well as the mean and the standard deviation.

The number and percentage of subjects receiving Chronocort® at each dose distribution level (in mg) at their last daily dose shall be presented, with the number of subjects reported overall and by their feeder study and previous treatment.

All treatment exposure data will be listed in detail.

Summary statistics for the total daily dose of Chronocort® in mg/day will be presented in terms of hydrocortisone based on the dose instructed by the investigator, by previous treatment and feeder study. Statistics will be grouped into time intervals, where each interval is defined as the period of time between scheduled visits (e.g. Baseline to Week 4; Week 4 to Week 12; Week 12 to Week 24 etc). Summary statistics will present the total daily dose of Chronocort®, in terms of hydrocortisone equivalent, per body surface area by treatment group. Dosing periods can be of differing lengths due to titration events. Therefore, the total daily dose will be calculated by considering the duration of time a patient is instructed to take a given quantity of Chronocort®:

$$Total\ Daily\ Dose = \frac{\sum_{i=1}^{N}(Dose_i * Duration_i)}{\sum_{i=1}^{N} Duration_i}$$

For $i = 1, 2, \ldots, N$ titration events. Where $Dose_i$ is the assigned quantity of Chronocort® at the i-th titration event and $Duration_i$ is the duration of exposure of the dose assigned at the i-th titration event.

Additionally, the total daily dose per body surface area of Chronocort® (mg/day/m^2) will be calculated as

$$\frac{Total\ daily\ dose\ of\ Chronocort^{®}\ (mg/day)}{Body\ Surface\ Area\ (m^2)}$$

The calculation for body surface area will use the Dubois formula as provided in Section 10.3.

13.2. 17-OHP and A4 levels

13.2.1. Disease control

Disease control will be based on whether 17-OHP levels are in the optimal range and also whether the A4 levels are in the normal range (both analysed separately), see

Table 8. A subject will be considered a responder (i.e. disease controlled) if their 09:00 results are in the optimal range for 17-OHP and then separately if their 09:00 results for A4 are in the normal range. The number and percentage of subjects achieving 17-OHP and A4 results in the optimal and normal range respectively, will be presented at each visit by feeder study and previous treatment. This will be repeated for the 13:00 values.

The number and percentage of subjects achieving a 17-OHP concentration of <36.4 nmol/L at 09:00 will be summarised at each visit overall and by feeder study and previous treatment.

Table 8: Optimal range for 17-OHP and normal reference range for A4.

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

[redacted]

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

Exploratory analyses will also be undertaken to assess the relationship between disease control and the proportion of daily dose given at night. A summary of the number and percentage of responders will be produced by proportion of daily dose given at night, previous treatment, feeder study and overall DIUR-006 study. The proportion of daily dose given at night will be split into the following categories:

- <=30%
- >30% - <=50%
- >50% - <= 70%
- >70% - <=90%
- >90%

13.2.2. SDS and absolute values

Change from pre-Chronocort® baseline at each visit in SDS, calculated as described in Section 9.2.2, will be summarised over time by overall DIUR-006 study, feeder study and previous treatment. In addition to presenting change from pre-Chronocort® baseline SDS at 09:00 and 13:00 separately, an arithmetic mean of the SDS at the two timepoints will be calculated and summarised over time by overall DIUR-006 study, feeder study and previous treatment.

Absolute values and change from pre-Chronocort® and Visit 1 baseline in 17-OHP and A4 at each visit at 09:00 and 13:00 will also be summarised over time by overall DIUR-006 study, feeder study and previous treatment. The geometric mean of the 17-OHP measurements at 09:00 over time (by visit) will be plotted along with the 95% confidence intervals for the overall DIUR-006 study. This plot may also be repeated by feeder study and previous treatment if this is deemed appropriate at the Data Review Meeting. These plots will be repeated for 17-OHP measurements at 13:00 and A4 measurements at 09:00 and 13:00. Individual subject profile plots may be produced displaying 17-OHP measurements at 09:00 over time (on a logarithmic scale). These profile plots may be repeated for 17-OHP measurements at 13:00 and A4 measurements at 09:00 and 13:00 if this is deemed appropriate at the Data Review meeting.

The intra-subject/within-subject change from pre-Chronocort® and Visit 1 baseline in 09:00 hours levels of 17-OHP and A4 will be listed by visit. Additionally, the subject-level change from pre-Chronocort® baseline along with the intra-subject arithmetic mean changes by visit shall also be displayed visually in a spaghetti plot for these parameters. The spaghetti plot will present the

subjects in the ascending order of their initial Chronocort® daily dose. If the plot is too crowded to draw any meaningful inference, it will be split by groups of participants (feeder study).

13.3. Bone markers and laboratory assessments of special interest

Changes from pre-Chronocort® baseline at each visit in:

a. Bone turnover markers – serum CTX, osteocalcin (after fasting)
b. Testosterone (total) by gender, separately
c. Fasting insulin and blood glucose levels, and HbA1c
d. hsCRP and PRA

Change from baseline will be calculated at each visit (every 6 months from baseline) and summary statistics will be presented for both absolute values and change from baseline for all biomarkers and laboratory assessments of special interest listed above by previous treatment, visit, feeder study and overall DIUR-006 study. 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 biomarkers 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.

Tables and figures which report on testosterone levels shall only display results by sex individually.

13.4. DEXA scans

Body composition (DEXA) scans will be performed at baseline for subjects entering from study DIUR-003 and then annually for all subjects, except in Germany. Summary statistics will be produced for the absolute values and change from pre-Chronocort® baseline (see Section 9.3.2) for each of fat mass, lean mass, total bone density, T scores and Z scores at each visit.

Due to the length of the study it is possibly that there will be changes in DEXA scanner at some sites. Therefore, the above summary tables will be repeated excluding data post scanner change.

In addition, to explore the potential impact of changes in scanner, an ANOVA 'Analysis of Variance' model will be created to explore whether there is any statistically significant difference in the DEXA results before and after this scanner change. The ANOVA will look at the DEXA scan results (T score and Z score separately and exclusively) at two timepoints: firstly, at the last timepoint for each subject prior to the change in scanner; and secondly at the first DEXA scan for each subject post-scanner change. The response variable in the ANOVA will be the change in the DEXA scan between these two timepoints (ie. the calculated 'post-scanner-result' minus 'pre-scanner-result' for each patient). The ANOVA will use the population of scan result origin as the categorical factor in the analysis: the first level of the population factor will be for 'All subjects' (ie. the Full <Interim> analysis set excluding those subjects with a change in scanner) and the second level of the population factor will be only those Full <Interim> Analysis set subjects who have been exposed to the new DEXA scanner. Using the ANOVA results, the effect size for the difference in mean change between the two populations will be calculated, along with a measure of its statistical significance. These results will be presented in a separate table: 'Change in DEXA scanner results by site population'.

If the difference in mean change between populations is found to be statistically significant at the 5% level, then a second version of the DEXA summary table 'Summary of absolute values of body composition – Dual Energy X-ray Absorptiometry (Full <Interim> analysis set)' will be created exclusively for those parameters, with the subjects' measurements following the scanner change adjusted upwards or downwards by the difference in mean changes between the 'Scanner change' population and the 'All subjects' population from the ANOVA.

In the event of multiple sites changing their DEXA scanners, a separate ANOVA model will be created for each site. Each resulting ANOVA model will continue to compare the 'All subjects' reference results against the site under analysis, but the 'All subjects' set will exclude any data collected from other sites at which the DEXA scanner is changed during the interval between the two timepoints under consideration in the given ANOVA model (ie. the 'All subjects' reference collection used in each ANOVA must compute each patient's change in DEXA scan results between the two timepoints using the same DEXA scanner).

A detailed listing of all DEXA scan results will be produced and will include the date of scanner change and a normal reference flag as described in Section 9.2.4.

13.5. Quality of life questionnaires

Quality of life will be assessed at baseline, week 24 and 6-monthly thereafter, measured using three instruments: SF-36®, MAF, EQ-5D™.

SF-36®

The SF-36v2 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).

The 8 health domain scales are referred to as:

- 'Physical Functioning',
- 'Role- Physical',
- 'Bodily Pain',
- 'General Health',
- 'Vitality',
- 'Social Functioning',
- 'Role-Emotional',
- and 'Mental Health'.

The 2 summary measures are referred to as the physical component score and mental component score.

Standardised scores will be generated using the validated scoring software package (QualityMetric Health Outcomes™ Scoring Software 4.5) for the 8 health domain scales and 2 summary measures using the raw data entered in the eCRFs.

For each summary measure and scale, the change from baseline and percentage change from baseline at each visit will be calculated. Summary statistics for absolute values at each visit, change

and percentage change from baseline will be tabulated by previous treatment group, visit, feeder study and overall DIUR-006 study.

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

Multidimensional Assessment of Fatigue

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 each visit will be calculated. Summary statistics for absolute values of GFI, change and percentage change from baseline will be tabulated by previous treatment group, visit, feeder study and overall DIUR-006 study.

Individual question scores and GFI 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 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 previous treatment group, visit and feeder study. The denominator for percentage calculations will be based on the number of subjects with an evaluable EQ-5D, at each scheduled visit. A shift table of baseline to end of study will be produced by domain, previous treatment group and feeder study. The denominator for percentage calculations will be based on the number of subjects with an evaluable EQ-5D, at each level of the pre-Chronocort® baseline assessment.

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 will be tabulated by previous treatment group, visit and feeder study.

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

14. Changes from the planned analyses

Due to the COVID-19 pandemic, subjects in the US may receive domiciliary visits to take blood samples for analysis of their 17-OHP and A4 levels. These samples are scheduled to be taken at baseline, Week 4, Week 12, Week 24 and 6-monthly visits at both 09:00 and 13:00 hours, but these domiciliary visits will only occur once daily (with a preference for 09:00 hours). As a result, at the time of finalising the SAP there will unavoidably be missing data from what is due to be collected.

15. References

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

16.1. List of planned tables

Study population	TFL num.	Shell name
Subject disposition (All subjects)	14.1.1	DS200
Major and minor protocol deviations by high level category (All subjects <Interim analysis set>)	14.1.2.1	DS201
Major and minor COVID-19 related protocol deviations by high level category (All subjects <Interim analysis set>)	14.1.2.2	DS201A
Analysis sets (All subjects assigned to treatment)	14.1.3	DM200
Demographic characteristics (Full <Interim> analysis set)	14.1.4	DM201
Baseline disease characteristics (Full <Interim> analysis set)	14.1.5	DM202
CAH medical history (Full <Interim> analysis set)	14.1.6.1	MH200
Other medical history excluding CAH related events (Full <Interim> analysis set)	14.1.6.2	MH201
Prior medications (Full <Interim> analysis set)	14.1.7.1	CM201
Concomitant medications excluding glucocorticoid steroids during study DIUR-006 (Full <Interim> analysis set)	14.1.7.2	CM200
Duration of exposure (Full <Interim> analysis set)	14.1.8.1.1	EX202
Duration of cumulative exposure (Full <Interim> analysis set)	14.1.8.1.2	EX202A
Dose titration decisions (Full <Interim> analysis set)	14.1.8.2	EX203
Dose increases, reductions and interruptions (Full <Interim> analysis set)	14.1.8.3	EX204
Subject compliance (Full <Interim> analysis set)	14.1.8.4	EX200
Disruptions due to COVID-19 pandemic (Full <Interim> analysis set – subset of subjects still in study at time of COVID-19 pandemic)	14.1.9	CV200
Safety		
Table of adverse events in any category - subject level (Full <Interim> analysis set)	14.3.1.1	AE220
Table of adverse events in any category - episode level (Full <Interim> analysis set)	14.3.1.2	AE2201
All adverse events (Full <Interim> analysis set)	14.3.1.3	AE200
Most common (>10% of subjects overall) adverse events (Full <Interim> analysis set)	14.3.1.4	AE206
Adverse events by severity (Full <Interim> analysis set)	14.3.1.5	AE205
Adverse events by outcome (Full <Interim> analysis set)	14.3.1.6	AE204
Adverse events by action taken (Full <Interim> analysis set)	14.3.1.7	AE203
Adverse events by causality (Full <Interim> analysis set)	14.3.1.8	AE202
Repeat above 7 tables for SAEs		
Adverse events leading to discontinuation of study treatment (Full <Interim> analysis set)	14.3.4.1	AE201
Listing of adverse events leading to discontinuation of study treatment (Full <Interim> analysis set)	14.3.4.2	AE102
Serious adverse events leading to discontinuation of study treatment (Full <Interim> analysis set)	14.3.4.3	AE2011

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Listing of serious adverse events leading to discontinuation of study treatment (Full <Interim> analysis set)	14.3.4.4	AE1021
Adverse events leading to use of sick day rules (Full <Interim> analysis set)	14.3.5.1	AE208
Adverse events leading to use of sick day rules by sick day medication (Full <Interim> analysis set)	14.3.5.1.1	AE2081
Adverse events leading to adrenal crises (Full <Interim> analysis set)	14.3.5.2.1	AE209
Adrenal crises per 100 patient years (Full <Interim> analysis set)	14.3.5.2.2	AE212
Adrenal crises per 100 patient years, excluding extreme cases (Full <Interim> analysis set)	14.3.5.2.3	AE213
Adverse events of unexpected therapeutic benefit (Full <Interim> analysis set)	14.3.5.3	AE211
Signs and symptoms of adrenal insufficiency and over treatment (Full <Interim> analysis set)	14.3.6	FA200
Repeat of AE Tables at episode level to be decided at Data Review meeting		
Haematology (1) laboratory variables (Full <Interim> analysis set)	14.3.7.1.1	LB200
Change from pre-Chronocort baseline in Haematology (1) laboratory variables (Full <Interim> analysis set)	14.3.7.1.2.1	LB201
Shift table for Haematology (1) laboratory variables (Full <Interim> analysis set)	14.3.7.1.3 14.3.7.1.4	LB202A LB202B
Haematology (1) results considered clinically significant by the investigator (Full <Interim> analysis set)	14.3.7.1.5	LB203
Repeat above 4 tables for Haematology (2), Haematology (3)		
Biochemistry (1) laboratory variables (Full <Interim> analysis set)	14.3.7.4.1	LB2003
Change from pre-Chronocort baseline in Biochemistry (1) laboratory variables (Full <Interim> analysis set)	14.3.7.4.2.1	LB2013
Shift table for Biochemistry (1) laboratory variables (Full <Interim> analysis set)	14.3.7.4.3 14.3.7.4.4	LB2023A LB2023B
Biochemistry (1) results considered clinically significant by the investigator (Full <Interim> analysis set)	14.3.7.4.5	LB2033
Repeat above 4 tables for Biochemistry (2), Biochemistry (3), Biochemistry (4)		
Vital signs variables (Full <Interim> analysis set)	14.3.8.1.1	VS200
Vital signs variables, change from pre-Chronocort baseline (Full <Interim> analysis set)	14.3.8.1.2	VS201
Vital signs shift table for SBP and DBP (Full <Interim> analysis set)	14.3.8.1.4 14.3.8.1.5	VS203 VS202
Abnormal findings in physical examination (Full <Interim> analysis set)	14.3.8.1.6	PE200
Efficacy		
Total daily dose of Chronocort (Full <Interim> analysis set)	14.2.1.1	EX205
Total daily dose of Chronocort, excluding extreme cases (Full <Interim> analysis set)	14.2.1.2	EX205A
Total daily dose of Chronocort per body surface area (Full <Interim> analysis set)	14.2.1.3	EX201

Total daily dose of Chronocort distribution table (Full <Interim> analysis set)	14.2.1.4	EX206
Disease control, 17-OHP at 09:00h (Full <Interim> analysis set)	14.2.2.1.1	EF200
Disease control, 17-OHP at 09:00h, excluding extreme cases (Full <Interim> analysis set)	14.2.2.1.2	EF200A
Disease control, 17-OHP at 09:00h by proportion of daily dose given at night (Full <Interim> analysis set)	14.2.2.1.3	EF201
Disease control, 17-OHP at 13:00h (Full <Interim> analysis set)	14.2.2.1.4	EF202
Disease control, 17-OHP at 13:00h, excluding extreme cases (Full <Interim> analysis set)	14.2.2.1.5	EF202A
Disease control, 17-OHP at 13:00h by proportion of daily dose given at night (Full <Interim> analysis set)	14.2.2.1.6	EF203
Subjects achieving <36.4 nmol/L for 17-OHP at 09:00 hours by visit (Full <Interim> analysis set)	14.2.2.1.7	EF206
Repeat above 6 tables for A4 parameter		
Change from pre-Chronocort baseline in SDS at 09:00h (Full <Interim> analysis set)	14.2.3.1.1	EF210
Change from pre-Chronocort baseline in SDS at 13:00h (Full <Interim> analysis set)	14.2.3.1.2	EF211
Change from pre-Chronocort baseline of mean SDS over time (Full <Interim> analysis set)	14.2.3.1.3	EF212
Absolute values of 17-OHP (nmol/L) over time (Full <Interim> analysis set)	14.2.3.2.1.1	EF204
Absolute values of 17-OHP (nmol/L) over time, excluding extreme cases (Full <Interim> analysis set)	14.2.3.2.1.2	EF204A
Change from pre-Chronocort baseline in 17-OHP (nmol/L) over time (Full <Interim> analysis set)	14.2.3.2.2.1	EF205
Change from pre-Chronocort baseline in 17-OHP (nmol/L) over time, excluding extreme cases (Full <Interim> analysis set)	14.2.3.2.2.2	EF205B
Change from Visit 1/Baseline in 17-OHP (nmol/L) over time (Full <Interim> analysis set)	14.2.3.2.2.3	EF205A
Change from Visit 1/Baseline in 17-OHP (nmol/L) over time, excluding extreme cases (Full <Interim> analysis set)	14.2.3.2.2.4	EF205C
Repeat above 6 tables for A4 parameter		
Summary of absolute values of body composition - Dual Energy X-ray Absorptiometry (Full <Interim> analysis set)	14.2.4.1.1	VS204
Summary of absolute values of body composition excluding measurements post scanner change - Dual Energy X-ray Absorptiometry (Full <Interim> analysis set)	14.2.4.1.2	VS2041
Summary of change from pre-Chronocort baseline in body composition - Dual Energy X-ray Absorptiometry (Full <Interim> analysis set)	14.2.4.2.1	VS205
Summary of change from pre-Chronocort baseline in body composition excluding measurements post scanner change - Dual Energy X-ray Absorptiometry (Full <Interim> analysis set)	14.2.4.2.2	VS2051
Change in Dual Energy X-ray Absorptiometry scanner results by site population (Full <Interim> analysis set)	14.2.4.3	VS206

Summary of absolute values for bone markers and laboratory assessments of special interest (Full <Interim> analysis set)	**14.2.5.1**	**LB210**
Summary of change from pre-Chronocort baseline for bone markers and laboratory assessments of special interest (Full <Interim> analysis set)	14.2.5.2	LB211
Shift table of pre-Chronocort baseline to minimum on-treatment for bone markers and laboratory assessments of special interest (Full <Interim> analysis set)	14.2.5.3	LB212
Shift table of pre-Chronocort baseline to maximum on-treatment for bone markers and laboratory assessments of special interest (Full <Interim> analysis set)	14.2.5.4	LB2121
Summary of clinically significant results for bone markers and laboratory assessments of special interest (Full <Interim> analysis set)	14.2.5.5	LB213
Summary of SF-36 scores (Full <Interim> analysis set)	14.2.6.1.1	QS207
Summary of SF-36 change from pre-Chronocort baseline (Full <Interim> analysis set)	14.2.6.1.2	QS208
Summary of SF-36 percentage change from pre-Chronocort baseline (Full <Interim> analysis set)	14.2.6.1.3	QS209
Summary of GFI score derived from the MAF (Full <Interim> analysis set)	14.2.6.2.1	QS204
Summary of GFI score derived from the MAF change from pre-Chronocort baseline (Full <Interim> analysis set)	14.2.6.2.2	QS205
Summary of GFI score derived from the MAF percentage change from pre-Chronocort baseline (Full <Interim> analysis set)	14.2.6.2.3	QS206
Summary of EQ-5D by domain (Full <Interim> analysis set)	14.2.6.3.1	QS200
Shift table of baseline to end of study for EQ-5D by domain (Full <Interim> analysis set)	14.2.6.3.2	QS210
Summary of EQ-5D absolute values (Full <Interim> analysis set)	14.2.6.3.3	QS201
Summary of EQ-5D change from pre-Chronocort baseline (Full <Interim> analysis set)	14.2.6.3.4	QS202
Summary of EQ-5D percentage change from pre-Chronocort baseline (Full <Interim> analysis set)	14.2.6.3.5	QS203

16.2. List of planned listings

Study population		
Listing of subject disposition (All subjects)	16.2.1	DS100
Listing of protocol deviations (All subjects <Interim analysis set>)	16.2.2.1	DV100
Listing of subjects with extreme visit deviations (Full <Interim> analysis set)	16.2.2.2	SV100
Listing of study visit disruptions due to COVID-19 pandemic (Full <Interim> analysis set – subset of subjects still in study during COVID-19 pandemic)	16.2.2.3	CV101
Listing of study medication disruptions due to COVID-19 pandemic (Full <Interim> analysis set – subset of subjects still in study during COVID-19 pandemic)	16.2.2.4	CV102
Listing of subjects excluded from Full <Interim> analysis set	16.2.3	DS102
Listing of demographic and baseline characteristics (Full <Interim> analysis set)	16.2.4.1	DM100
Listing of congenital hyperplasia medical history (Full <Interim> analysis set)	16.2.4.2	MH101
Listing of other medical history excluding CAH events (Full <Interim> analysis set)	16.2.4.3	MH100
Listing of prior medications (Full <Interim> analysis set)	16.2.4.4	CM101
Listing of concomitant medications excluding glucocorticoid steroids (Full <Interim> analysis set)	16.2.4.5	CM100
Safety		
Listing of steroids, sick day medication and other glucocorticoids taken in addition to IMP (Full <Interim> analysis set)	16.2.4.6	CM103
Listing of Chronocort exposure (Full <Interim> analysis set)	16.2.5.1.1	EX100
Listing of drug accountability (Full <Interim> analysis set)	16.2.5.2	EX101
Listing of sick day pack accountability (Full <Interim> analysis set)	16.2.5.3	CM102
Subject compliance (Full <Interim> analysis set)	16.2.5.4	EX102
Listing of signs and symptoms of adrenal insufficiency and over treatment (Full <Interim> analysis set)	16.2.7.5	FA100
Listing of all adverse events (Full <Interim> analysis set)	16.2.7.1.1	AE100
Listing of all COVID-19 related adverse events (Full <Interim> analysis set)	16.2.7.1.2	AE100A
Listing of SAEs leading to death (Full <Interim> analysis set)	16.2.7.2	AE1011
Listing of AEs leading to use of sick day rules (Full <Interim> analysis set)	16.2.7.3	AE108
Listing of AEs leading to Adrenal crises (Full <Interim> analysis set)	16.2.7.4.1	AE109
All subjects experiencing adrenal crisis (Full <Interim> analysis set)	16.2.7.4.2	AE110
Adverse events of unexpected therapeutic benefit (Full <Interim> analysis set)	16.2.7.5	AE111
Signs and symptoms of adrenal insufficiency and over treatment (Full <Interim> analysis set)	16.2.7.6	FA100
Listing of Haematology (1) laboratory variables (Full <Interim> analysis set)	16.2.8.1	LB100
Repeat for Haematology (2), Haematology (3)		

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Listing of Biochemistry (1) laboratory variables (Full <Interim> analysis set)	16.2.8.4	LB1003
Repeat for Biochemistry (2), Biochemistry (3), Biochemistry (4)		
Listing of vital signs (Full <Interim> analysis set)	16.2.9.1	VS100
Listing of physical examination (Full <Interim> analysis set)	16.2.9.2	PE100
Listing of pregnancy test results (Full <Interim> analysis set)	16.2.9.3	FA101
Efficacy		
17-OHP and A4 (Full <Interim> analysis set)	16.2.6.1.1	SD100
Intra-subject/within-subject absolute change from pre-Chronocort baseline by visit in 17-OHP, A4 and weight (Full <Interim> analysis set)	16.2.6.1.2	SD101
Intra-subject/within-subject absolute change from Visit 1/Baseline by visit in 17-OHP, A4 and weight (Full <Interim> analysis set)	16.2.6.1.3	SD101A
Listing of DEXA scan parameters (Full <Interim> analysis set)	16.2.6.2	VS101
Listing of bone markers and laboratory assessments of special interest (Full <Interim> analysis set)	16.2.6.3	LB1007
Listing of SF-36 scores (Full <Interim> analysis set)	16.2.6.4.1	QS102
Listing of MAF scores and GFI (Full <Interim> analysis set)	16.2.6.4.2	QS101
Listing of EQ-5D scores (Full <Interim> analysis set)	16.2.6.4.3	QS100

16.3. List of planned figures

16.3.1. Summary figures

Safety		
Boxplot of change from pre-Chronocort® baseline over time for red blood cell count (Full <Interim> analysis set)	14.3.7.1.2.2	LB300
Repeat above figure for other Haematology (1) parameters, Haematology (2), Haematology (3), Biochemistry (1), Biochemistry (2), Biochemistry (3), Biochemistry (4) laboratory parameters.		
Boxplot of change from pre-Chronocort® baseline over time for systolic blood pressure (Full <Interim> analysis set)	14.3.8.1.3.1	VS300
Repeat above figure for other vital signs of interest		
Efficacy		
Geometric mean +/- 95% CI over time for 17-OHP at 09:00h (Full <Interim> analysis set)	14.2.3.2.3	EF300
Geometric mean +/- 95% CI over time for 17-OHP at 13:00h (Full <Interim> analysis set)	14.2.3.2.5	EF302
Repeat above figure for A4		
Spaghetti plot of intra-subject/within-subject absolute change from baseline by visit in 17-OHP, A4 and weight (Full <Interim> analysis set)	14.2.3.4.1	EF304
Boxplot of change from pre-Chronocort® baseline over time for fasting serum CTX (Full <Interim> analysis set)	14.2.5.2.1	LB310
Repeat above figure for other bone markers and laboratory assessments of special interest		

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16.3.2. Individual subject figures

Efficacy		
Individual 17-OHP profile plot (on a logarithmic scale) over time at 09:00h (Full <Interim> analysis set)	14.2.3.2.4	EF301
Individual 17-OHP profile plot (on a logarithmic scale) over time at 13:00h (Full <Interim> analysis set)	14.2.3.2.6	EF303
Repeat above figure for A4		

17. 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 9. 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 9: 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
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

Protocol lab name (for display)	Abbreviated display name	SDTM lab test code	SDTM lab test name
AST/GOT	AST	AST	Aspartate Aminotransferase
Total creatinine 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

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