

STATISTICAL ANALYSIS PLAN

Title A 12-Week Phase 2 Open-Label, Sequential Dose Cohort Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of CRN04894 Treatment in Participants with Congenital Adrenal Hyperplasia

Protocol: CRN04894-03

Investigational Product: CRN04894

Phase: 2

Sponsor: Crinetics Pharmaceuticals, Inc.

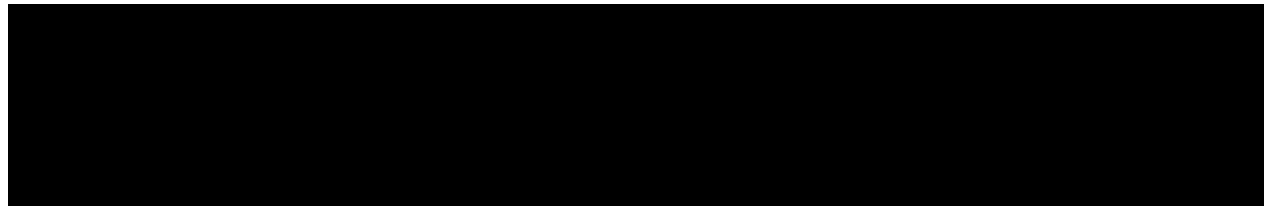
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ABBREVIATIONS

11-DOC	11-deoxycorticosterone
17-OHP	17-hydroxyprogesterone
21-OHD	21-hydroxylase deficiency
A4	androstenedione
ACTH	adrenocorticotrophic hormone
AE	adverse event
AESI	adverse events of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the curve
BLQ	below the limit of quantification
BMI	body mass index
BSA	body surface area
CAH	congenital adrenal hyperplasia
CRF	case report form
CRO	clinical research organization
ECG	electrocardiogram
EOS	end of study
EOT	end of treatment
FAS	full analysis set
FSH	follicle stimulating hormone
GC	glucocorticoid
LH	luteinizing hormone
LLOQ	lower limit of quantitation

LSM	least squares mean
MedDRA	medical dictionary for regulatory activities
MRI	magnetic resonance imaging
NCA	noncompartmental analysis
OLE	Open label extension
PD	pharmacodynamics
PK	pharmacokinetics
PT	preferred term
QD	once daily
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected using Fridericia's formula
QTcF	QT interval corrected using Bazett's formula
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
SRC	safety review committee
██████	████████████████████
TB	total bilirubin
TEAE	treatment-emergent adverse event
ULN	upper limit of normal

1. INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide technical and detailed elaboration of the statistical analyses of efficacy, safety, pharmacokinetics (PK), and pharmacodynamics (PD) data as outlined and/or specified in the study protocol (version 3.1 (region-specific [US, UK, BR]) dated 14Aug2024).

2. STUDY DESIGN

Study CRN04894-03 is a Phase 2, open-label, sequential dose cohort study to evaluate the efficacy, safety, PK, and PD of CRN04894 when administered for 12 weeks in participants with congenital adrenal hyperplasia (CAH) caused by 21-hydroxylase deficiency (21-OHD).

Up to approximately 30 participants will be enrolled in Cohorts 1-3 of the study with an additional 6-12 participants in Cohort 4 (up to 42 participants total across the 4 cohorts). Each cohort will enroll at least 6 participants, with a possible expansion of up to an additional 6 participants in cohorts 1, 2 and 4, to a maximum of 12 evaluable participants in those cohorts.

During Screening, modification of glucocorticoid (GC) doses will not be allowed except for stress (emergency) dosing. Preexisting doses of fludrocortisone will also be maintained throughout the study. After the Screening Period, participants will be assigned to a dose cohort in an open-label fashion. The dose cohorts will run sequentially.

Participants in Cohorts 1-3 will continue their preexisting glucocorticoid replacement dosing regimens/doses throughout the study. Glucocorticoid replacement dosing will be reduced during Weeks 2-10 for participants in Cohort 4. In addition, starting the night of Day 1 and ending the night before the Week 12/End of Treatment (EOT) visit, Cohorts 1-3 will administer CRN04894 between 22:00-24:00 (at approximately the same time each night) once daily (QD) before sleep, and Cohort 4 will administer 80 mg CRN04894 between 6:00-10:00 (at approximately the same time each morning) once daily along with their morning GC replacement dose.

Participants in Cohort 1 will receive 80 mg QD in the evening. After at least 3 participants have completed 2 weeks of dosing with 80 mg QD in Cohort 1, an analysis evaluating PD, PK, efficacy, and safety will be reviewed by the Safety Review Committee (SRC). If it is safe to continue, the SRC will recommend dosing of 120 mg in Cohort 2. However, the SRC can recommend a lower dose (i.e., 40 mg QD CRN04894) in Cohort 2 based on review of safety data. The SRC also has the option to recommend increasing enrollment up to a total of 12 participants each in Cohorts 1 and 2. In this situation, expanded enrollment in the cohort will be completed, and data from the expanded cohort will be reviewed by the SRC prior to enrollment in the subsequent cohort.

Cohort 1 will first complete enrollment with at least 6 participants prior to commencing Screening for Cohort 2. The same initial dosing and SRC review process as used for the initiation of Cohort 2 would be followed for the optional Cohort 3, in which participants would receive up to 160 mg QD. The follow-up period will extend from weeks 12 to 16.

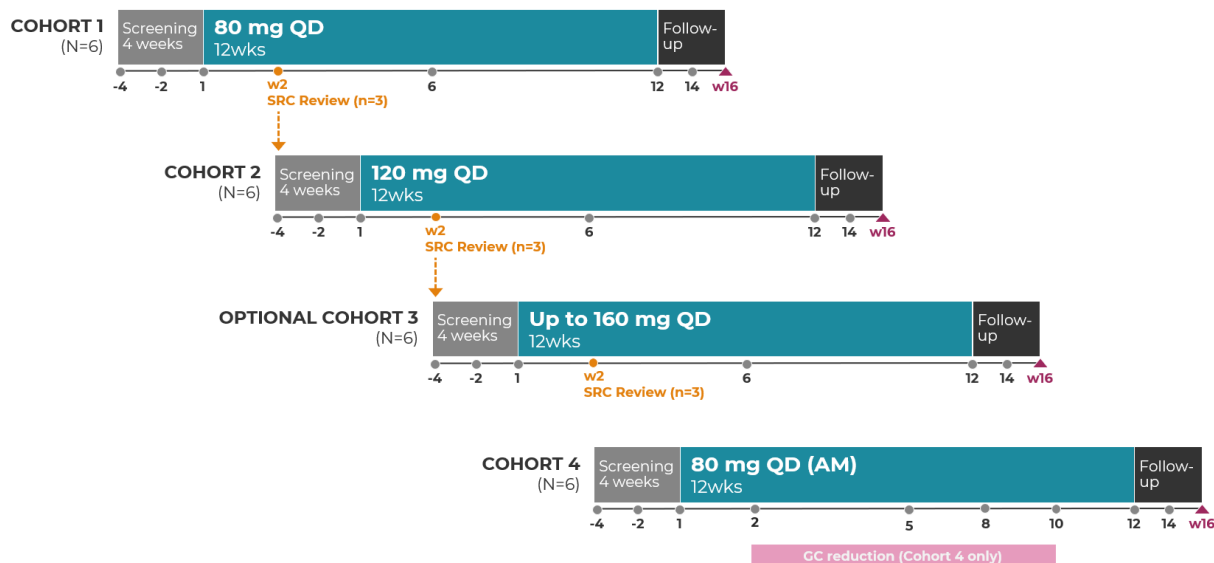
Cohort 4, receiving 80 mg once daily in the morning, will be enrolled after Cohorts 1-3 have completed enrollment.

For all cohorts, safety and PD biomarkers will be obtained at the end of week 14 of the follow-up period. Participants will receive a safety phone call for safety evaluation at the end of the week 16 (end of study, EOS).

If eligible, participants may be enrolled in a separate long-term open label extension (OLE) study, during which they will receive CRN04894. All participants who have completed Week 12 (EOT) may be offered participation in a separate long-term extension study. If the long-term extension study is opened at the investigative site and participants sign informed consent for the long-term extension study, the safety Follow-up Visit and the EOS Visit are not applicable, as treatment on CRN04894 will not be interrupted. Those participants, who do not opt for the OLE or are not deemed eligible, will continue to be monitored during a 4-week safety Follow-up Visit and the EOS Visit.

At any time during the study, the SRC may determine that study drug dosing should be adjusted or halted based on safety and tolerability data. The study design is shown in [Figure 1](#).

Figure 1: Study Schema



SRC=safety review committee, W=week

^a The SRC can recommend a lower dose (i.e., 40 mg QD CRN04894) in Cohort 2 based on review of safety data. The SRC also has the option to recommend increasing enrollment up to a total of 12 participants per cohort in Cohort 1 or Cohort 2. In this situation, expanded enrollment in the cohort will be completed, and data from the expanded cohort will be reviewed by the SRC prior to enrollment in the subsequent cohort.

Refer to [Appendix 2](#) for Schedule of Activities.

2.1. Blinding and Randomization Methods

This is an unblinded, open-label study. Participants will be sequentially assigned to a dose cohort, starting with Cohort 1.

3. STUDY OBJECTIVES AND ENDPOINTS

Objectives and Endpoints

Objectives	Endpoints
Primary Safety Objective	Primary Safety Endpoints
To evaluate the safety and tolerability of CRN04894	Incidence of treatment-emergent adverse events (TEAEs), including treatment -emergent serious adverse events (SAEs) and any adverse events (AEs) leading to discontinuation
Primary Efficacy Objective	Primary Efficacy Endpoint
To evaluate efficacy of CRN04894, measured by change from Baseline in serum androstenedione (A4)	Change from baseline in morning (before 11:00) serum A4 at Week 12
Secondary Efficacy Objective	Secondary Efficacy Endpoint
To evaluate efficacy of CRN04894, measured by change from Baseline in serum 17-hydroxyprogesterone (17-OHP)	Change from baseline in morning (before 11:00) serum 17-OHP at Week 12
Exploratory Objectives	Exploratory Endpoints

Objectives	Endpoints

4. SAMPLE SIZE CONSIDERATIONS

The sample size is based on practical considerations. No formal sample size and power calculation will be carried out for the efficacy endpoints in the study.

Up to approximately 30 participants will be enrolled in Cohorts 1-3 in the study. Each cohort will enroll at least 6 participants, with a possible expansion of up to an additional 6 participants in any single cohort, to a maximum of 12 evaluable participants in that cohort. Cohort 4 will enroll an additional 6-12 participants.

5. INTERIM ANALYSIS

For either Cohort 1 or Cohort 2, after 3 or more participants in the given cohort have completed 2 weeks of dosing, an analysis will be prepared for SRC purpose including PD, PK, efficacy, and safety endpoints. After all participants in Cohort 2 have gone through the treatment period or discontinued study treatment early, an analysis of efficacy and safety endpoints are planned to support regulatory interactions and decision-making.

6. SAFETY REVIEW COMMITTEE

An SRC composed of Crinetics physicians, clinical research organization (CRO) medical monitor, and other study team members has been established for the ongoing monitoring of participant safety in this study. After careful evaluation of all safety, pharmacokinetic, and exposure data, the SRC will approve the next dose level. Enrollment for the next cohort will not occur until SRC approval of dose and the ongoing cohort has enrolled at least 6 participants.

Because data review from 6 patients dosed with 80 mg has been conducted by the SRC, an SRC review will not be required to commence Cohort 4. An ad hoc SRC will be permitted as needed during the conduct of Cohort 4.

6.1. Early Safety Data Review and/or Committee

Participant safety will be monitored by the SRC.

- Early aggregated safety data review will be performed, the goal of which is to allow for a stepwise approach of CRN04894 administration. An initial safety review for this study is planned for after the first 3 participants have provided PD, PK, efficacy, and safety data for 2 weeks after administration of CRN04894 at 80 mg (Cohort 1). The SRC will also review safety data after the first 3 participants completed 2 weeks of dosing in the subsequent cohorts.

All data collected will be summarized and reviewed by SRC for agreement of next steps as defined in the SRC charter.

- During the SRC review period of the first 3 dosed participants in any cohort (N=3), enrollment of that cohort (up to 6 total is planned) will continue during the SRC review of the initial 3 participant's safety data. No enrollment into subsequent cohorts will occur unless 1) the SRC approves cohort advancement and 2) the preceding cohort has enrolled at least 6 participants. Please refer to the SRC charter for more details.

7. DEFINITIONS

7.1. Morning Window Value

Cohorts 1-3:

For PD biomarkers (17-OHP, ACTH [plasma], testosterone, A4, [REDACTED] 11-DOC, 21-deoxycortisol, [REDACTED]), morning window value on a given day is defined as the average of any early morning samples on or after 06:00 but no later than 11:00. On a given day, all scheduled assessments including circadian and non-circadian assessments from central labs will be considered and unscheduled assessments will not be used unless there is no scheduled assessment on or after 06:00 but no later than 11:00. Local labs will not be considered.

Cohort 4:

For PD biomarkers, morning window value on a given day is defined as the average of any early morning samples on or after 06:00 but no later than 11:00 prior to receiving the morning CRN04894 dose. On a given day, all scheduled assessments from central labs will be considered and unscheduled assessments will not be used unless there is no qualified scheduled assessment. Local labs will not be considered.

7.2. Baseline

For PD biomarkers, baseline is defined as the last non-missing morning window value prior to or on the same day as the first dose date of CRN04894, unless otherwise specified.

For other clinical laboratory tests, baseline is defined as the last non-missing central lab assessment prior to the first dose of CRN04894. When lab collection time is unknown, then baseline is defined as the last non-missing central lab assessment prior to or on the same day as the first dose date of CRN04894. All central lab samples including scheduled, unscheduled, regular, and circadian samples will be considered. If multiple central lab assessments have the same date and time, then the average of these values will be used as the baseline.

For ECG parameters, baseline is defined as the last non-missing assessment prior to the first dose of CRN04894. When ECG collection time is unknown, then baseline is defined as the last non-missing assessment prior to or on the same day as the first dose date of CRN04894. All samples including scheduled and unscheduled assessments will be considered. For quantitative assessments, if multiple assessments have the same date, then the average of these values will be

used as the baseline. For overall evaluation, only evaluable interpretations (i.e. normal and abnormal) will be considered. If multiple assessments have the same date, then the worst overall evaluation will be used as the baseline.

For imaging data, baseline is defined as the closest assessment to the first dose of CRN04894 including scheduled and unscheduled assessments and any post-baseline assessments up to 7 days after the first dose of CRN04894.

For other assessments, baseline is defined as the last non-missing assessment prior to the first dose of CRN04894, unless otherwise specified.

7.3. Exposure and Compliance

Duration of exposure in days is defined as $\min(\text{date of last dose of CRN04894, data cutoff date}) - \text{date of first dose of CRN04894} + 1$.

The overall compliance for each participant will be calculated as $100 \times (\text{the number of tablets actually taken}) / (\text{expected number of tablets that should have been taken})$.

The number of tables actually taken will be derived by summing up the number of tablets taken daily as recorded on the case report form (CRF). The expected number of tablets that should have been taken will be calculated by multiplying the duration of exposure in days by the number of planned tablets to be taken per day (i.e. the planned daily dose level divided by the unit dose strength).

7.4. Study Day

If the visit date is on or after the first dose of CRN04894:

Study day = $(\text{visit date} - \text{date of the first dose of CRN04894} + 1)$

If the visit date is prior to the first dose of CRN04894:

Study day = $\text{visit date} - \text{date of the first dose of CRN04894}$

There is no study day 0 in the study.

7.5. AGE at Time of Informed Consent

The age at time of informed consent recorded on CRF will be used.

7.6. Body Surface Area (BSA)

BSA (m^2) will be calculated as $\sqrt{\frac{\text{Weight in kg} \times \text{Height in cm}}{3600}}$.

8. ANALYSIS POPULATIONS

8.1. Full Analysis Set

The Full Analysis Set (FAS) will consist of all participants who received at least one dose of CRN04894. The FAS will be used for all demographics, disease characteristics, safety, and efficacy analyses.

8.2. Pharmacokinetics Analysis Set

The Pharmacokinetics Analysis Set (PK Analysis Set) will consist of all participants in the FAS who have at least one postbaseline sample with evaluable drug concentration. The PK Analysis Set will be used for PK analyses.

9. DATA SCREENING AND ACCEPTANCE

9.1. General Principles

Data will be reviewed periodically. Any questionable data will be reported to the clinical data manager promptly for query and resolution.

9.2. Handling of Missing and Incomplete Data

Missing clinical outcome data can occur for multiple reasons, including missed participant visits, scales or measures with missing item scores, and etc. Missing and incomplete data will be identified through the data quality review plan for this study. Missing and incomplete data will be identified for investigation, and possible resolution, by Data Management prior to the study database lock or snapshot.

Unless specified otherwise, only the observed data (not imputed data) will be presented in listings.

9.2.1. Missing Medical History Related Dates

Generally, missing portions of start dates for medical history will not be imputed. However, the missing portions of start dates for CAH will be imputed as follows.

- If only day is missing, impute 1.
- If month is missing, impute January 1st.
- If year is missing, then no imputation will be done; the date will be missing.

If the imputed date is earlier than the birth date, then the birth date will be used.

9.2.2. Missing Date Imputation for Adverse Events and Concomitant Medications

The following conventions will be used to impute missing portions of dates for adverse events and concomitant medications. Note that the imputed values outlined here may not always provide the most conservative date.

Missing Start Dates

- If the day is unknown, then:
 - If the month and year match the month and year of the first dose of CRN04894 in this study, then impute the day of the first dose date.
 - Otherwise, assign the first day of the month.
- If the month is unknown, then:
 - If the year matches the year of the first dose of CRN04894 date in this study, then impute the month of the first dose date in this study.
 - Otherwise, assign 'January'
- If the year is unknown, then the date will not be imputed and will be assigned a missing value.

If the imputed date is earlier than birth date, then birth date will be used. If the imputed start date is later than the end date, then the start date will be set as the same date as the end date.

Missing Stop Dates and Not Ongoing

- If the day is unknown, then assign the last day of the month.
- If the month is unknown, then assign 'December.'
- If the year is unknown, then the date will not be imputed and will be assigned a missing value. If the AE has been recorded as resolved/recovered, all efforts should be made to obtain the date from the Investigator.

If the resulting end date is after the date of study completion/discontinuation/data cutoff, set the imputed end date as close to the date of study completion/discontinuation/data cutoff as possible without overwriting existing information.

9.2.3. Incomplete Data for Safety Lab, PD, and PK Endpoints

For safety lab data, if the raw data is " $\leq xx$ ", then the imputed value will be $0.9 * xx$. If the raw data is " $\geq xx$ ", then the imputed value will be $1.1 * xx$.

For PD biomarkers, if the raw data is reported as " $< xx$ ", then it will be imputed as LLOQ/2 when the lower limit of quantitation (LLOQ) is available or otherwise as $0.5 * xx$ if LLOQ is not available for tables. If the raw data is " $\geq xx$ ", then the imputed value will be $1.1 * xx$.

For PK data, if the raw data is " $< LLOQ$ ", then it will be presented as below the limit of quantification (i.e. "BLQ") in listings. It will be presented as 0 in summary tables and treated as 0 for calculation of summary statistics. For the noncompartmental analysis (NCA) of circadian PK profiles, BLQ data prior to the first measurable concentration will be set to 0, whereas all embedded and trailing BLQ values will be set to missing.

9.3. Visit Time Windows

For Cohorts 1-3: All PD biomarker assessments will be mapped to analysis visit as specified in [Table 1](#) below. After mapping, morning window value will be derived on a given day. If there

are multiple morning window values within a post-baseline visit window, the one closest to the scheduled date will be used unless multiple values are equally close, in which case the latest one will be used for analysis. For Cohort 4: Morning window value will be derived on a given day. PD biomarker assessments collected at unscheduled or early termination visit will be mapped to analysis visit as specified in [Table 2](#) below. The morning window value at the scheduled nominal post-baseline visit will be used if available. Otherwise, the morning window value from the mapped unscheduled or early termination assessments will be used at the post-baseline visit. If there are multiple morning window values from the mapped unscheduled or early termination assessments available within a post-baseline visit window, the one closest to the scheduled date will be used unless multiple values are equally close, in which case the latest one will be used for analysis. All PD assessments (scheduled and unscheduled) including central and local labs will be presented in data listings.

Table 1: Cohorts 1-3: Analysis Windows for PD Biomarkers

Mapped Visit	Scheduled Visit Day	Study Day Window
Baseline	1	≤ 1
Week 2	14	[2, 28]
Week 6	42	[29, 63]
Week 12	84	[64, 91]
Week 14	98	≥ 92

Table 2: Cohort 4: Analysis Windows for Unscheduled or Early Termination PD Biomarker Assessments

Mapped Visit	Scheduled Visit Day	Study Day Window
Baseline	1	≤ 1
Week 2	14	[2, 35]
Week 8	56	[36, 70]
Week 12	84	[71, 91]
Week 14	98	≥ 92

For other clinical laboratory tests, only central labs at scheduled nominal visits will be used in tabulations. If central lab circadian samples were drawn in addition to the regular central lab samples at the same nominal visit, then the regular central lab samples will be used and central lab circadian assessments will only be used if there is no regular central lab result available at the visit. All assessments (scheduled and unscheduled) including central and local labs will be presented in data listings.

For Cohorts 1-3: All imaging assessments will be mapped to analysis visit as specified in [Table 3](#) below. If there are multiple values within a post-baseline visit window, the one closest to the scheduled date will be used unless multiple values are equally close, in which case the latest one will be used for analysis. For Cohort 4: Imaging assessments collected at unscheduled or early termination visit will be mapped to analysis visit as specified in [Table 3](#). The scheduled assessment will be used if available. Otherwise, the mapped unscheduled or early termination

assessment will be used at the post-baseline visit. If there are multiple mapped unscheduled or early termination assessments available within a post-baseline visit window, the one closest to the scheduled date will be used unless multiple values are equally close, in which case the latest one will be used for analysis. Baseline and change from baseline to Week 12 will be summarized. All imaging assessments (scheduled and unscheduled) including those done during the follow-up period between Weeks 14-16 if clinically indicated as judged by the Investigator will be presented in data listings.

Table 3: Analysis Windows for Imaging Data

Mapped Visit	Scheduled Visit Day	Study Day Window
Baseline	1	≤ 7
Week 12	84	[70, 98]
Follow-up*	105	≥ 99

* An MRI and [REDACTED] may be done during the follow-up period between Weeks 14-16 (i.e. days 98-112) if clinically indicated as judged by the Investigator.

Other assessments will be summarized using the nominal visit labels provided in the data.

9.4. Software

SAS® software version 9.4 or higher will be used to perform statistical analyses unless otherwise specified.

10. STATISTICAL METHODS OF ANALYSES

10.1. General Principles

Unless otherwise specified, summaries will be performed descriptively by cohort. Continuous, quantitative (absolute values at each timepoint and change from baseline if applicable) variable summaries will include the number of participants (n) with non-missing values, mean, standard deviation (SD), standard error (SE) of the mean, median, minimum, and maximum values.

Categorical, qualitative variable summaries will include the frequency and percentage of participants in the particular category. In general, the denominator for the percentage calculation will be based upon the total number of participants in the study population for the cohorts.

Nominal p-values will be presented as a supporting evidence measure of the strength of the treatment effect relative to baseline rather than formal tests of hypotheses. Confidence intervals will be 2-sided 95% confidence intervals, unless stated otherwise. There will be no multiplicity adjustments, or adjustments for multiple comparisons.

10.2. Disposition and Participant Accountability

The number of screened participants and number of participants enrolled will be tabulated.

The number and percentage of participants included in the FAS and PK Analysis Set will be summarized by cohort and overall. Participants excluded from an analysis set will be listed.

Participant disposition will be summarized for the FAS. The number and percentage of participants who completed the treatment period, prematurely discontinued treatment with the reason, completed the study, and prematurely discontinued the study with the reason will be presented for each cohort and overall. All disposition information will be presented in a data listing.

10.3. Protocol Deviations

Protocol deviations will be summarized using the FAS by cohort. All protocol deviations will be listed.

10.4. Investigational Product Administration

10.4.1. Demographic and Baseline Characteristics

Demographic parameters (age, sex, reproductive status (if female), ethnicity, race, weight, height, body mass index [BMI], BSA, waist circumference, etc) and other baseline characteristics (time since CAH diagnosis, adrenal androgens and precursors at baseline, baseline GC daily dose, etc) will be summarized descriptively by cohort for the FAS.

Demographics and baseline characteristics will be presented by participant in data listing.

10.4.2. Medical History

Medical history data will be coded by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) Version 26.0 or newer. Participants reporting medical history will be summarized by SOC and PT for FAS.

Medical history information will be presented by participant in a data listing.

10.4.3. Prior and Concomitant Medication

Prior medication is defined as any medication started before the date of the first dose of CRN04894 (medication start date prior to the first dose date).

Concomitant medication is defined as any medication taken on or after the date of the first dose of CRN04894 (medication end date on or after first dose date [or ongoing]).

Medications with completely missing start date will be considered as both prior and concomitant.

Both prior and concomitant medications will be coded by drug name and therapeutic class using WHO Drug Version Dictionary Global B3, March 2023 or newer.

The number and percentage (n, %) of participants who receive prior and concomitant medications will be summarized separately, by drug class (i.e., atomic therapeutic class) for each cohort using FAS. If a participant took a specific medication multiple times or took multiple medications within a specific therapeutic class, that participant will be counted only once for the coded drug name or therapeutic class.

Prior and concomitant medication information will be reported by a data listing.

10.4.4. Extent of Exposure

The duration of exposure to CRN04894 for FAS will be summarized by cohort. Number and percentage of participants with at least one dose modification and the corresponding reason will be also produced. Although a participant may have multiple dose modifications with the same reason, participant will be counted only once for each distinct reason.

All treatment exposure data will be listed in detail.

10.4.5. Measurement of Treatment Compliance

Summary statistics will be produced for overall compliance by cohort for the FAS. Number and percentage of participants with compliance <80%, 80-120%, and >120% will also be tabulated. A listing of participant compliance will be produced.

10.4.6. Use of GC

For Cohort 4: GC daily dose at each visit (i.e. baseline, week 2, week 8 and week 12) will be derived as the sum of GC daily doses taken from 3 days prior to the A4 analysis visit date to 1 day prior to the A4 analysis visit date divided by the number of days on which the GC dose is taken during the 3-day window. For example, if the morning window value on 14Mar2025 is used for A4 analysis at week 2, then the GC doses taken from 11Mar2025 to 13Mar2025 (inclusive) will be used to derive the GC daily dose at week 2. If no A4 is available for analysis at this visit, then the analysis visit date for 17-OHP will be used. If neither is available, then the most frequent analysis visit date for the rest PD biomarkers will be used at this visit. If no PD biomarker is available for analysis at this visit, then the analysis visit date for safety labs will be used. If both PD biomarkers and safety labs are not available for analysis at the visit, then the analysis visit date for vital signs will be used.

For Cohorts 1-3, baseline GC dose will be derived similarly to the baseline GC dose for Cohort 4. It is expected that the baseline GC dose should remain stable throughout the study unless there is concern for or a risk of adrenal insufficiency. In such case, the dose of glucocorticoid may be modified after a discussion with the study doctor according to the stress/sick day rules.

For all cohorts, use of GC as reported on the CRF will be listed.

Table 4: Conversion of Glucocorticoid Dose to Equivalent Hydrocortisone Dose

Glucocorticoid	Equivalent Doses (mg)	Conversion Factor	Equivalent Hydrocortisone Dose (mg)
Hydrocortisone	20	1	20
Cortisone	25	0.8	20
Prednisone	5	4	20
Prednisolone	5	4	20
Meprednisone	5	4	20
Methylprednisolone	4	5	20
Triamcinolone	4	5	20
Dexamethasone	0.75	30	22.5
Betamethasone	0.6	30	18

10.5. Efficacy Analysis

Efficacy analyses will be conducted on the FAS population according to the planned cohort at enrollment.

10.5.1. General Analysis Methods

The study has no formal statistical primary endpoint hypothesis. The intent is to evaluate the safety and tolerability, explore potential efficacy, and characterize pharmacokinetics of CRN04894 in participants with CAH.

All efficacy endpoints will be presented in by-participant data listings. Tables will include descriptive statistics by cohort.

10.5.1.1. Analyses of Continuous Data

Continuous variables will be summarized using descriptive statistics (e.g., n, mean, median, SD, minimum and maximum). For the analyses of change from baseline, the mean at baseline and at the visit will be calculated for all participants with at least one post-baseline value at the specific visit by cohort.

10.5.1.2. Analyses of Categorical Data

Qualitative variables will be summarized by frequency counts and percentages. Unless otherwise specified, the calculation of proportions will include the missing category. Therefore, counts of missing observations will be included in the denominator and presented as a separate category.

10.5.2. Analysis of Primary Efficacy Endpoint

10.5.2.1. Primary Analysis

The estimand for the primary analysis is defined by the following components.

Question of interest: For the participants with CAH caused by 21-hydroxylase deficiency, what would be the expected effect of CRN04894 on morning (before 11:00) serum A4, while CRN04894 is being taken up to 12 weeks?

Population: The target population is participants with CAH caused by 21-hydroxylase deficiency, as defined by the protocol inclusion and exclusion criteria. The analysis population is FAS.

Variable: The variable is the primary efficacy endpoint, defined as the change from baseline in morning (before 11:00) serum A4 at Week 12.

Intercurrent Events and Handling Rules: Treatment discontinuation is considered an intercurrent event. All morning (before 11:00) serum A4 assessments following the intercurrent event will be considered as missing and will be imputed with the last available value prior to the intercurrent event (while-on-treatment policy) in the analyses. For missing data not due to intercurrent event (e.g. due to missed visit or insufficient sample, etc), missing data will be imputed with the last available value prior to visit.

Statistical Analysis: For Cohorts 1-3: The primary efficacy analysis will use an analysis of covariance (ANCOVA) model including cohort and sex as fixed effects and baseline morning (before 11:00) serum A4 value as a covariate. For Cohort 4: The primary efficacy endpoint will be summarized using descriptive statistics.

Population-level Summary: For Cohorts 1-3: The least squares mean (LSM) from the ANCOVA model will be presented. Summary statistics will also be presented. For Cohort 4: Summary statistics will be presented.

10.5.2.2. Sensitivity Analyses

To assess the robustness of the primary analysis, the following sensitivity analyses of the primary efficacy endpoint will be performed.

Supportive Estimand I for the Primary Efficacy Endpoint

Question of interest: For participants with CAH caused by 21-hydroxylase deficiency, what would be the expected effect of CRN04894 on morning (before 11:00) serum A4 at Week 12, if taken as directed for the entire 12 weeks?

Intercurrent Events and Handling Rules: Treatment discontinuation is considered an intercurrent event. All morning (before 11:00) serum A4 assessments following the intercurrent event will be considered as missing in the analyses (hypothetic policy). Missing data will not be imputed.

All other components of the estimand defined in Section 10.5.2.1 stay the same.

Supportive Estimand II for the Primary Efficacy Endpoint

Question of interest: For the participants with CAH caused by 21-hydroxylase deficiency, what would be the expected effect of CRN04894 on morning (before 11:00) serum A4 at Week 12?

Intercurrent Events and Handling Rules: Treatment discontinuation is considered an intercurrent event. All available morning (before 11:00) serum A4 assessments will be included in the analysis, regardless of intercurrent event (treatment policy). Missing data will not be imputed.

All other components of the estimand defined in Section 10.5.2.1 stay the same.

10.5.3. Analyses of Secondary Efficacy Endpoint

The secondary efficacy endpoint is the change from baseline in morning (before 11:00) serum 17-OHP at week 12. The same primary and supportive estimands for the primary efficacy endpoints as described in Section 10.5.2 will be defined for the secondary efficacy endpoints.

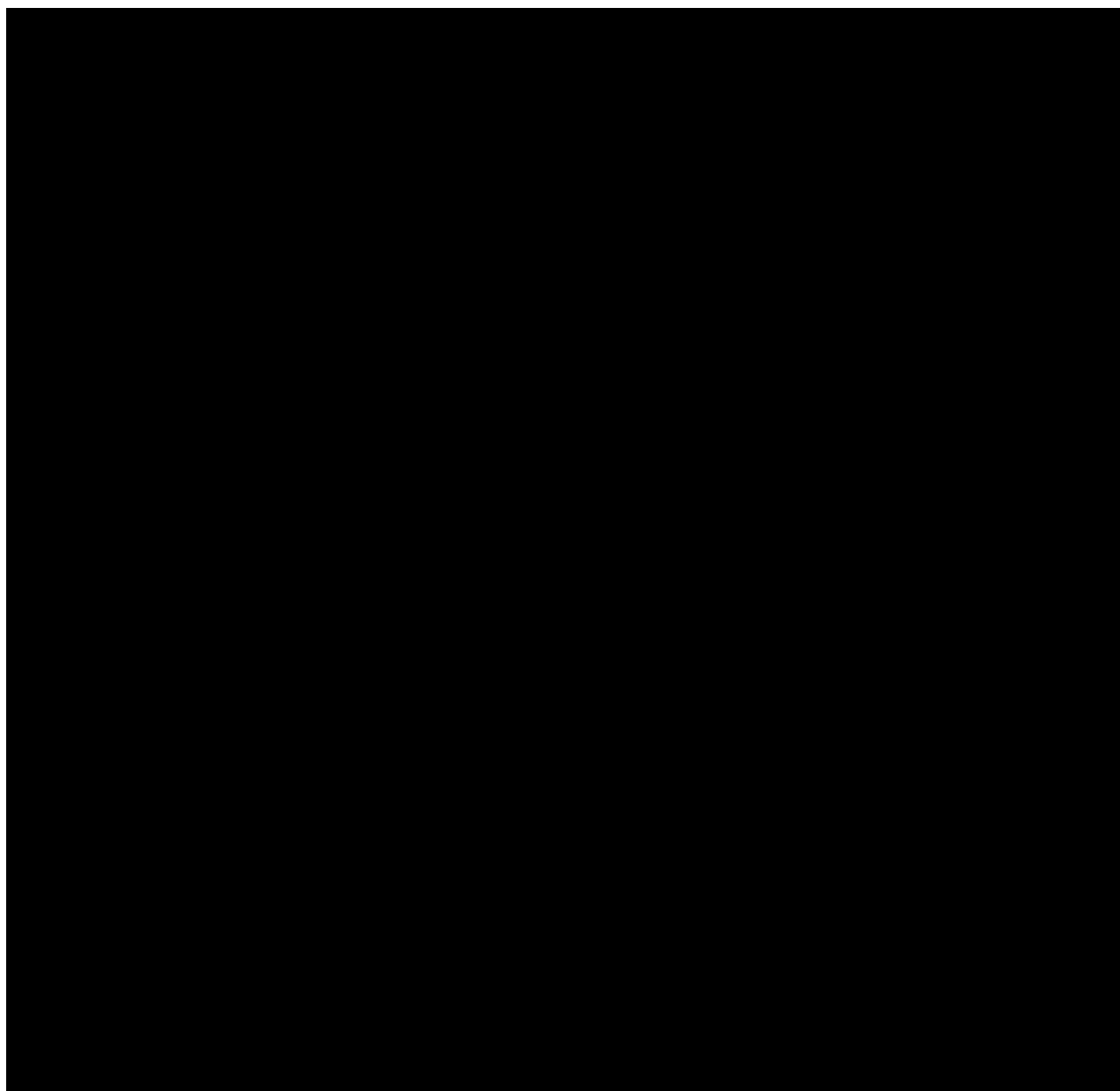
10.5.4. Multiplicity Adjustment

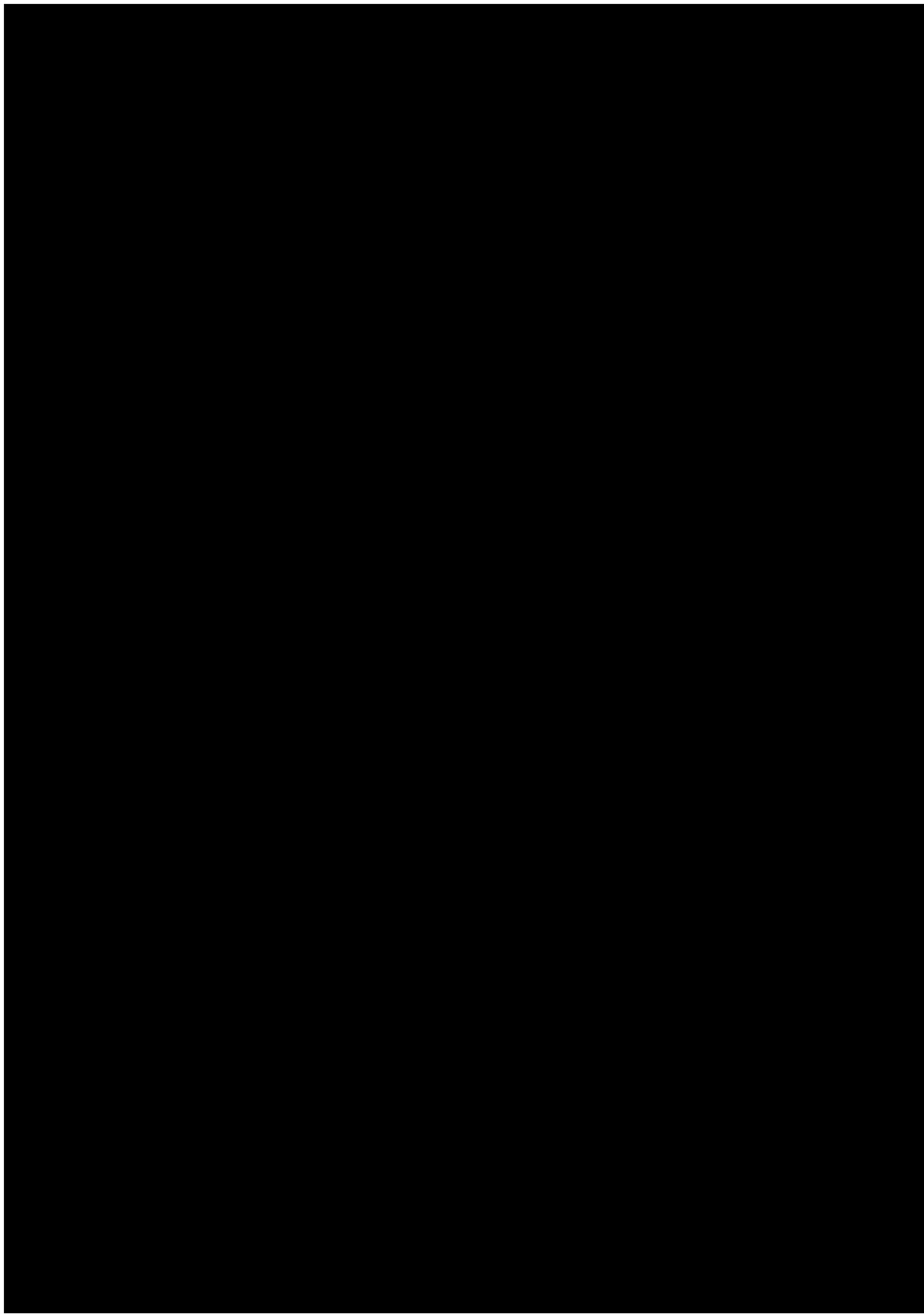
No adjustments will be made for multiplicity. The nominal p-values will be computed as a measure of strength of the treatment effect relative to baseline rather than formal tests of hypotheses.

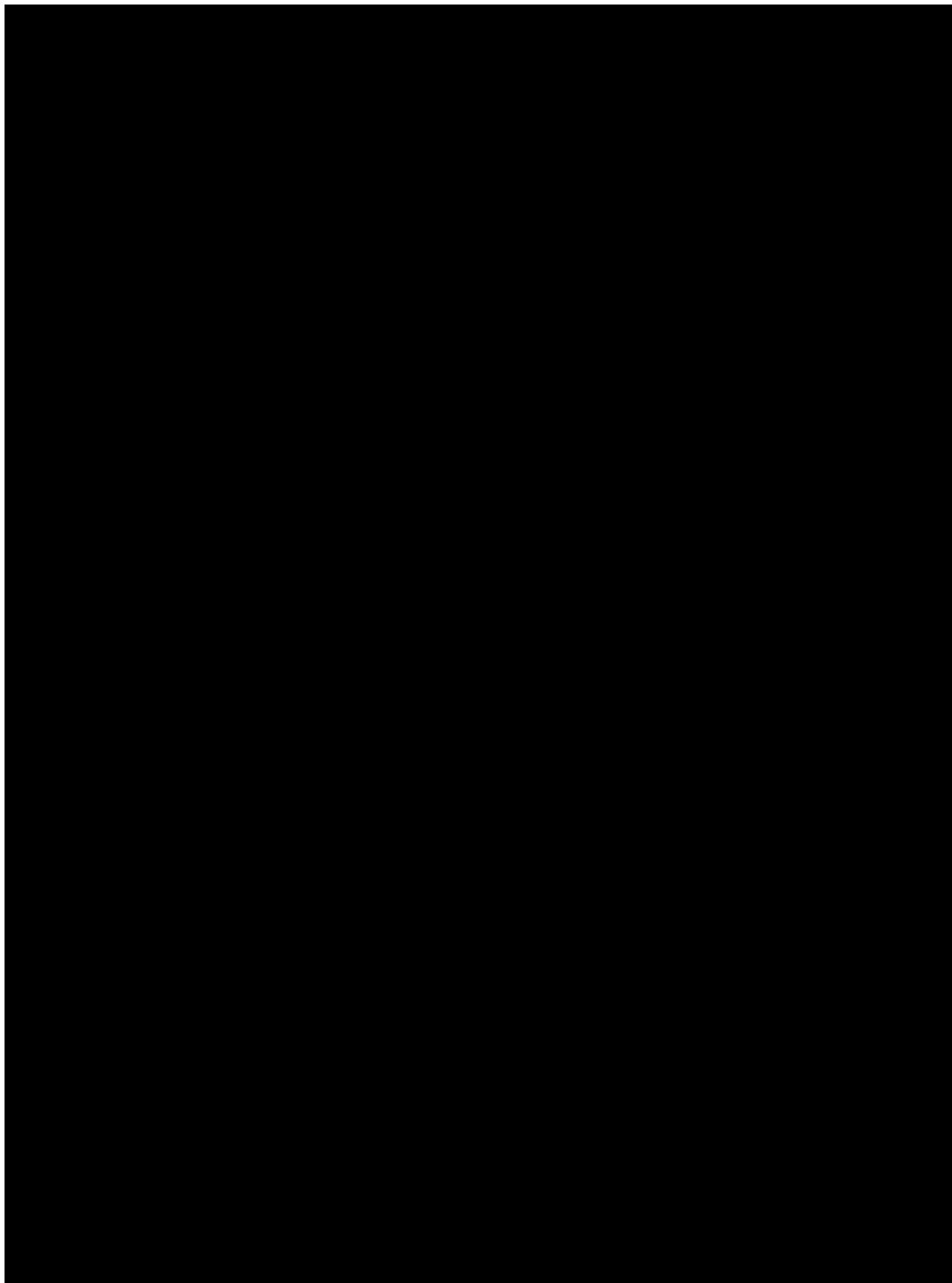
10.5.5. Analyses of Subgroup

Given the overall study small sample size, no formal subgroup analyses will be performed. However, descriptive statistics of the primary efficacy endpoint will be provided for the following subgroups. All morning (before 11:00) assessments will be used regardless of treatment discontinuation. Missing data will not be imputed.

- Age (<65 years; ≥65 years)
- Sex
- Baseline GC daily dose (<11 mg/m²/day hydrocortisone equivalent, ≥11 mg/m²/day hydrocortisone equivalent)







10.5.6.4. Circadian Assessments for Cohorts 1-3

The following continuous endpoints will be summarized descriptively by cohort for sites participating in circadian studies. All assessments will be used regardless of treatment discontinuation. Missing data will not be imputed.

- Change from baseline in 24-hour AUC value measured in plasm/serum 17-OHP, ACTH, testosterone, A4, [REDACTED], 11-DOC, 21-deoxycortisol, [REDACTED] at weeks 2 and 12
- Change from baseline in peak value measured in plasm/serum 17-OHP, ACTH, testosterone, A4, [REDACTED], 11-DOC, 21-deoxycortisol, [REDACTED] at weeks 2 and 12
- Change from baseline in trough value measured in plasm/serum 17-OHP, ACTH, testosterone, A4, [REDACTED], 11-DOC, 21-deoxycortisol, [REDACTED] at weeks 2 and 12
- Change from baseline in 24-hour AUC value measured in salivary A4, 17-OHP, testosterone, [REDACTED] at weeks 2 and 12
- Change from baseline in peak value measured in salivary A4, 17-OHP, testosterone, [REDACTED] at weeks 2 and 12
- Change from baseline in trough value measured in salivary A4, 17-OHP, testosterone, [REDACTED] at weeks 2 and 12

10.5.6.5. Menstrual Cycle (Women Only)

Baseline menstrual cycle length is reported on the CRF. Menstrual cycles are also documented prospectively during the study by recording the exact dates of the start and end of each menstrual cycle using a diary. End of study menstrual cycle length will be derived by averaging the cycle

lengths collected during the study. Cycle length will also be categorized as regular (i.e. cycle length >21 days and <35 days) or irregular (i.e. cycle length ≤ 21 days or ≥ 35 days).

Descriptive statistics for the baseline cycle length and change from baseline to the end of study will be presented by cohort. A shift table from baseline to the end of study menstrual regularity will also be presented.

10.5.6.6. Patient-Reported CAH Questionnaires

The CAH severity items questionnaire assess patient-reported severity of acne, CAH and hirsutism (in women). The categorical responses (no/none, mild, moderate, and severe) will be presented by cohort at each scheduled visit using counts and percentages.

The CAH change items questionnaire assess patient-reported change in severity of acne, CAH and hirsutism (in women) between the start and end of treatment. The categorical responses (much better, moderately better, a little better, no change, a little worse, moderately worse, and much worse) will be presented by cohort at week 12 using counts and percentages.

10.5.6.7. Treatment Satisfaction Questionnaires

These questionnaires assess overall participant satisfaction of the treatment. Categorical responses will be summarized descriptively by cohort at week 12.

10.5.6.8. Percent Change from Baseline in GC Daily Dose for Cohort 4

Percent change from baseline in GC daily dose ($\text{mg}/\text{m}^2/\text{day}$) will be summarized descriptively at each visit. All GC dose data will be used regardless of treatment discontinuation. Missing data will not be imputed.

Similarly, percent change from baseline in GC daily dose ($\text{mg}/\text{m}^2/\text{day}$) while morning serum A4 $\leq$ ULN will be summarized descriptively at each visit. If a participant experiences a decrease in GC daily dose but morning serum A4 $>$ ULN, the percent change from baseline in GC daily dose will be set to zero at the visit. Any increases from baseline in GC daily dose will be reported as such, regardless of A4 value. All morning A4 assessments and GC dose data will be used regardless of treatment discontinuation. Missing data will not be imputed.

10.6. Safety Analysis

The safety analysis will be performed using the FAS. All analyses will be presented by cohort according to the actual dose received. The safety parameters will include AEs, clinical laboratory, vital sign, and electrocardiogram (ECG) parameters. For safety endpoints, all analyses will be based on the observed data (i.e., with no imputation of missing data), unless otherwise stated.

10.6.1. Adverse Events

Adverse events will be coded by system organ class and preferred term using the MedDRA Version 26.0 or newer.

An AE (classified by preferred term) will be considered a TEAE if it occurred on or after the first dose of study drug and was not present prior to the first dose, or it was present at the first dose but increased in severity during the study.

Participant incidence of TEAEs will be tabulated as the following but not limited to:

- Summary of overall TEAEs by cohort
- TEAEs by cohort, SOC, and PT
- TEAEs by cohort, SOC, PT, and maximal severity
- Serious TEAEs by cohort, SOC, and PT
- Serious related TEAEs by cohort, SOC, and PT
- TEAEs leading to discontinuation of study treatment by cohort, SOC and PT
- TEAEs leading to discontinuation of study by cohort, SOC and PT
- TEAEs by cohort and PT
- TEAEs by cohort and PT (reported by $\geq 5\%$ of total participants)
- Related TEAEs by cohort and PT

Detailed listings for all AEs, serious TEAEs, related TEAEs, TEAEs leading to the discontinuation of study treatment, and death will also be generated.

10.6.1.1. Adverse Events of Special Interest

An adverse event of special interest (AESI) is an AE of special medical or scientific interest to the Sponsor. For this study, [REDACTED] is considered AESI.

Participant incidence of AESI will be tabulated by cohort and PT. Detailed listings for all AESIs will also be presented by participant.

10.6.2. Clinical Laboratory Parameters

The following laboratory tests will be performed at each scheduled visit as specified in the protocol:

- Hematology
- Chemistry
- Coagulation
- Urinalysis
- Hormone
- Serology
- Toxicology

For quantitative laboratory parameters, descriptive statistics for scheduled clinical laboratory values (in SI units) from central labs and changes from the baseline values at each scheduled assessment visit will be presented by cohort.

The following liver test abnormality criteria will be assessed by considering both scheduled and unscheduled, central and local lab assessments (including regular and circadian samples if circadian samples were drawn). Liver test abnormalities will be presented in a by-participant listing.

- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $>3\times\text{ULN}$ (for participants with ALT and AST $\leq\text{ULN}$ at baseline)
- ALT or AST $>3\times\text{ULN}$ and $>2\times\text{Baseline}$ (for participants with ALT or AST $>\text{ULN}$ at baseline)
- Total bilirubin (TB) $>2\times\text{ULN}$ (for participants with TB $\leq\text{ULN}$ at baseline)
- TB $>2\times\text{ULN}$ and $>2\times\text{Baseline}$ (for participants with TB $>\text{ULN}$ at baseline)
- Alkaline phosphatase (ALP) $>3\times\text{ULN}$ (for participants with ALP $\leq\text{ULN}$ at baseline)
- ALP $>3\times\text{ULN}$ and $>2\times\text{Baseline}$ (for participants with ALP $>\text{ULN}$ at baseline)

Data listings for all laboratory assessments, including data from unscheduled and local laboratory tests, will be provided.

10.6.3. Vital Signs

Descriptive statistics for the following vital signs and changes from baseline values at each scheduled visit will be presented by cohort.

- Supine Systolic Blood Pressure (mmHg)
- Standing Systolic Blood Pressure (mmHg)
- Supine Diastolic Blood Pressure (mmHg)
- Standing Diastolic Blood Pressure (mmHg)
- Supine Heart Rate (beats/min)
- Standing Heart Rate (beats/min)
- Respiratory Rate (breaths/min)
- Temperature ($^{\circ}\text{C}$)
- Weight (kg)
- Waist Circumference (inches)

Data listing for vital signs including height and BMI will be provided.

10.6.4. Electrocardiogram

The ECG assessments will be performed in triplicate. QT interval corrected for heart rate (QTc) will be calculated using both the Fridericia (QTcF) and Bazett (QTcB) corrections. The average of the triplicate ECGs for the following quantitative parameters at the visit will be used for analysis. Descriptive statistics for ECG parameters and changes from baseline values will be summarized by cohort at each scheduled visit as specified in the protocol.

- Heart Rate (beats/min)
- PR Interval (msec)
- RR Interval (msec)
- QRS Duration (msec)
- QT Interval (msec)
- QTcB Interval (msec)
- QTcF Interval (msec)

ECG data will be evaluated by the investigator and abnormalities, if present, will be listed. The worst overall evaluation by the investigator of triplicate ECGs at the visit will be used for analysis.

Additionally, frequency counts and percentage of participants having notable QTcF values according to the following categories will be summarized at each nominal scheduled visit. A similar summary will also be presented for the maximal QTcF using the same categories by considering both scheduled and unscheduled assessments:

- QTc: >450 and ≤470, >470 and ≤500, >500 msec
- Change from baseline in QTc: >30 and ≤60, >60 msec
- Maximum QTc: >450 and ≤470, >470 and ≤500, >500 msec
- Change from baseline to maximum QTc: >30 and ≤60, >60 msec

All quantitative ECG results and investigator's evaluations including both scheduled and unscheduled visits will be presented by participant in a data listing. Separate listing will be generated for participants with notable ECG values.

10.7. Pharmacokinetics and Pharmacodynamics Analysis

The PK Analysis Set will be used in all pharmacokinetic analyses. Whole blood and plasma PK concentration data for CRN04894 will be presented separately. Circadian assessments of plasma PK concentration data for CRN04894 will be presented separately for Cohorts 1-3 participants who consented to circadian rhythm research. All PK data will be listed. Summary tables and arithmetic mean figures of the PK concentrations versus nominal PK sampling timepoint will be presented by cohort. BLQ data will be set to 0 for calculation of summary statistics.

For Cohorts 1-3:

NCA will be performed only for circadian assessments of PK and PD data to calculate the 24-hour AUC, peak, and trough values. For NCA of circadian PK data, BLQ data prior to the first measurable concentration will be set to 0, whereas all embedded and trailing BLQ values will be set to missing. For NCA of circadian PD data, BLQ data will be treated as LLOQ/2, as described in Section 9.2.3.

Blood samples will be collected for circadian PK and PD assessments every 4 hours for a 24-hour period at Baseline (PD biomarkers only), Week 2, and Week 12, commencing at approximately 10:00 (12 hours pre-dose) to be followed by samples at 14:00, 18:00, predose 22:00, 02:00, 06:00, and 10:00 (12 hours post-dose). Saliva will be collected simultaneously with circadian blood samples except at 02:00 (to allow the participant to sleep) for measurement of applicable PD biomarkers.

The actual relative sampling time will be calculated relative to the dose administered at the visit during circadian assessments, such that the actual relative sampling time will include negative and positive values. For calculation of 24-hour AUC, peak, and trough values, the modified relative sampling time will be calculated relative to the 12-hour pre-dose collection time, such that time 0 occurs at the first sampling timepoint, and the modified relative sampling time will only include positive values. If the actual relative PK or PD sampling time is missing, then the modified relative time may be imputed using the nominal sampling timepoint and adding 12 hours.

NCA will be completed using Phoenix WinNonlin version 8.4 or higher. Calculation of PK and PD parameters for Cohorts 1-3 will include:

24-hour AUC (AUC_{0-last}):	Area under the concentration-time curve, calculated using the linear-up/log-down method from time 0 to time t, where t is the time of the last quantifiable concentration
Peak (C_{max}):	Maximum observed concentration, obtained directly from the concentration-time data
Trough (C_{min}):	Minimum observed concentration, obtained directly from the concentration-time data

Circadian PK or PD profiles may be considered as not evaluable and will be excluded from the NCA if:

- There is a protocol violation (eg, a missed dose, large discrepancies from nominal sampling time) that impacts the PK or PD.
- There are insufficient data in the concentration-time profile (ie, if any timepoints are missing from the circadian assessments).

Any data exclusions will be documented and justified in the clinical study report.

For Cohort 4:

NCA will be completed for serial PK profiles on Week 2 and Week 12 for all participants in the PK analysis set using Phoenix WinNonlin version 8.4 or higher. Calculation of PK parameters for Cohort 4 will include:

6-hour AUC (AUC_{0-last}):	Area under the concentration-time curve, calculated using the linear-up/log-down method from time 0 to time t, where t is the time of the last quantifiable concentration
Peak (C_{max}):	Maximum observed concentration, obtained directly from the concentration-time data
Trough (C_{min}):	Minimum observed concentration, obtained directly from the concentration-time data
T_{max} :	Time of maximum observed concentration, obtained directly from the concentration-time data

Serial PK profiles may be considered as not evaluable and excluded from the NCA if there are insufficient data, or if there is a protocol violation that impacts the PK. Any data exclusions will be documented and justified in the clinical study report.

11. CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

Not applicable.

12. APPENDICES

APPENDIX 1. VERSION HISTORY

Version	Date	Author(s)	Summary of Changes
1.0	18Dec2024	████████	N/A
2.0	17Sep2025	████████	Major changes: 1. Updated study design (Section 2), objectives/endpoints (Section 3), and sample size (Section 4) for the addition of Cohort 4 2. Added morning window value definition for PD biomarkers for Cohort 4 (Section 7.1) 3. Added analysis visit mapping of PD biomarker and imaging data for Cohort 4 (Section 9.3) 4. Added derivation of GC daily dose at each visit for Cohort 4 and modified the derivation of baseline GC daily dose for Cohorts 1-3 for consistency with Cohort 4 (Section 10.4.6) 5. Defined analyses for the primary efficacy endpoint for Cohort 4 (Section 10.5.2) 6. Added responder analysis for proportion of participants with serum early morning $A4 \leq \text{ULN}$ and physiologic GC dose (████ mg/m²/day) over time for Cohort 4 (Section 10.5.6.1) 7. Added analysis for percent change from baseline in GC daily dose over time for Cohort 4 (Section 10.5.6.8) 8. Added PK analysis for Cohort 4 (Section 10.7)

APPENDIX 2. SCHEDULE OF ACTIVITIES

Schedule of Activities (Cohorts 1-3)

	Screening Period		Treatment Period				Follow-up Period	
Visit	1	2	3	4	5	6/EOT	7	8/EOS
Week ^a	-4	-2	1	2 ^a	6 ^a	12 ^a	14 ^a	16 ^a
Day	-28 to -1		1	14 (±2)	42 (±2)	84 (±2)	98 (±3)	112 (±3)
Onsite Visit	X	X	X	X	X	X	X	
Phone Visit								X
Informed consent ^b	X							
Medical history	X							
Full physical exam, height, weight, waist circumference, and vital signs	X		X			X	X	
Symptom-directed physical examination, weight, waist circumference and vital signs				X	X			
Drug screens	X	X						
ECG (triplicate)	X		X	X	X	X	X	
AE review	X	X	X	X	X	X	X	X
Review of prior or concomitant medications (Section 6.3.3)	X	X	X	X	X	X	X	X
Review of lifestyle considerations (Section 6.3.1 and 6.3.2)		X	X	X	X	X	X	X
Adrenal insufficiency awareness training			X					
MRI of adrenal glands ^c	X					X		
Study drug dispensing ^d			X	X	X			
Study drug accountability				X	X	X		
Provide diaries with instructions for CRN04894 Dosing/ Glucocorticoid Administration diary and Menstrual Cycle Diary ^e	X							
Glucocorticoid Administration Diary review		X	X	X	X	X	X	X
CRN04894 dosing diary review				X	X	X		
Urinalysis	X			X		X	X	
Hematology, clinical chemistry, INR, PT/PTT	X		X	X	X	X	X	
Fasting lipid panel and glucose		X	X			X		

[REDACTED]

[REDACTED], 11-DOC=11-Deoxycorticosterone, [REDACTED], 17-OHP=17-hydroxyprogesterone, A4=androstenedione, ACTH=adrenocorticotrophic hormone, AE=adverse event, [REDACTED], ECG=electrocardiogram, EOS=end of study, EOT=end of treatment, FSH=follicle-stimulating hormone, GC=glucocorticoid, HbA1C=hemoglobin A1C, HBsAg=hepatitis B surface antigen, HIV=human immunodeficiency virus, INR=international normalized ratio, LH=luteinizing hormone, MRI=magnetic resonance imaging, PD=pharmacodynamic, PK=pharmacokinetic, PT=prothrombin time, PTT=partial thromboplastin time, SHBG=sex hormone binding globulin, T4=thyroxine, TSH=thyroid-stimulating hormone, VAMS=volumetric absorptive microsampling, WOCBP=women of childbearing potential.

^a Visits will occur at the end of the designated week. For example, Visit 4 occurs on Day 14 (± 2) at the end of Week 2.

^b Informed consent form may be signed up to a week prior to Visit 1.

^d Starting the night of Day 1 and ending the night before the Week 12/EOT Visit, each cohort will administer CRN04894 between 22:00-24:00, at approximately the same time each night, once daily (QD) before sleep.

^e Glucocorticoid administration portion of diary should be completed by the study participant every day starting at Visit 1 and continuing through Visit 8. CRN04894 administration portion of diary should be completed by the study participant every day starting at Visit 3 and continuing through the night before Visit 6. Menstrual cycle diary should be completed by all female study participant every day starting on Visit 1 and continuing through Visit 8.

^f For Visits 2-7: Prior to receiving the morning GC replacement dose, a total of 2 blood draws (approximately 1 hour apart) for PD biomarkers will be drawn. The first blood draw for biomarkers should be one of the first visit activities performed at the start of the visit. Visits should start as early in the morning as possible (preferably 07:00-08:00), so as to minimize any delay in administration of the morning GC dose and the timing of each study visit should be as consistent as possible. The second blood draw for PD biomarkers should be drawn no later than 11:00. Visit 1 (Week-4) PD biomarker blood draws can be done at any time after the informed consent form is signed. For Screening Visit 2 (Week 2): Blood draw should be done prior to receiving the morning GC dose.

^g One blood draw for PK at each visit. At Visit 4 and Visit 6, a Mitra VAMS sample will also be collected at the time of PK collection.

^h For participants on fludrocortisone (mineralocorticoid) replacement, serum aldosterone and plasma renin activity will be obtained prior to administration of this medication.

ⁱ A Mitra VAMS PK sample will be collected by the study participant before dosing the night before Visit 4 and Visit 6.

^j Serum pregnancy test to be conducted by central lab at Screening and urine pregnancy test every 2 weeks thereafter, to be conducted locally unless otherwise specified by local regulations or in the judgment of the Investigator. If a urine pregnancy test does not coincide with an onsite visit, then a home pregnancy test will be performed. The home pregnancy test(s) will be provided to the participants and the study staff will contact the participants for results. If positive, the study drug will be discontinued, and an onsite blood pregnancy test will be conducted to confirm the results in an unscheduled visit.

^k To confirm participant reproductive category, 2 FSH tests must be conducted 2-4 weeks apart during Screening for the participant sub-population of women who are postmenopausal with less than 1 year of amenorrhea. A documented, historical test result measured prior to Screening may be used as 1 of the 2 measurements. The FSH value should be ≥ 30 IU/L to confirm menopausal status.

^l Circadian assessments will be performed at selected sites in settings with 24-hour blood sampling capabilities. Assessments will take place between Day -7 to Day 1, Day 12 to Day 17, and between Day 70 to Day 86. Study drug will be administered at approximately 22:00 during the assessments that occur in the treatment period (between Day 12 to Day 17 and Day 70 to Day 86). Blood will be drawn for measurement of PK (visits on Day 12 to Day 17 and Day 70 to Day 86 only), ACTH, A4, 17-OHP, [REDACTED], 11-DOC, [REDACTED] every 4 hours for a 24-hour period commencing at approximately 10:00 to be followed by samples at 14:00, 18:00, predose 22:00, 02:00, 06:00, and 10:00. Saliva will be collected simultaneously with blood for measurement of A4, 17-OHP, [REDACTED], and testosterone except at 02:00 (to allow the participant to sleep). In addition, blood will be drawn for testosterone, [REDACTED] once at 06:00. Participants included in the circadian assessments will not have separate PD biomarkers or PK samples drawn for Visits 3, 4, or 6 if the circadian assessment and the visit fall on the same day.

Schedule of Activities (Cohort 4 [Includes Morning Dosing and Glucocorticoid Reduction])

	Screening Period		Treatment Period						Follow-up Period	
Visit	1	2	3	4	5	6	7	8/EOT	9	10/EOS
Week ^a	-4	-2 ^b	1	2 ^a	5	8	10	12	14	16
Day	-28 to -1		1	14 (±2)	35 (±2)	56 (±2)	70 (±2)	84 (±2)	98 (±3)	112 (±3)
Onsite Visit	X	X	X	X		X		X	X	
Phone Visit					X		X			X
Informed consent ^c	X									
Medical history	X									
Full physical exam, height, weight, waist circumference, and vital signs	X		X					X	X	
Symptom-directed physical examination, weight, waist circumference and vital signs				X		X				
Drug screens	X									
ECG (triplicate)	X		X	X		X		X	X	
AE review	X	X	X	X	X	X	X	X	X	X
Review of prior or concomitant medications (Section 6.3.3)	X	X	X	X	X	X	X	X	X	X
Review of lifestyle considerations (Section 6.3.1 and Section 6.3.2)		X	X	X	X	X	X	X	X	X
Adrenal insufficiency awareness training			X							
MRI of adrenal glands ^d	X							X		
Study drug dispensing ^e			X	X		X				
Study drug accountability				X		X		X		
Provide diaries with instructions for CRN04894 Dosing/ Glucocorticoid Administration diary and Menstrual Cycle Diary ^f	X									
Glucocorticoid reduction				X ^g	X ^g	X ^g	X ^g			
Glucocorticoid Administration Diary review		X	X	X	X	X	X	X	X	X

	Screening Period		Treatment Period						Follow-up Period	
Visit	1	2	3	4	5	6	7	8/EOT	9	10/EOS
Week ^a	-4	-2 ^b	1	2 ^a	5	8	10	12	14	16
Day	-28 to -1		1	14 (±2)	35 (±2)	56 (±2)	70 (±2)	84 (±2)	98 (±3)	112 (±3)
Onsite Visit	X	X	X	X		X		X	X	
Phone Visit					X		X			X
CRN04894 dosing diary review				X	X	X	X	X		
CRN04894 dosing onsite			X	X		X		X		
Urinalysis	X			X				X	X	
Hematology, clinical chemistry, INR, PT/PTT	X		X	X		X		X	X	
Fasting lipid panel and glucose		X	X					X		
HbA1C	X							X		
Free T4, TSH	X							X	X	
PD biomarkers 17-OHP, ACTH (plasma), testosterone, A4, ██████████ 11-DOC, ██████████ ██████████ ██████████	X	X ^h	X ^h	X ^h		X ^h		X ^h	X ^h	
Aldosterone ⁱ			X			X		X	X	
21-hydroxylase gene mutation screening			X							
Plasma renin ⁱ			X			X		X	X	
Serology HIV antibody, HBsAg, and hepatitis C virus antibody		X								
PK onsite				X ^j		X ^k		X ^j	X ^l	
Mitra device PK sampling				X ^m				X ^m		
Pregnancy test (WOCBP) ⁿ	X		X	X	X	X	X	X	X	
Menstrual cycle diary review (women only)		X	X	X	X	X	X	X	X	X
██████████			X					X		
FSH (women who are postmenopausal with less than 1 year of amenorrhea only) ^o	X	X								

	Screening Period		Treatment Period						Follow-up Period	
Visit	1	2	3	4	5	6	7	8/EOT	9	10/EOS
Week ^a	-4	-2 ^b	1	2 ^a	5	8	10	12	14	16
Day	-28 to -1		1	14 (±2)	35 (±2)	56 (±2)	70 (±2)	84 (±2)	98 (±3)	112 (±3)
Onsite Visit	X	X	X	X		X		X	X	
Phone Visit					X		X			X
Sex hormone binding globulin (SHBG)			X					X		
Adrenal insufficiency assessments	X	X	X	X	X	X	X	X	X	X

, 11-DOC=11-Deoxycorticosterone, , 17-OHP=17-hydroxyprogesterone, A4=androstenedione, ACTH=adrenocorticotrophic hormone, AE=adverse event, , ECG=electrocardiogram, EOS=end of study, EOT=end of treatment, FSH=follicle-stimulating hormone, GC=glucocorticoid, HbA1C=hemoglobin A1C, HBsAg=hepatitis B surface antigen, HIV=human immunodeficiency virus, INR=international normalized ratio, LH=luteinizing hormone, MRI=magnetic resonance imaging, PD=pharmacodynamic, PK=pharmacokinetic, PT=prothrombin time, PTT=partial thromboplastin time, SHBG=sex hormone binding globulin, T4=thyroxine, TSH=thyroid-stimulating hormone, VAMS=volumetric absorptive microsampling, WOCBP=women of childbearing potential.

^a Visits will occur at the end of the designated week. For example, Visit 4 occurs on Day 14 (±2) at the end of Week 2.

^b For Cohort 4, Visit 2 may occur between Day -21 and Day -14.

^c Informed consent form may be signed up to a week prior to Visit 1.

^e Starting the morning of Day 1 and ending the morning of the Week 12/EOT Visit, each participant will administer CRN04894 between 06:00 and 10:00 at approximately the same time each morning, once daily (QD).

^f Glucocorticoid administration portion of diary should be completed by the study participant every day starting at Visit 1 and continuing through Visit 10. CRN04894 administration portion of diary should be completed by the study participant every day starting at Visit 3 and continuing through Visit 8. Menstrual cycle diary should be completed by all female study participants every day starting on Visit 1 and continuing through Visit 10.

^g See Section 5.1 for GC reduction guidance. A follow-up phone call should be conducted one week later (±2 days) to assess tolerability and symptoms of adrenal insufficiency.

^h For Visits 2-8: Prior to receiving the morning GC replacement dose and CRN04894, if applicable, a total of 2 blood draws (approximately 1 hour apart) for PD biomarkers will be drawn. The first blood draw for biomarkers should be one of the first visit activities performed at the start of the visit. Visits should start as early in the morning as possible (preferably 07:00-08:00), to minimize any delay in administration of the morning GC dose and the timing of each study visit should be as consistent as possible. The second blood draw for PD biomarkers should be drawn prior to 11:00. Visit 1 (Week -4) PD biomarker blood draws can be done at any time after the informed consent form is signed.

ⁱ For participants on fludrocortisone (mineralocorticoid) replacement, serum aldosterone and plasma renin activity will be obtained prior to administration of this medication.

^j CRN04894 dose and morning GC dose (if applicable) will be held and administered in clinic. PK sampling at timepoints predose, 1, 2, 4, and 6 hours (±20 minutes) post dose. To be performed Week 2 and Week 12. Fasting status will be collected.

- ^k Dose to be held and administered in clinic. PK sampling at timepoints predose and 1 hour (± 20 minutes) post dose. Fasting status will be collected.
- ^l A single PK sample will be collected.
- ^m A Mitra VAMS PK sample will be collected by the study participant at home approximately 12 to 18 hours post dose at Week 2 and Week 12.
- ⁿ Serum pregnancy test to be conducted by central lab at Screening and urine pregnancy test every 2 weeks thereafter, to be conducted locally unless otherwise specified by local regulations or in the judgment of the Investigator. If a urine pregnancy test does not coincide with an onsite visit, then a home pregnancy test will be performed. The home pregnancy test(s) will be provided to the participants and the study staff will contact the participants for results. If positive, the study drug will be discontinued, and an onsite blood pregnancy test will be conducted to confirm the results in an unscheduled visit.
- ^o To confirm participant reproductive category, 2 FSH tests must be conducted 2-4 weeks apart during Screening for the participant sub-population of women who are postmenopausal with less than 1 year of amenorrhea. A documented, historical test result measured prior to Screening may be used as 1 of the 2 measurements. The FSH value should be ≥ 30 IU/L to confirm menopausal status.

STATISTICAL ANALYSIS PLAN AND AMENDMENT

Protocol: CRN04894-03

Submitted by:

Date _____

Approved by:

Date _____

Date _____

Signature Page for VV-CLIN-003141 v1.0
CRN04894-03 SAP v2.0

Approval	 18-Sep-2025 17:53:12 GMT+0000
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