



**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**

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Sponsor:	Crinetics Pharmaceuticals, Inc. 6055 Lusk Blvd San Diego, CA 92121 United States
Protocol Version:	3.2 (region-specific [US, UK, BR])
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Protocol Version: 3.2 (region-specific [US, UK, BR])

Protocol Date: 28 March 2025

Sponsor's Approval

The protocol has been approved by Crinetics Pharmaceuticals, Inc. (herein, Crinetics or Sponsor).

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Crinetics Pharmaceuticals, Inc

Medical Monitor name and contact information will be provided separately.

Protocol Number: CRN04894-03**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 Version:** 3.2 (region-specific [US, UK, BR])**Protocol Date:** 28 March 2025

I have read and I understand this protocol. I will conduct this protocol as outlined herein and will make all reasonable efforts to complete the study within the designated time.

I agree to conduct this study in accordance with the Declaration of Helsinki, the International Council for Harmonisation (ICH), Guideline for Good Clinical Practice (GCP), and all applicable regulatory requirements.

I will provide copies of the protocol and access to all information furnished by Crinetics Pharmaceuticals, Inc. to study personnel under my supervision. I will discuss material with them to ensure that they are fully informed about the study.

I understand that the study may be terminated, or enrollment suspended at any time, by Crinetics Pharmaceuticals, Inc., with or without cause, or by me, if it becomes necessary to do so in the best interests of the study participants.

Site name: _____**Site address:** _____**Phone number:** _____**Principal Investigator:**

Name and title (printed): _____

Signature: _____

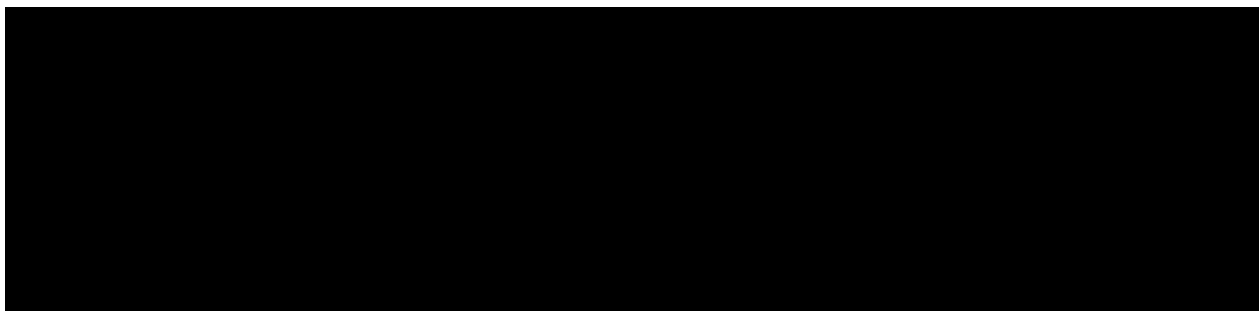
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1. LIST OF ABBREVIATIONS

11-DOC	11-deoxycorticosterone
17-OHP	17-hydroxyprogesterone
21-OHD	21-hydroxylase deficiency
A4	androstenedione
ACTH	adrenocorticotrophic hormone
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphate
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AT II	angiotensin type 2 receptor
AUC	area under the curve
AxMP	auxiliary medicinal product
BMI	body mass index
CAH	congenital adrenal hyperplasia
cAMP	cyclic adenosine monophosphate
CD	Cushing's disease
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C _{max}	maximum plasma concentration
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CRH	corticotrophin releasing hormone
CRN	Crinetics Pharmaceuticals
CRO	contract research organization
CS	Cushing's syndrome
CSR	clinical study report
CTFG	Clinical Trial Facilitation Group
CYP	cytochrome P450
DDI	drug-drug interaction
DPO	data protection officer

EAS	ectopic ACTH syndrome
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EOS	end of study
EOT	end of treatment
ET	early termination
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GC	glucocorticoid
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
G _s	G-protein
h	hour
HbA1c	hemoglobin A1C
HDPE	high-density polyethylene
HPA	hypothalamic-pituitary-adrenal
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	institutional ethics committee
IMP	investigational medicinal product
INR	international normalized ratio
IP	investigational product
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous, intravenously
kg	kilogram
LAM	lactational amenorrhea method
MATE	multidrug and toxin extrusion
MATE1	multidrug and toxin extrusion protein 1
MATE2-K	multidrug and toxin extrusion protein 2 kidney-specific
MC2R	melanocortin 2 receptor
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities

MRAP	melanocortin 2 receptor accessory protein
MRI	magnetic resonance imaging
NIMP	noninvestigational medicinal product
OLE	open-label extension
PD	pharmacodynamic(s)
P-gp	P-glycoprotein
pH	potential of hydrogen; negative log of h^+ concentration
PK	pharmacokinetic(s)
PR	time interval between P and R waves
PT	preferred term
PV	Pharmacovigilance
QD	once daily
QRS	time interval of the QRS complex
QT	time interval between Q and T wave
QTL	quality tolerance limit
QTcF	corrected QT by the Fridericia formula
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SHBG	sex hormone binding globulin
SOA	schedule of assessments
SOC	system organ class
SOP	standard operating procedure
SRC	safety review committee
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	terminal elimination half-life
	
TB	total bilirubin
TEAE	treatment-emergent adverse event(s)
t_{max}	time to maximum plasma concentration
TSH	thyroid-stimulating hormone
UFC	urinary free cortisol
ULN	upper limit of normal
US	United States
VAMS	volumetric absorptive microsampling
WBC	white blood cell
ULN	upper limit of normal
WOCBP	women of childbearing potential
WONCBP	women of nonchild bearing potential

2. PROTOCOL SUMMARY

2.1. Synopsis

Protocol 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

Brief Title: Evaluate the Safety, Efficacy, and Pharmacokinetics of CRN04894 in Participants with Congenital Adrenal Hyperplasia

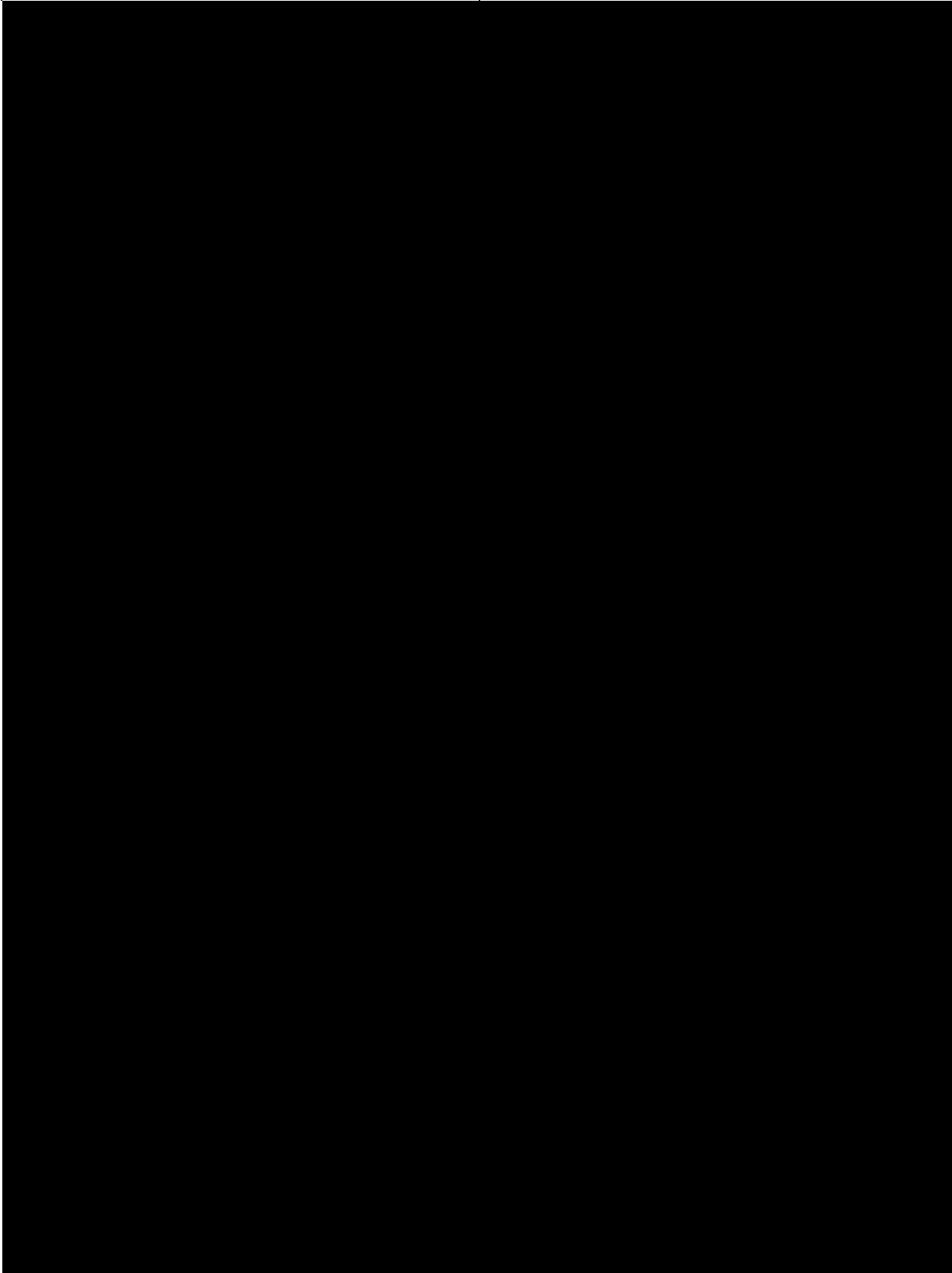
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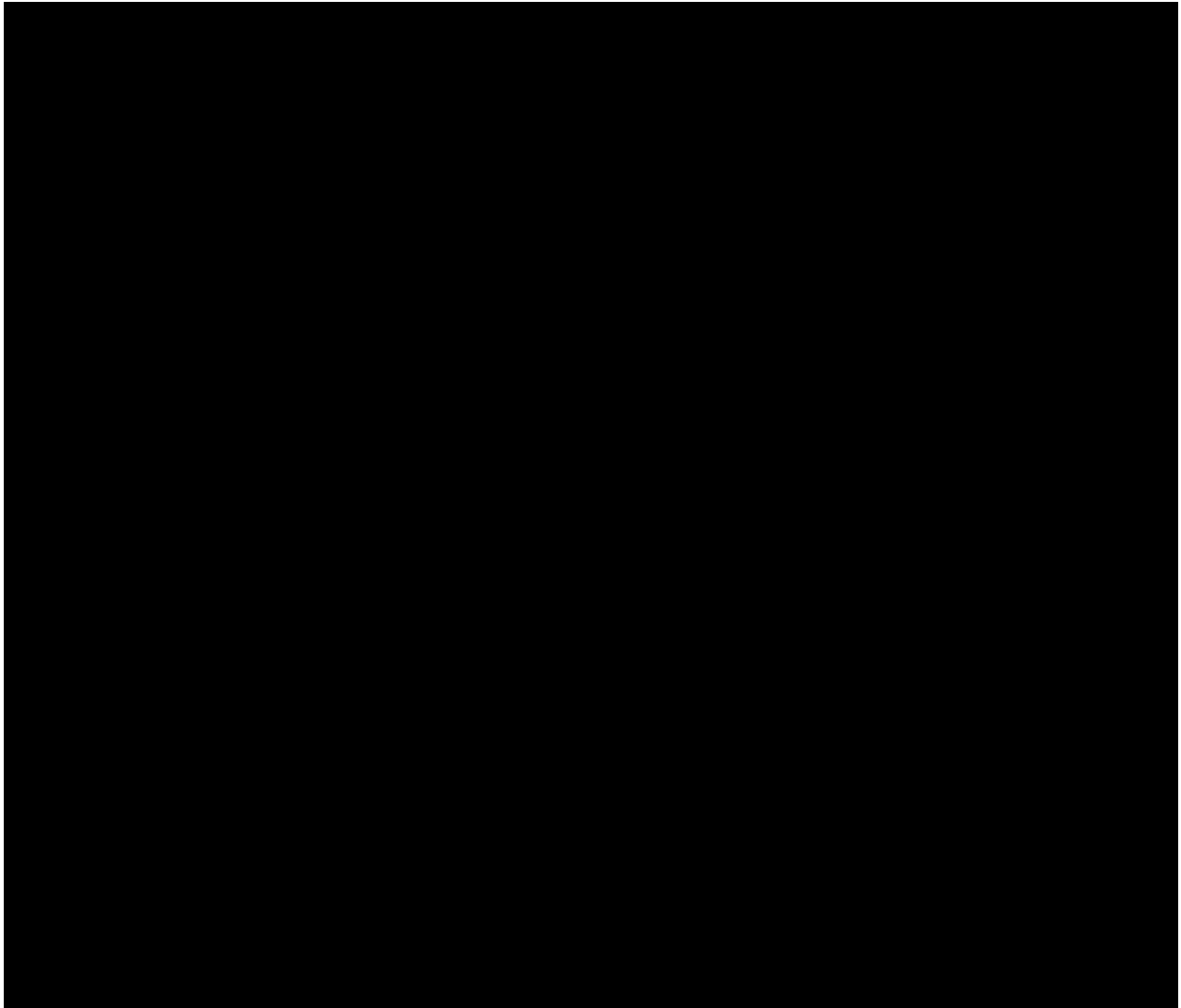
CRN04894 is a potent and selective orally administered nonpeptide melanocortin 2 receptor (MC2R) or adrenocorticotrophic hormone (ACTH) antagonist currently under development by Crinetics for the treatment of congenital adrenal hyperplasia (CAH) and other diseases caused by excess ACTH, ie, Cushing's disease (CD) and ectopic ACTH syndrome (EAS). By acting selectively at MC2R, CRN04894 is a potential novel treatment for diseases that are characterized by ACTH-mediated pathological elevations of adrenal steroid hormones ([Clark 2016](#); [Newfield 2010](#)). This predicted ability to suppress adrenally derived androgens while maintaining mineralocorticoid production (due to lack of activity on angiotensin type 2 [AT II] receptor) makes CRN04894 a novel treatment option for CAH. To date, CAH is only treated with exogenous glucocorticoids and there are no nonhormonal treatments approved by regulatory authorities.

The purpose of this study is to evaluate the safety, efficacy, and pharmacokinetics (PK) of CRN04894 in participants with classic CAH caused by 21-hydroxylase deficiency.

Objectives and Endpoints:

Safety Objectives	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
	



Overall Design Synopsis:**Brief Summary:**

The purpose of this study is to evaluate the safety, efficacy, and pharmacokinetics (PK) of CRN04894 in participants with CAH caused by 21-hydroxylase deficiency.

Study details include:

- Male and female participants ≥ 18 to 75 years of age, who have a diagnosis by hormonal testing of CAH caused by 21-hydroxylase deficiency, and who maintain their stable regimen of glucocorticoid replacement therapy throughout the study. Participants who are treated with fludrocortisone prior to the study will continue on a stable mineralocorticoid replacement dose throughout the study. Participants ≥ 16 years of age may be included in sites located in the United States (US).
- Up to 3 dose cohorts may be included for evening dosing. Participants in Cohort 1 will be administered CRN04894 at a dose of 80 mg daily. Subsequently, participants in Cohort 2 will be administered a dose of 120 mg daily; however, depending on an analysis of the pharmacodynamics (PD), PK, and safety parameters observed from Cohort 1, a lower dose (ie, CRN04894 40 mg QD) may be recommended by the safety review committee (SRC). After an analysis of the safety, PD, and PK data from Cohorts 1 and 2, the Sponsor may opt to include a third cohort of participants given a dose to be determined (up to 160 mg daily).
- A fourth cohort will be administered CRN04894 at a dose of 80 mg once daily each morning (between 06:00 and 10:00) to examine the effects of AM dosing and GC reduction (see Section 5.1 and rationale in Section 5.3). Because data review from 6 patients dosed with 80 mg has been conducted by the SRC with no safety concerns nor any required changes to safety assessment or the protocol, an SRC review will not be required to commence Cohort 4.
- The treatment duration will be up to Day 84 (Week 12) per participant.
- The total study duration will be up to 140 days (up to 4 weeks of screening, 12 weeks of treatment, and 4 weeks of follow-up) per participant.
- For Cohort 1-3, the visit frequency will be at Screening (2 visits), on Day 1 (Baseline), and at Weeks 2 (Day 14), 6 (Day 42), and 12 (Day 84). For Cohort 4, the visit frequency will be at Screening (2 visits), on Day 1 (Baseline), and at Weeks 2 (Day 14), 8 (Day 56), and 12 (Day 84). A Safety Follow-up Visit will occur 2 weeks following the last dose of CRN04894 (Week 14; Day 98), and a telephone call to collect any AEs will occur at 4 weeks after the last dose of CRN04894 (Week 16, Day 112).

Number of Participants: 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).

Note: Enrolled means participants' or their legally acceptable representatives' agreement to participate in a clinical study following completion of the informed consent process and

Screening. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled.

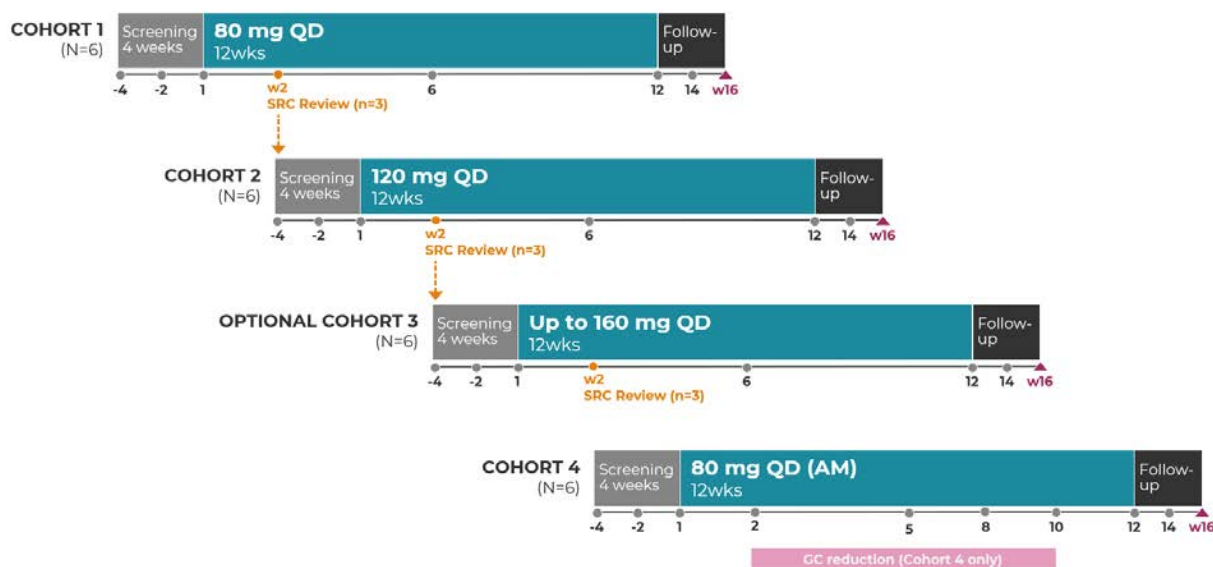
Study Arms and Duration:

In each dose cohort, participants will receive CRN04894 for up to 12 weeks.

Independent Data Monitoring Committee: No

Safety Review Committee: Yes (see Section 12.1.6)

2.2. Schema



SRC=safety review committee, V=visit, W=week

^a The SRC can recommend a lower dose (ie, CRN04894 40 mg QD) 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 and/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.

2.3. Schedule of Activities

2.3.1. 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 Section 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		
HbA1C	X					X		
Free T4, TSH	X					X	X	

	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
PD biomarkers 17-OHP, ACTH (plasma), testosterone, A4, [REDACTED] , 11-DOC, 21-deoxycortisol, [REDACTED] [REDACTED]	X	X ^f	X ^f	X ^f	X ^f	X ^f	X ^f	
Aldosterone ^h			X		X	X	X	
21-hydroxylase gene mutation screening			X					
Plasma renin ^h			X		X	X	X	
Serology HIV antibody, HBsAg, and hepatitis C virus antibody		X						
Sparse PK onsite				X ^g	X	X ^g	X	
Trough PK				X ⁱ		X ⁱ		
Pregnancy test (WOCBP) ^j	X		X	X	X	X	X	
Menstrual cycle diary review (women only)		X	X	X	X	X	X	X
[REDACTED]			X			X		
FSH (women who are postmenopausal with less than 1 year of amenorrhea only) ^k	X	X						
Sex hormone binding globulin (SHBG)			X			X		
Adrenal insufficiency assessments	X	X	X	X	X	X	X	X
Circadian assessments at selected sites ^l		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 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.

2.3.2. 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									

	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
Glucocorticoid reduction				X ^g	X ^g	X ^g	X ^g			
Glucocorticoid Administration Diary review		X	X	X	X	X	X	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							
██████████			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		

	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
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								
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.
- ^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.

3. INTRODUCTION

3.1. Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia (CAH) is a series of rare autosomal recessive diseases of the adrenal glands due to mutations in key enzymes involved in adrenal steroidogenesis (White 2000). The most common cause of CAH is 21-hydroxylase deficiency (21-OHD), accounting for over 90% of cases of CAH. The “classic form” is due to complete loss of 21-OH activity and has a worldwide incidence in most studies ranging from ~1:14,000 to 1:18,000. Classic CAH due to 21-OHD results in a lack of cortisol and aldosterone production, which can cause salt-wasting adrenal crises in the neonate and life-long adrenal insufficiency.

In the absence of cortisol, the hypothalamus and pituitary gland are not subject to negative feedback, resulting in elevated adrenocorticotrophic hormone (ACTH) levels, which in turn drives excess adrenal androgen production (Figure 1). This excess ACTH acting on the adrenal glands results in bilateral adrenal hyperplasia and, due to 21-OHD, steroid precursors such as androstenedione (A4) which can cause clinical hyperandrogenism (El-Maouche 2017).

In females, hyperandrogenism can result in hirsutism, acne, male-pattern baldness, menstrual irregularities, oligomenorrhea or amenorrhea, infertility, short stature, and frank virilization, manifesting in the newborn as ‘intersex’ (Cantù-Reyna 2016; Milunsky 2010; Speiser 2018; Warrell 2005).

Poorly controlled childhood CAH results in short stature. Childhood hyperandrogenism in boys results in premature puberty/adrenarche with resultant premature fusion of the epiphyses. In men, hyperandrogenism can suppress gonadotropin secretion, resulting in reduced testes size, reduced testicular testosterone secretion, and spermatogenesis. Furthermore, chronic ACTH stimulation may also contribute to the formation of [REDACTED] in men, and which can be confused with malignant testicular tumors, cause irreversible testicular damage and potential infertility. There are no therapies to prevent the development of [REDACTED] other than intensified glucocorticoid treatment.

3.1.1. Diagnosis of CAH

The diagnosis of classic 21-OHD is based on elevated levels of the immediate enzyme substrate 17-hydroxyprogesterone (17-OHP). Screening is routinely performed in newborn screening programs by measuring 17-OHP. An elevated level is sensitive for CAH, but falsely high 17-OHP levels can occur in premature, sick, and stressed infants. Second-tier screening can confirm elevated levels seen on the newborn screen. In cases where the data are equivocal, a stimulation test demonstrating an exaggerated rise in 17-OHP in response to an exogenous dose of ACTH may be required (Speiser 2018).

3.1.2. Current Treatment of CAH

Current treatment of CAH centers on replacing deficient adrenal hormones (ie, cortisol and aldosterone) and suppressing excess androgen production. Given that there are no other approved nonhormonal medications for CAH in the United States (US), glucocorticoid therapy must not only serve to replace the deficiency but also provide feedback inhibition at the pituitary to decrease ACTH-secretion and thereby reduce adrenal androgen production. However, the doses

of glucocorticoids required to suppress androgen production in classic CAH participants are often higher than required for physiologic replacement resulting in the well-documented side effects of chronic supraphysiologic glucocorticoid exposure, essentially a state of iatrogenic Cushing syndrome (CS).

Thus, there is a delicate balance between under- and overtreatment as participants with CAH often suffer chronically from various degrees of hyperandrogenism caused by the disease and the manifold complications of chronic supraphysiologic glucocorticoid therapy used to treat the disease ([Stikkelbroeck 2003](#)). [Table 1](#) highlights the clinical indicators that are used by physicians to achieve this balance.

Table 1: Risks Associated with Under- or Over-replacement of Glucocorticoids (Exogenous Glucocorticoids, Mineralocorticoids) in CAH

Body System	Under-replacement	Over-replacement
Cardiovascular	Low blood pressure, hyponatremia, hyperkalemia due to absent mineralocorticoid	High blood pressure, volume retention, edema, hyponatremia, hypokalemia
Liver	Hypoglycemia due to decreased gluconeogenesis	Hyperglycemia, hypertriglyceridemia due to increased gluconeogenesis and lipolysis
Bone	Reduced final adult height due to early epiphyseal closure as a result of increased adrenal androgens Increased bone mass	Osteopenia, osteoporosis due to glucocorticoid-induced inhibition of osteoclast function, vitamin D antagonism
Adipose tissue	Weight loss	Increased fat mass (adrenocortical obesity), predominantly of centripetal distribution
Muscle	Muscle weakness, myalgia	Muscle atrophy, myopathy

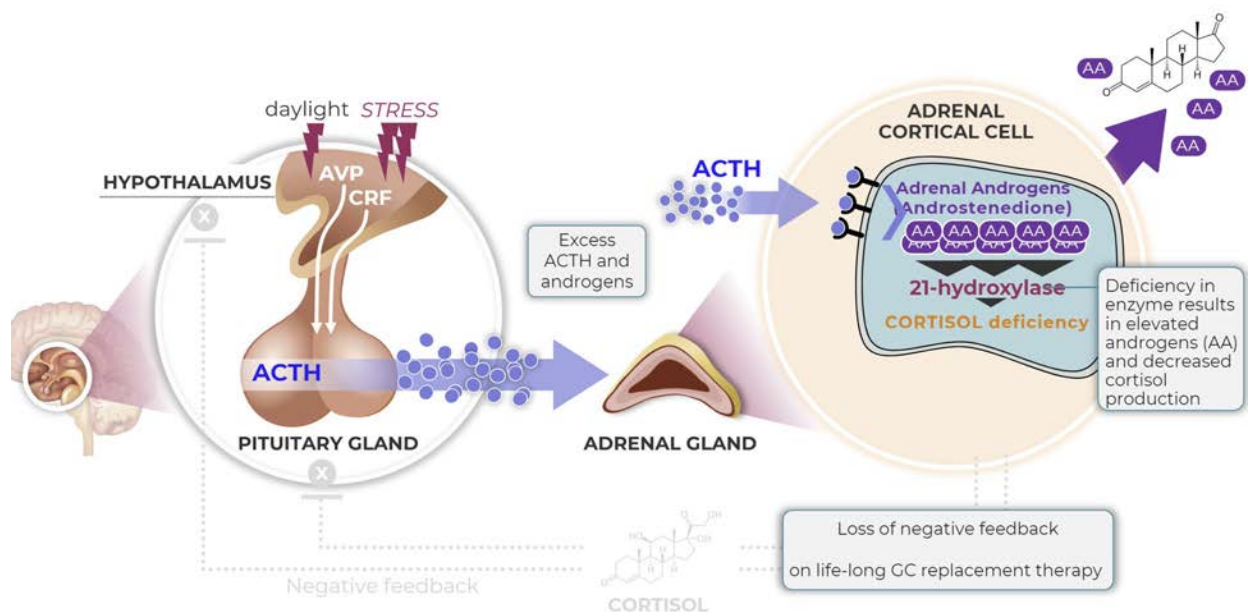
Source: Adapted from ([Reisch 2011](#)).

CAH=congenital adrenal hyperplasia

3.1.3. The Hypothalamic-pituitary-adrenal Axis

ACTH is a 39-amino acid peptide synthesized by anterior pituitary corticotrophic cells and is secreted in response to hypothalamic corticotrophin releasing hormone (CRH) and stressful stimuli ([Clark 2016](#)). As part of the hypothalamic-pituitary-adrenal (HPA) axis, ACTH activates the melanocortin 2 receptor (MC2R) on the adrenal gland. MC2R is expressed on the adrenal cortex ([Angelousi 2000](#); [Malik 2015](#); [Mountjoy 1992](#)) and requires the MC2R accessory protein (MRAP) for both surface expression and binding to ACTH ([Cooray 2011](#); [Metherell 2005](#); [Rodrigues 2015](#)). Binding of ACTH to the MC2R/MRAP complex on adrenal cortical cells activates its G-protein (Gs) to elevate intracellular cyclic adenosine monophosphate (cAMP) levels, which in turn stimulate cortisol synthesis and secretion by regulating multiple steps in the steroidogenic pathway ([Connelly 2009](#); [Hu 2001](#); [Mavridou 2010](#); [Webb 2010](#)).

Figure 1: Inability to Produce Cortisol Leads to Loss of Negative Feedback and Excess ACTH in CAH Participants



AA=adrenal androgens; ACTH=adrenocorticotrophic hormone; AVP=arginine vasopressin; CRF=corticotropin releasing factor

3.1.4. CRN04894

CRN04894 is an oral, first-in-class ACTH receptor antagonist that binds to the MC2R to block ACTH-mediated steroidogenesis from the adrenal gland. It is being developed for target diseases associated with excess ACTH-driven adrenal steroids, specifically ACTH-dependent Cushing's syndrome (Cushing's disease [CD] and ectopic ACTH syndrome [EAS]) and classic CAH.

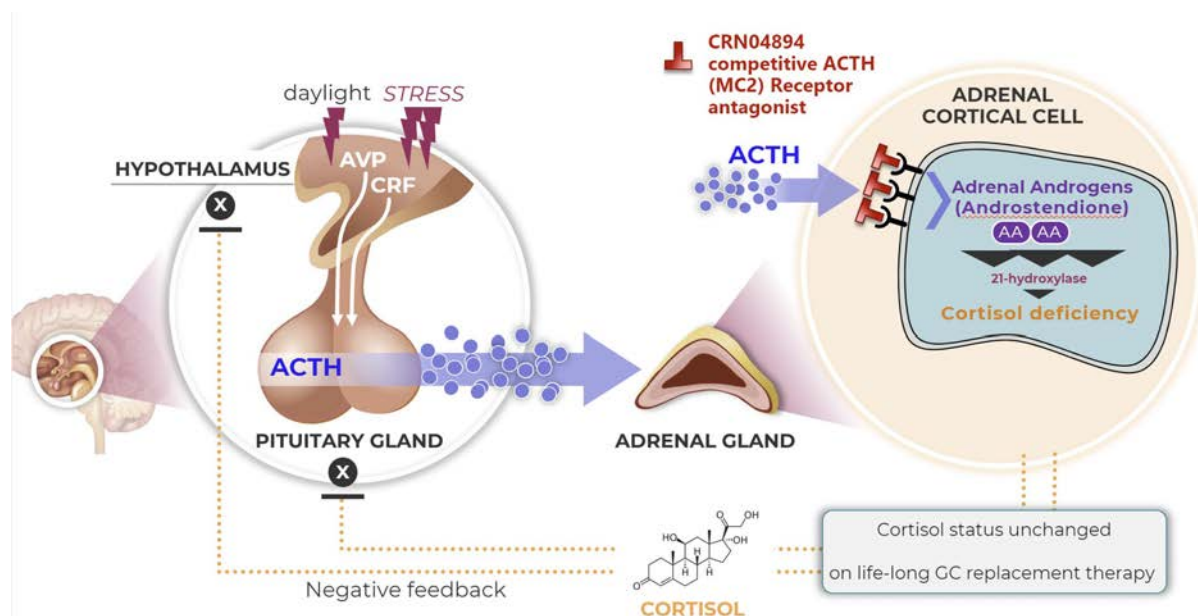
CRN04894 was well tolerated in healthy volunteers with no serious adverse events (SAEs). All nonserious adverse events (AEs) were considered mild/moderate. Data from the first-in-human study, CRN04894-01, demonstrated favorable oral bioavailability. The median time to maximum plasma concentration (t_{max}) was approximately 1 hour for the dose range evaluated. After the maximal concentration was attained, CRN04894 plasma concentrations declined with an apparent terminal elimination half-life ($t_{1/2}$) of approximately 20 hours. The increase in systemic exposures (maximum plasma concentration [C_{max}] and area under the curve [AUC]) appeared to be dose-proportional in dose range evaluated (between 10 mg and 80 mg). Overall, at higher daily doses (60 mg and 80 mg once daily at 22:00 for 10 days) CRN04894 demonstrated favorable bioavailability and pharmacokinetics (PK).

Rapid and dose-dependent reductions in cortisol levels were observed in healthy volunteers upon oral administration of CRN04894. Pharmacodynamic confirmation of the ability of CRN04894 to antagonize ACTH action was demonstrated by lowering basal/unstimulated morning cortisol (08:00, the time of peak serum cortisol), reducing 24-hour AUC for serum cortisol, reducing peak serum cortisol response to exogenous ACTH (1-24) stimulation, and reducing 24-hour urinary free cortisol (UFC) excretion.

Androstenedione (A4) is the principal biochemical measure of disease activity in adult CAH participants due to 21-OHD. After administration of CRN04894 (80 mg, once daily) for 10 days, the peak serum A4 following ACTH (1-24) stimulation was reduced by 25%.

The reduction in adrenal steroidogenesis by CRN04894 (80 mg, once daily, 10 days) occurred despite a feedback-induced approximately 5-fold increase in plasma ACTH.

Figure 2: Predicted Ability of CRN04894 to Reduce Adrenal Androgen (Particularly Androstenedione Secretion)



AA=adrenal androgens; ACTH=adrenocorticotrophic hormone; AVP=arginine vasopressin; CRF=corticotropin releasing factor

3.2. Study Rationale

CRN04894 is a potent and selective orally administered nonpeptide MC2R or ACTH antagonist currently under development by Crinetics for the treatment of CAH and other diseases caused by excess ACTH, ie, CD and EAS. By acting selectively at MC2R, CRN04894 is a potential novel treatment for diseases that are characterized by ACTH-mediated pathological elevations of adrenal steroid hormones (Clark 2016; Newfield 2010). This predicted ability to suppress adrenally derived androgens (Figure 2) while maintaining mineralocorticoid production (due to lack of activity on AT II receptor) makes CRN04894 a novel treatment option for CAH. To date, CAH is only treated with exogenous glucocorticoids and there are no nonhormonal treatments approved by regulatory authorities.

The purpose of this study is to evaluate the safety, efficacy, and PK of CRN04894 in participants with classic CAH 21-hydroxylase deficiency.

3.3. Benefit/Risk Assessment

This study is the first clinical study to investigate the use of CRN04894 in participants with CAH with classic CAH 21-hydroxylase deficiency.

3.3.1. Risk Assessment

[Table 2](#) provides a summary of study procedure-related risks and other potential risks for participants, along with mitigation strategies to prevent or minimize these risks.

Table 2: Risks and Mitigation Strategies

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention – CRN04894		
Adrenal insufficiency (including hypotensive adrenal insufficiency). See Table 4 for signs and symptoms of adrenal insufficiency.	CRN04894 is an ACTH antagonist and therefore expected to lower serum cortisol levels. Adrenal insufficiency and hypotensive adrenal insufficiency are defined in Section 7.9.1.	All participants in Cohort 1, 2, and 3 will be on long-term, stable doses of glucocorticoid replacement therapy that will not be reduced during the study. Participants in Cohort 4 will have stepwise reductions in GC dose to physiological doses (<11 mg/m²/day) between Weeks 2 and 10 i.e. to doses taken by patients with non-CAH causes of adrenal failure. Participants will have weekly in person or telephone review to ensure tolerance of the dose reduction, specifically focused on symptoms suggestive of adrenal insufficiency or related to dose reduction, such as fatigue, myalgia, and nausea (GC withdrawal syndrome [He 2022])). Investigators and participants will be permitted to increase the GC dose as judged clinically appropriate. CRN04894 suppresses ACTH-induced cortisol production, and while unlikely, it is possible that participants on stable doses of glucocorticoids with residual cortisol production may experience symptoms of adrenal insufficiency. Other risk factors for adrenal insufficiency for participants on long-term glucocorticoid therapy, include intercurrent illness and/or poor adherence with glucocorticoid replacement. Participants entering the study will be educated to recognize the signs and symptoms of adrenal insufficiency and about the importance of increasing the dose of glucocorticoid therapy, according to local practices, if necessary for periods of stress (sick day rules). Participants are required to document glucocorticoid dose and regimen daily in a diary that will be reviewed at study visits. Participants will also be regularly assessed for clinical evidence of hypoadrenalism and instructed on when to contact the study doctor. Unscheduled visits may be necessary to assess cases of suspected or confirmed adrenal insufficiency. Assessment and treatment guidelines in this protocol are derived from the Endocrine Society Guidelines for primary adrenal insufficiency (Bornstein S 2016) and guidelines for adrenal insufficiency due to hypopituitarism (Fleseriu M 2016).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Procedures		
Venipuncture	Additional blood draws may be necessary if the initial draw is not successful. As with any venipuncture procedure, there is the potential for a venous blood clot and/or infection.	Study staff are to follow safe practices for venipuncture.
Electrocardiogram (ECG)	The patches applied to the skin for the procedure could cause skin irritation and/or hair removal. Extensive chest hair may need to be shaved before the procedure.	Shaving items may be used in case a participant needs to have his chest hair shaved.
Magnetic resonance imaging scans (MRI)	Claustrophobia, dizziness, mild nausea, numbness, tingling, muscle twitches, tiny flashing lights in field of vision, or momentary imbalance after leaving the magnet. Possible use of intravenous contrast with associated risk of renal injury (in people with severe kidney disease) or hypersensitivity reaction. The strong, static magnetic field of the MRI scanner may pull on magnetic materials and may cause unwanted movement of a medical device.	Standard of care symptomatic and preventive management measures
Ultrasound	Ultrasound waves may heat the tissues slightly and, in some cases, it can also produce small pockets of gas in body fluids or tissues.	Symptomatic measures
Risk to pregnancy	Recommendation for contraceptive requirements and pregnancy testing during clinical studies with CRN04894 are presented in line with {HMA.EU.CTFG, 2020 #51622} for an investigational medicinal product where human data on pregnancies is limited or not available.	Participants are to adhere to the contraception requirements described in Section 12.4.

3.3.2. Benefit Assessment

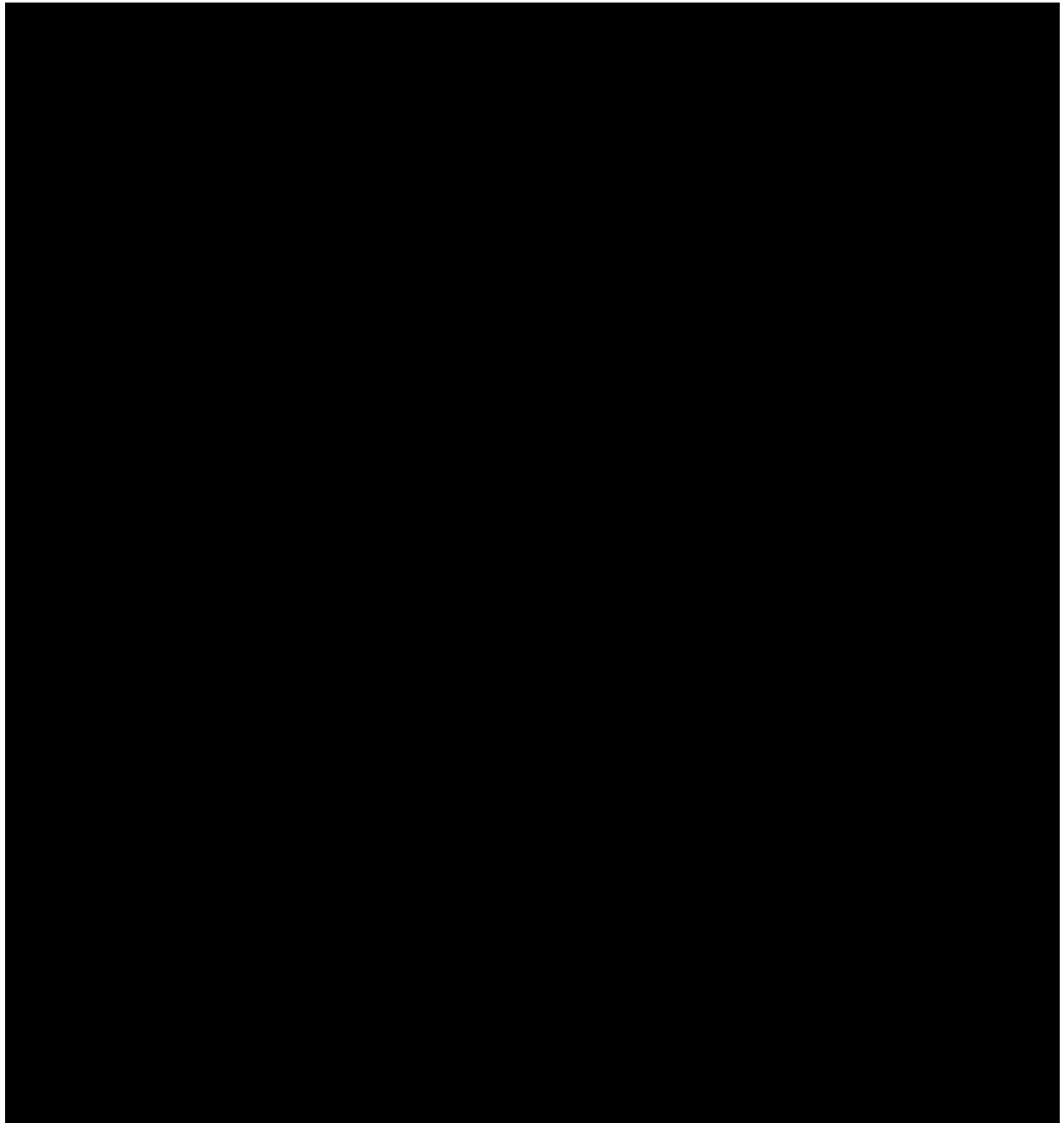
CRN04894 has been shown to antagonize the ability of ACTH to stimulate adrenal androgen secretion in healthy volunteers. These findings suggest that CRN04894 may be an effective treatment for the hyperandrogenism observed in CAH and may result in improvement in the associated problems, such as hirsutism, acne, menstrual irregularity. In men, antagonism of ACTH action may result in improvement of [REDACTED] if present.

3.3.3. Overall Benefit-Risk Conclusion

Based on the available information, the known and potential risks of treatment with CRN04894 are considered acceptable in relation to the potential benefits of treatment in participants with CAH. The risk of hypoadrenalism is considered to be low, because participants in Cohorts 1-3 will continue glucocorticoid replacement regimens during the study. Glucocorticoid replacement dosing will be reduced during Weeks 2-10 for participants in Cohort 4 (see [Table 2](#) for risk mitigation strategies). Participants will be educated about how to recognize and treat hypoadrenalism should it occur related to intercurrent illness or lack of adherence to glucocorticoid replacement.

4. OBJECTIVES AND ENDPOINTS

Safety Objectives	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



5. STUDY DESIGN

5.1. Overall Design

This Phase 2, open-label, sequential dose cohort study will evaluate the efficacy, safety, PK, and PD of CRN04894 when administered for 12 weeks in participants with CAH caused by 21-hydroxylase deficiency.

Up to approximately 30 participants will be enrolled in Cohorts 1-3 of the study while Cohort 4 will enroll an additional 6-12 participants (up to 42 participants total). 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 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 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/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. 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 interim 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 (ie, CRN04894 40 mg QD) 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/or 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 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 review of safety and tolerability data.

Overview of Glucocorticoid Reduction Period (Week 2 to Week 10) for Cohort 4

Participants will gradually decrease their glucocorticoid dosage in up to 4 steps to reach a target dose of 8-9 mg/m²/day (hydrocortisone equivalents) between Week 2 and Week 10 (see Section 5.3 for rationale). The glucocorticoid dose reduction schedule will not be biomarker (A4) dependent and reductions below 8 mg/m²/day hydrocortisone equivalents are discouraged, although doses below 8 mg/m²/day are permitted if the Investigator feels this is clinically indicated and acceptable. The Investigator is encouraged to communicate weekly with the participant to assess response to GC reductions at a minimum once weekly between Weeks 2 and 10. Following each visit resulting in glucocorticoid reduction, the Investigator will contact the participant by telephone within a week of the study visit to assess the tolerability of glucocorticoid reduction which should be reconsidered if signs or symptoms of glucocorticoid deficiency occur. Mineralocorticoid doses will be adjusted as needed during as glucocorticoids are reduced. Glucocorticoid reduction should be halted and reevaluated if the participant exhibits symptoms or signs of glucocorticoid insufficiency. The suggested glucocorticoid reduction at each specified time point is 5-10 mg of hydrocortisone equivalent but alternative reduction regimens may be implemented based on the Investigator's clinical judgment with the intent of achieving physiological doses by Week 10. GC doses increases can be made at Investigators' or participants' discretion. Unscheduled visits may be arranged if clinical assessments or lab tests are needed.

Week 2: Onsite Visit

- The Investigator provides instructions for the first GC dose reduction
- Study assessments including blood sample collection for PD biomarkers and routine safety checks (specify procedures)
- A follow-up phone call should be done in a week ± 2 days to assess tolerability, participant well-being, and any TEAEs

Week 5: Phone Call

- If necessary, the second GC dose reduction step will be instructed.
- A follow-up phone call within a week ± 2 days to assess tolerability, participant well-being, and any TEAEs

Week 8: Onsite Visit

- If necessary, instructions for the third GC dose reduction step will be provided
- Study assessments including blood sample collection for PD biomarkers and routine safety checks

- A follow-up phone call within a week ± 2 days to assess tolerability, participant well-being, and any TEAEs

Week 10: Phone Visit

- If necessary, the fourth GC dose reduction step is instructed.
- A follow-up phone call within a week ± 2 days to assess tolerability, participant well-being, and any TEAEs

Conditions for Halting GC Dose Reduction:

- The dose should be reverted to the previous tolerable level if any of the signs/symptoms below are present:
- Unacceptable hyperandrogenism symptoms (e.g., hirsutism, acne)
- Signs or symptoms of glucocorticoid withdrawal or glucocorticoid insufficiency (see [Table 4](#))

5.2. Scientific Rationale for Study Design

CRN04894 is a potent and selective orally administered nonpeptide MC2R or ACTH receptor antagonist currently under development by Crinetics for the treatment of CAH and other diseases caused by excess ACTH (ie, CD and EAS). By acting selectively at MC2R, CRN04894 is a potential novel treatment for diseases that are characterized by ACTH-mediated pathological elevations of adrenal steroid hormones ([Clark 2016](#); [Newfield 2010](#)). The predicted ability to suppress adrenally derived androgens ([Figure 2](#)) makes CRN04894 a novel treatment option for CAH which to date is only treated with exogenous glucocorticoids and for which there are no nonhormonal treatments approved by regulatory authorities.

Prior to this study, CRN04894 has been evaluated in healthy volunteers for up to 10 days of dosing. The purpose of this study is to evaluate the safety, efficacy, and PK of CRN04894 in participants with classic CAH 21-hydroxylase deficiency. In addition to evaluating the direct impact of CRN04894 on adrenal androgen secretion, the cause of numerous adverse effects in participants with CAH, the potential effects on adrenal size and function over a longer period of time (3 months of continuous dosing) will be evaluated. The duration of therapy in this Phase 2 study is based on the available nonclinical toxicity studies.

CAH is seen in the elderly population and therefore the inclusion of participants 66 to 75 years, allowing for efficacy and safety investigations of this potential new medication, is warranted. Note that the protocol excludes any participants that have clinically significant unstable medical conditions, chronic disease other than CAH, renal insufficiency, or significant liver disease.

5.3. Justification for Dose

Doses of 60 mg and 80 mg CRN04894 have previously been shown to lower basal morning (08:00) cortisol and antagonize the ability of synthetic ACTH to stimulate cortisol secretion in healthy volunteers. These outcomes were achieved despite compensatory elevations of endogenous ACTH. No differences in cortisol concentrations were seen with 80 mg doses of CRN04894 compared to placebo in the evening (18:00-24:00) time frame. Because CRN04894 is a competitive antagonist, the persistence and magnitude of effective ACTH receptor

antagonism and adrenal androgen lowering may be dose-dependent. In healthy volunteers, CRN04894 80 mg/day for 10 days resulted in an approximately 5-fold increase in 24-hour AUC plasma ACTH compared to Baseline; levels comparable with those seen in poorly controlled CAH. CRN04894 reduced the peak A4 after stimulation with exogenous ACTH(1-24) by 25%. This suggests the need to explore doses higher than 80 mg, aiming to treat a heterogeneous group of participants with varying degrees of ACTH-related hyperandrogenism observed in CAH.

A fourth cohort with morning dosing and GC reduction was added to:

- Confirm previous observations that the PK of morning dosing is comparable to evening dosing
- Evaluate efficacy, safety, and tolerability of CRN04894 during and following GC dose reduction

The current nonclinical data supports the proposed clinical doses up to 160 mg/day in CAH participants. For a discussion of the nonclinical data supporting human dosing, see the Investigator's Brochure (IB).

5.4. End of Treatment and End of Study Definitions for Individual Participants

For analysis purposes, the following terms will be study conventions as they relate to individual participants:

- End of Treatment (EOT): The date of the last dose of study drug.
- End of Study (EOS): The date that final data are collected after a participant completes the Follow-up Visit (Final Visit/EOS) or after Early Termination.
- Treatment Period: The study period that begins on the day of enrollment and ends at EOT.
- A participant is considered to have completed the study if he/she has completed the last scheduled procedure specified at the EOS Visit.

5.5. End of Study Conduct Definition

For regulatory purposes, the EOS conduct is defined as the date of the last visit for the last enrolled participant at all study sites.

6. STUDY POPULATION

Participants with CAH caused by 21-hydroxylase deficiency will be recruited for this study.

6.1. Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply:

1. Male or female participants ≥ 18 to 75 years of age at the time of signing the informed consent form (ICF). Participants ≥ 16 years of age may be included in sites located in the US.
2. Willing and able to understand and adhere to the study procedures.
3. Classic 21-hydroxylase deficiency confirmed by the Investigator and approved by the Medical Monitor.
4. The A4 and 17-OHP values taken before morning glucocorticoid dose during Screening Visit 2 (at Week-2 [may occur between Day -21 and Day -14 for Cohort 4]), should meet these criteria:
 - a. A4 $\geq 1.5 \times$ upper limit of normal (ULN) and
 - b. 17-OHP ≥ 1000 ng/dL (30.3 nmol/L); historical results from within the last 2 years will be accepted if the participant has been on the current dose of GC since that time.

Participants who failed Screening based on findings the Investigator believes are temporary and not reflective of the usual state of the participant (eg, normal A4 levels when the participant usually is well above this value) can be considered for rescreening. These cases should be discussed with the Medical Monitor.

5. On a stable (defined as no dose change of >5 mg/day hydrocortisone equivalent within 6 months prior to Screening [1 month stable dose for participants in Cohort 4]) regimen of glucocorticoid replacement (eg, hydrocortisone, prednisolone, prednisone, methylprednisolone).
6. Compliance, as judged per Investigator discretion, with glucocorticoid replacement and mineralocorticoid replacement (if applicable) regimen documented during the Screening Period.
7. Minimum total daily dose of ≥ 15 mg hydrocortisone (or equivalent). For Cohort 4, the mean daily dose of ≥ 11 mg/m²/day of hydrocortisone or hydrocortisone equivalents will be used for inclusion.
8. If on estrogen therapy (any route), dose must be stable for at least 3 months prior to Screening.
9. Female participants who engage in heterosexual intercourse must:
 - a. Be of nonchildbearing potential, defined as either surgically sterile (ie, hysterectomy, bilateral salpingectomy, tubal ligation for at least 3 months, or bilateral oophorectomy), OR
 - b. Be postmenopausal with at least 1 year of amenorrhea. In participants with less than 1 year of amenorrhea, confirmation with 2 FSH measurements conducted 2 to 4 weeks apart is required during the Screening Period. 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, OR

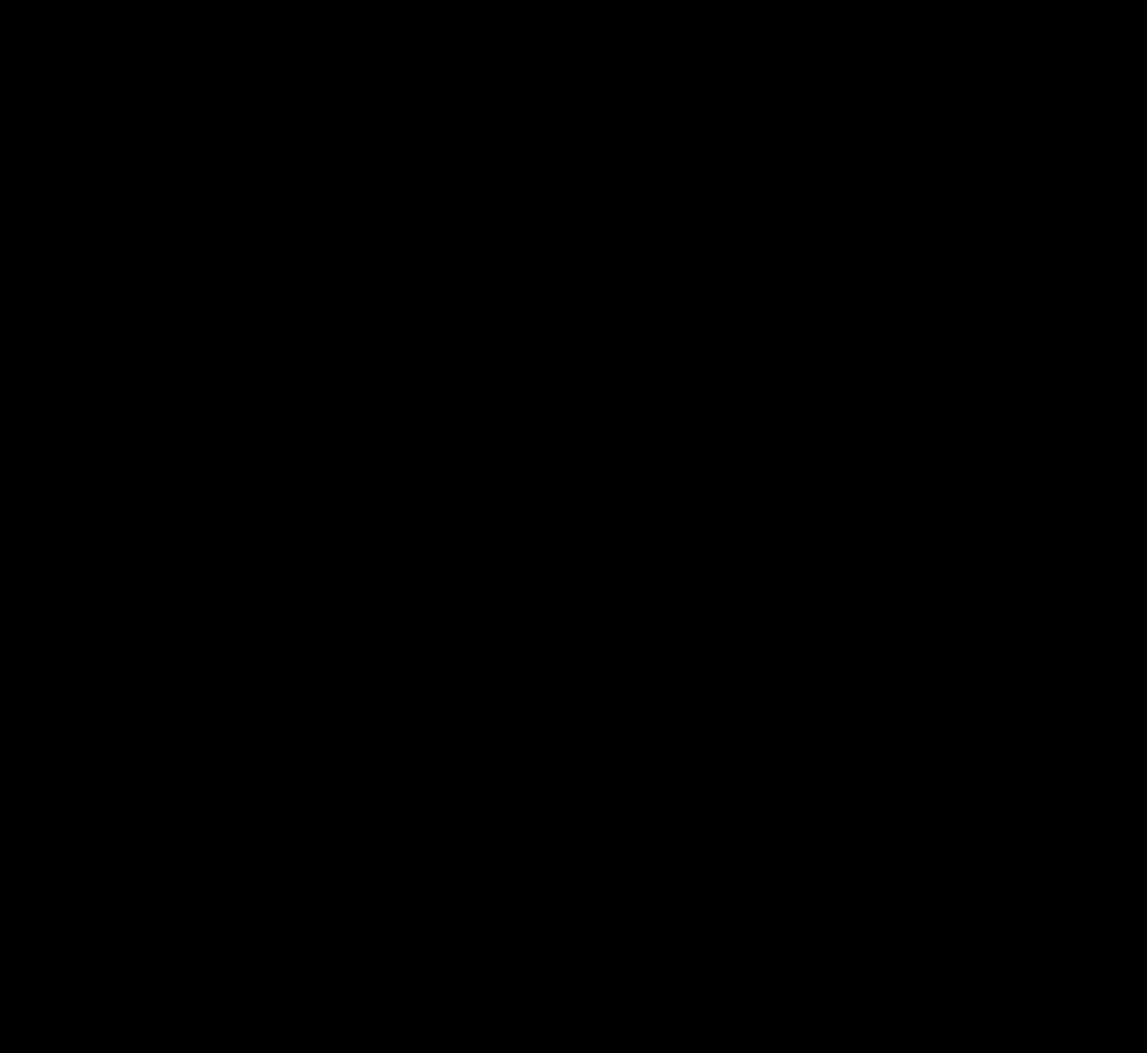
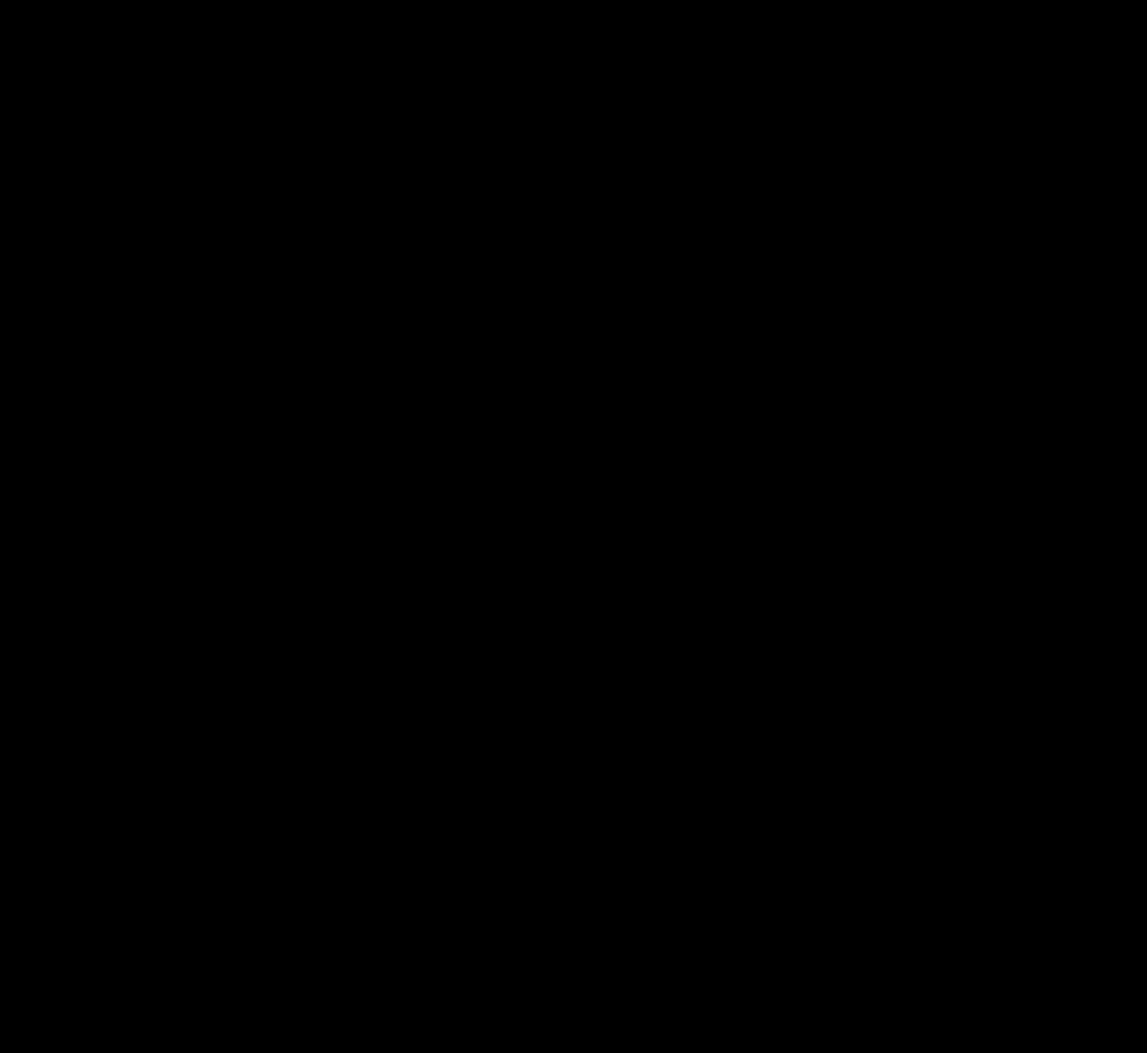
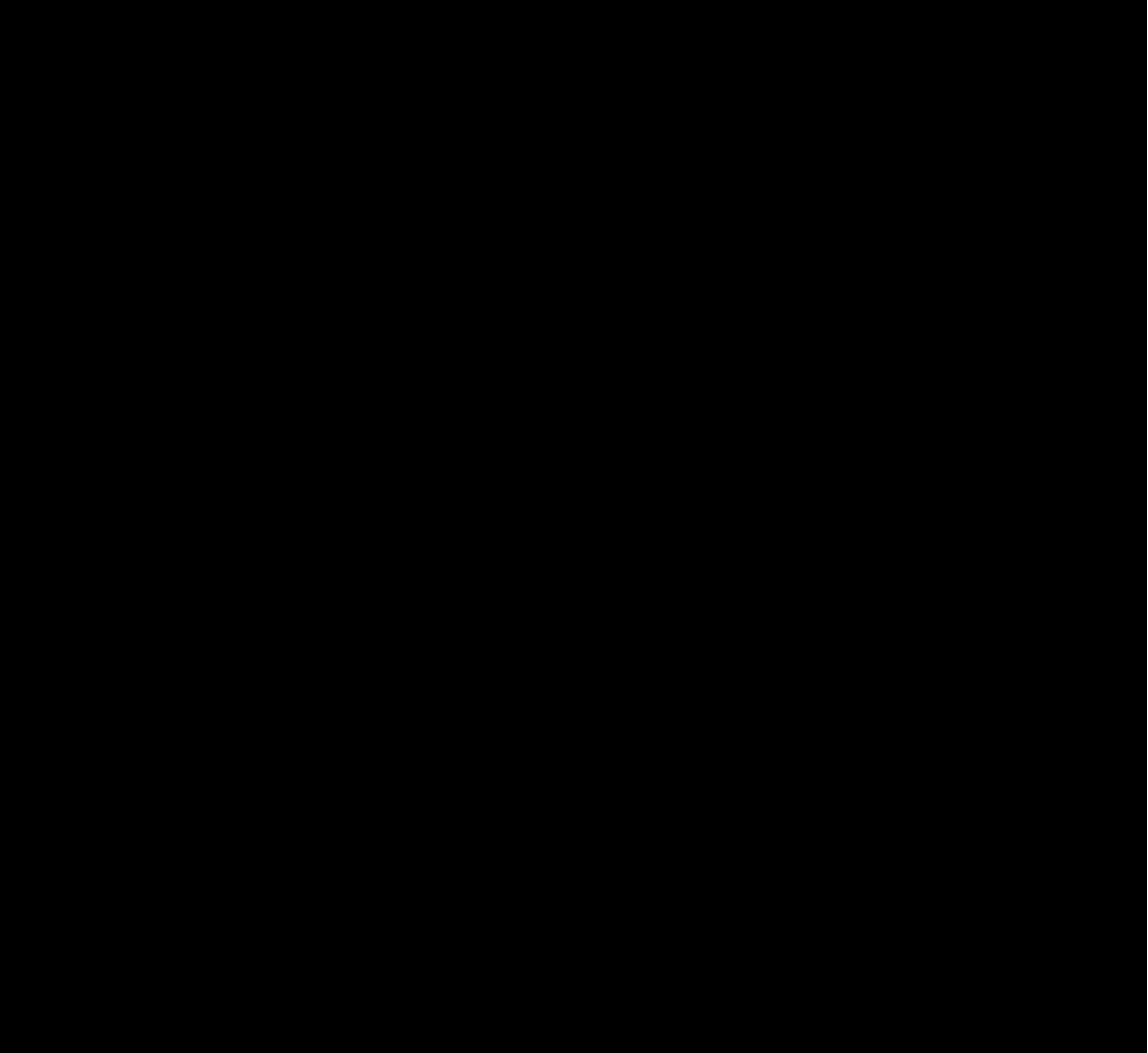
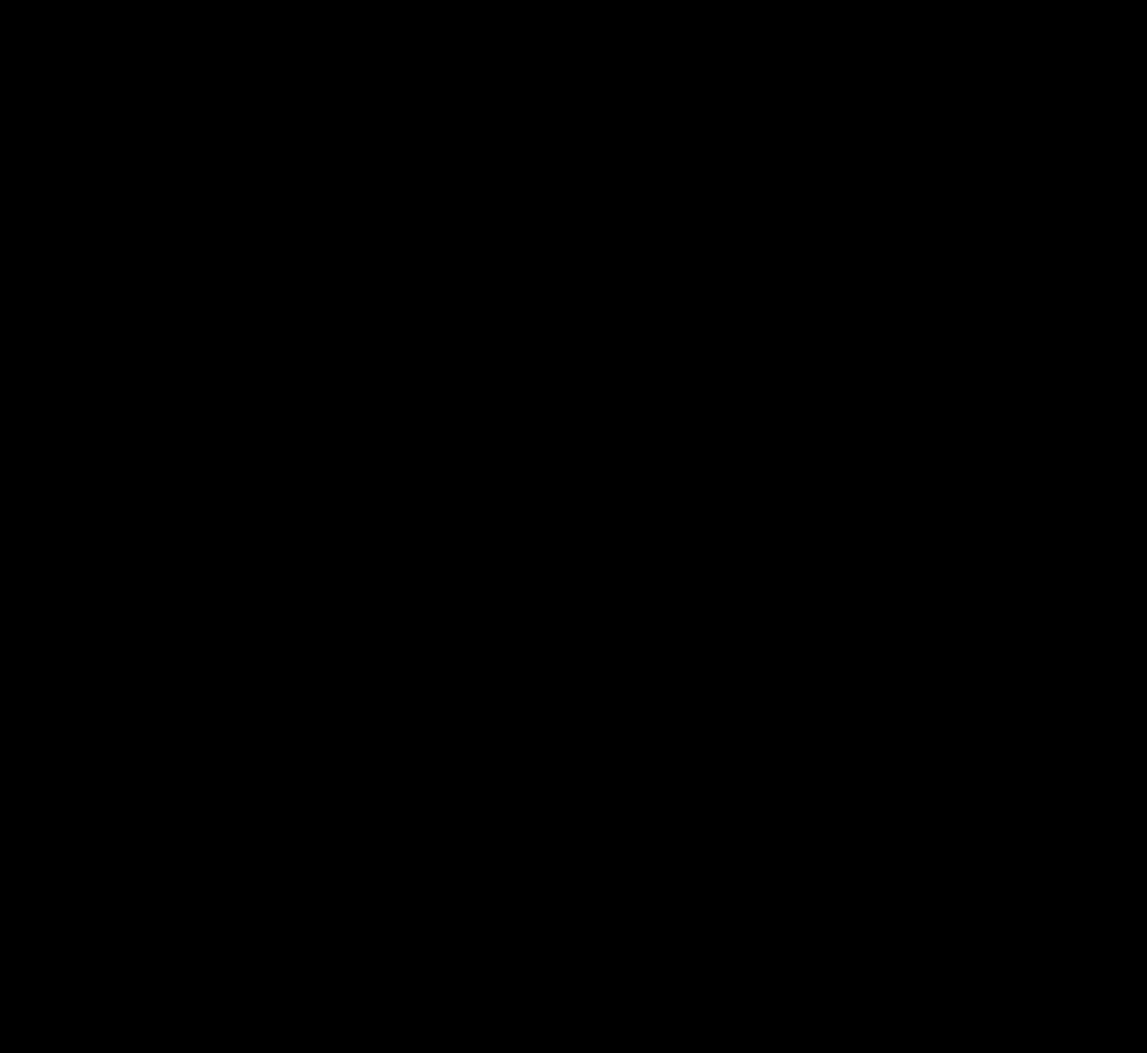
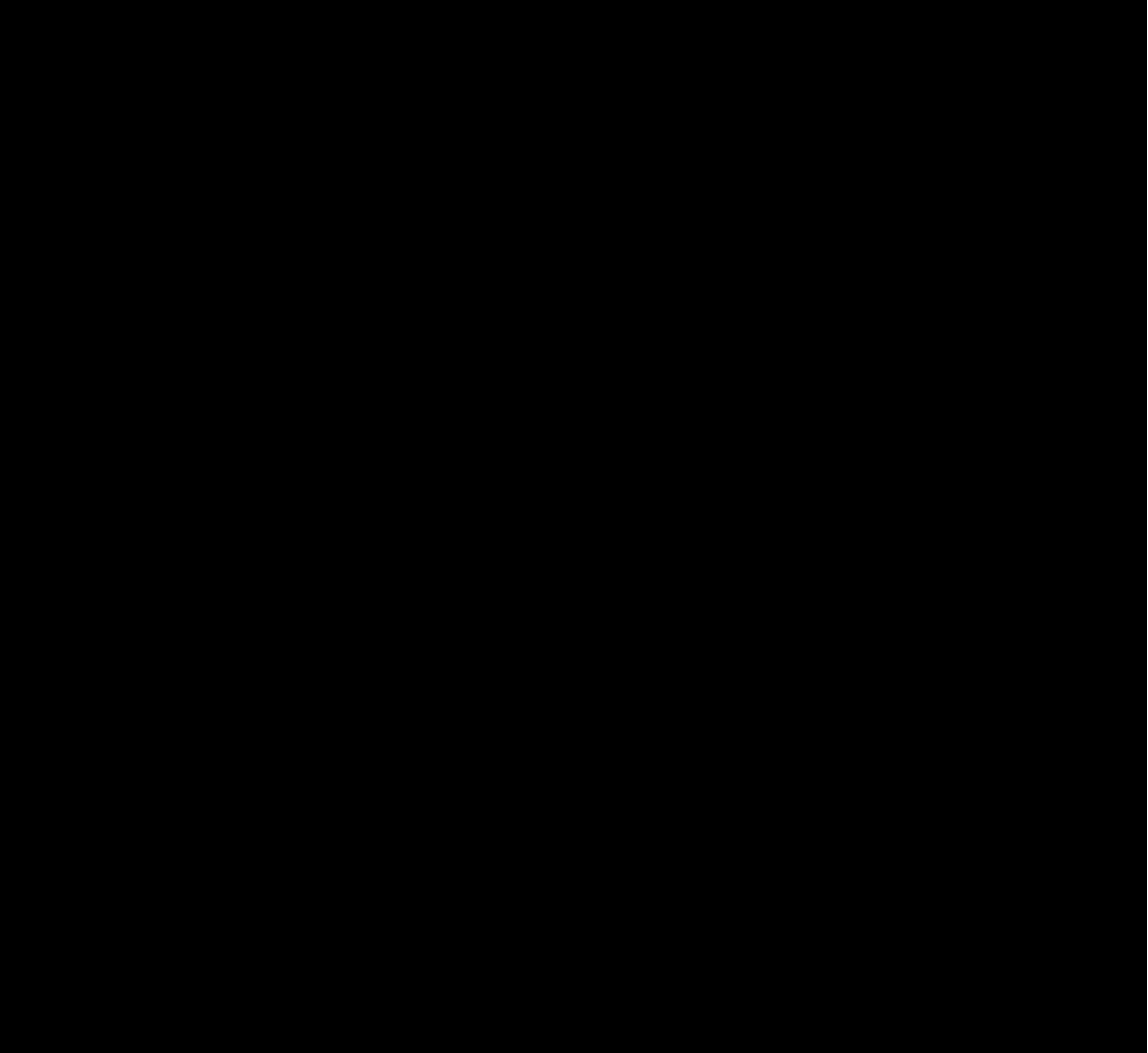
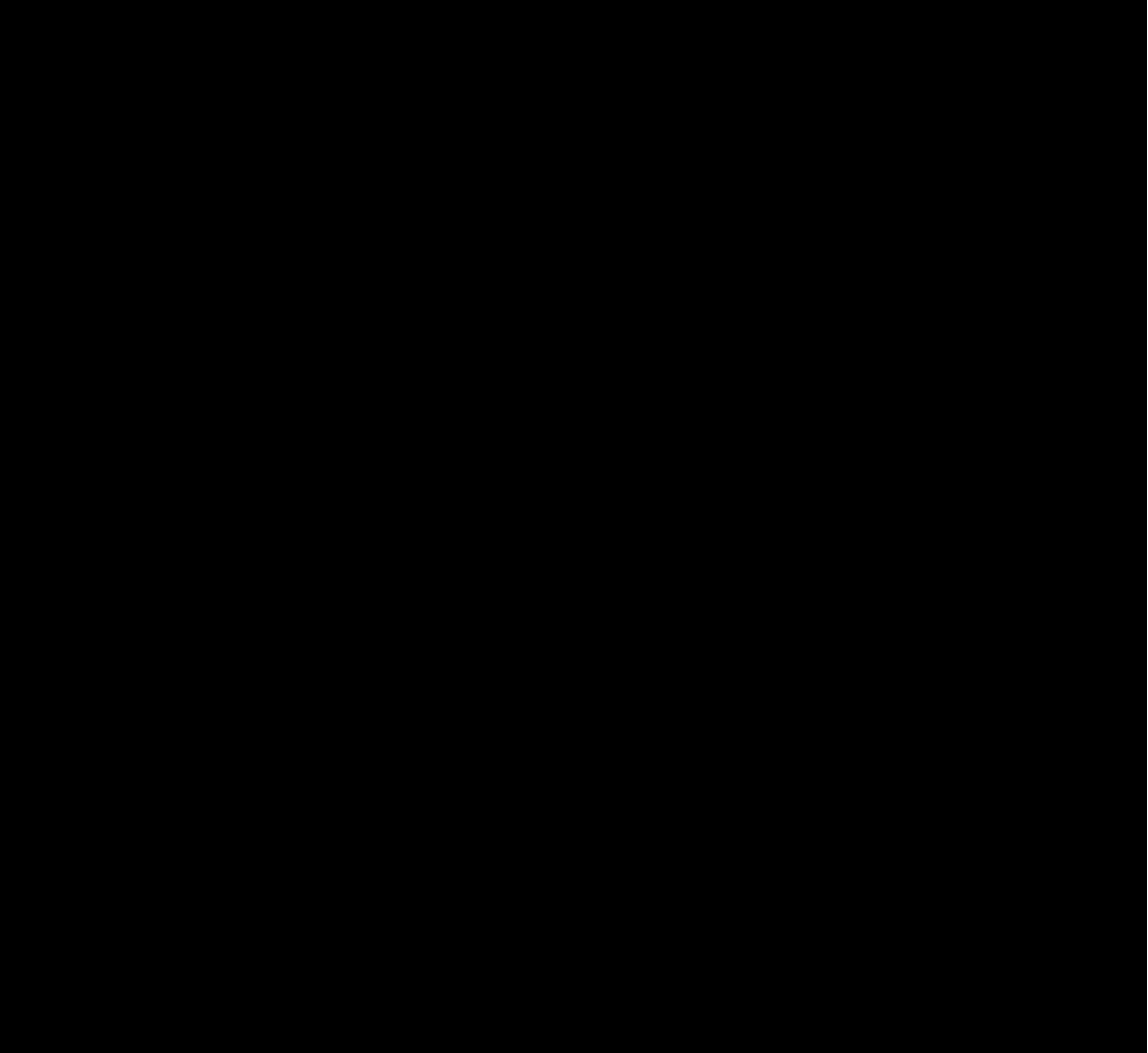
Agree to use a highly effective or a clinically acceptable method of contraception from the beginning of Screening until at least 2 weeks after the last dose of study drug. Contraceptive use by men and women also should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. Periodic abstinence (ie, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception. See Section 12.4 for additional acceptable contraceptive and barrier guidance.

10. Male participants: The participant should agree to use a condom when sexually active with a female partner of childbearing potential from Screening until at least 2 weeks after the last dose of study drug (or be surgically sterile [ie, vasectomy with a confirmed absence of sperm in ejaculate]); or agree to remain abstinent on a long-term and persistent basis). Male participants should also agree to not donate sperm for the duration of the study and until at least 2 weeks after the last dose of study drug.

6.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Diagnosis of any other form of CAH other than classic 21-hydroxylase deficiency
2. Dexamethasone or oral betamethasone use within 30 days of Screening for Cohorts 1-3. In Cohort 4, [REDACTED], but dexamethasone is acceptable.
3. History of bilateral adrenalectomy, hypopituitarism, or other condition requiring chronic glucocorticoid therapy
4. Night shift workers or any other reason for abnormal sleep/wake cycles (see Section 6.3 for details)
5. Clinically significant medical condition or abnormal laboratory tests, as judged by the Investigator, other than CAH
6. History of major surgery/surgical therapy for any cause within 4 weeks prior to Screening
7. Diabetes mellitus treated with insulin for less than 6 weeks prior to Screening, or with change in total daily insulin dose by $>15\%$ within 6 weeks prior to Screening
8. Poorly controlled diabetes mellitus defined as having a hemoglobin A1c (HbA1c) $\geq 8.5\%$ (≥ 69 mmol/mL), or estimated HbA1c based on fructosamine if HbA1c is not evaluable (eg, due to hemoglobinopathies)
9. Participants with hypothyroidism who are not receiving adequate hormone replacement therapy based on thyroid hormone levels measured at the time of Screening, as determined by the Investigator
10. History of unstable angina or acute myocardial infarction within 12 weeks prior to Screening or other clinically significant cardiac disease at the time of Screening as judged by the Investigator

11. 
12. History of cancer excluding cured/treated dermal squamous or basal cell carcinoma or cervical carcinoma in situ
13. Women who are pregnant or lactating or, if of childbearing potential, who are unwilling to use highly effective contraception as described in this study. Male participants who are unwilling to use highly effective contraception as described in this study.
14. Known history of illicit drug or alcohol abuse within the last year
15. Use of antiandrogen therapy in the past 3 months (eg, spironolactone, finasteride, cyproterone acetate, flutamide)
16. Use of testosterone, androgen-containing supplements, aromatase inhibitors, or growth hormone
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6.3. Lifestyle Considerations During this Study

6.3.1. Meals and Dietary Restrictions

Participants are to refrain from consumption of

starting 7 days before the first dose of CRN04894 until after the final dose.

6.3.2. Activity

Per exclusion criteria (Section 6.2), night shift work or any other activity resulting in abnormal sleep/wake cycles is to be avoided. The expectation is for participants to be consistently asleep before midnight (00:00). Participants attending occasional, late-night events within 5 days of a study visit should reschedule the study visit. Deviations from typical sleep schedules should be reported to the Investigator. Changes in baseline patterns of exercise should not occur during the study.

6.3.3. Prohibited Therapies

6.3.3.1. Potential Interactions with Therapeutic and Other Substances

Atumelnant is an inhibitor of CYP3A4, P-gp, and multidrug and toxin extrusion protein 1 (MATE1) or multidrug and toxin extrusion protein 2 kidney-specific (MATE2-K) based on in vitro assessments. Clinical assessment for these drug-drug interaction (DDI) potentials has not been conducted. Investigators should consider altered PK and potential DDIs when coadministering sensitive CYP3A4-metabolized drugs or agents absorbed or cleared by sensitive MATE or P-gp transporter system with a narrow therapeutic window, and caution should be used when coadministered with atumelnant. The investigator should contact the Medical Monitor (Sponsor or contract research organization [CRO]) to discuss DDIs of potential clinical concern, including the need for dose reduction of the substrate and/or additional clinical monitoring.

In addition to adhered to protocol-specified prohibited concomitant medications (see Section 6.3.3), the investigator must exercise clinical judgement and medical oversight relative to the emerging medical signs and symptoms in the context of the benefit-risk of treatment with concomitant medication(s) and atumelnant. Please refer to the “Summary of Data and Guidance for the Investigators” section of the IB for examples and known drugs (and drug classes) with potential DDIs and a link to a database of relevant drugs. Additionally, the investigator should consult the current approved label of the concomitant medication(s) under consideration.

6.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently dosed with study drug because they did not meet study eligibility criteria. A participant can screen fail any time from consent up to enrollment. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to

meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

A participant may rescreen once to meet eligibility requirements; however, if the Investigator considers the result of an assessment as a transient factor and/or not representative of the normal state of the participant, some assessments can be repeated without screen failing, as specified in Section 9.

Participants who rescreen will need to sign a new ICF.

6.5. Criteria for Temporarily Delaying Enrollment / Randomization / Administration of Study Drug

Not applicable.

7. STUDY DRUG(S) AND CONCOMITANT THERAPY

7.1. Study Drugs Administered

Table 3: Study Drugs Administered

Drug Label	CRN04894	Glucocorticoid Therapy
Active Ingredient	CRN04894 [REDACTED]	Various agents, including hydrocortisone, prednisolone, prednisone, methylprednisolone, and fludrocortisone
Dosage Form	Tablet	Variable per participant
Unit Dose Strength(s)	[REDACTED] mg ^a	Variable per participant
Dosage Level(s)	Cohort 1: Single dose, 80 mg ([REDACTED] mg) Cohort 2: Single dose, up to 120 mg ([REDACTED] mg) Optional Cohort 3: To be determined (up to 160 mg [REDACTED] mg) Cohort 4: Single dose, 80 mg ([REDACTED] mg)	Variable per participant
Administration	Oral, once daily (QD)	Oral
Use	Experimental	Background intervention
IMP and NIMP/AxMP	IMP	NIMP/AxMP
Sourcing	Provided centrally by the Sponsor	Standard of Care
Packaging and Labeling	Study drug will be provided in HDPE bottles with child-resistant closure and desiccant. Each container will be labeled as required per country requirement.	Approved commercial packaging.

AxMP=auxiliary medicinal product, HDPE=high-density polyethylene, IMP=investigational medicinal product, NIMP=noninvestigational medicinal product

^a free base equivalent

7.2. Preparation, Handling, Storage, and Accountability

The Investigator or designee will be responsible for handling study drug (ie, responsible for the receipt and accountability of the study drug). The individuals will be identified and documented in the Study Site Responsibility Log. All study drugs will be transported, received, stored, and handled strictly in accordance with the container or product label, the instructions supplied in the Pharmacy Manual and applicable regulations.

7.2.1. Packaging and Labeling

Study drug (CRN04894 tablets, [REDACTED] mg) will be packaged and labeled according to Good Manufacturing Practices (GMP) and applicable regulatory requirements of the country. CRN04894 tablets, [REDACTED] mg will be packaged in high-density polyethylene bottles (36 tablets per

bottle) containing desiccant and labeled in a manner consistent with study design while meeting applicable country and regional regulations for investigational drug. CRN04894 tablets will be supplied as ready-to-use tablets and are to be dispensed in accordance with the protocol.

Refer to the Pharmacy Manual for details and instructions about container closure and label.

7.2.2. Storage

All study drugs must be stored in a secure, environmentally controlled, and monitored area in accordance with the labeled storage conditions with access limited to the Investigator or designee at the study site. Appropriate storage temperature and transportation conditions will be maintained from the point of shipment to storage. Study drug (CRN04894 tablets) must be received by the Investigator or designee at the study site and promptly transferred to store at the appropriate temperatures between 15° to 30°C.

The appointed study staff must contact the site monitor in case of any temperature deviations. Refer to the Pharmacy Manual for storage instruction procedures.

7.2.3. Accountability

Crinetics Pharmaceuticals, Inc. will supply CRN04894 tablets, ■ mg to the study site. The study site is responsible for accurate study drug inventory, reconciliation and record maintenance (ie, receipt, reconciliation, and final disposition records). Study drug accountability must be performed for all delivered dispensed drug.

At the end of the study and following reconciliation and documentation by the site monitor, all study drugs and related materials will be either returned to the Sponsor, Sponsor's designee, or destroyed locally following the review of the site's destruction procedures. Refer to the Pharmacy Manual for additional information.

7.3. Assignment to Study Drug

Participants will be sequentially assigned to a dose cohort, starting with Cohort 1.

7.4. Blinding, Masking

This is an unblinded, open-label study.

7.5. Study Drug Compliance

Dose administration compliance will be assessed via review of participants' dosing diaries and documented in the source records and electronic case report form (eCRF) by recording the date and time of each dose administration. Reasons for any noncompliance will be recorded.

7.6. Dose Modification

Once participants have been assigned to receive a dose of CRN04894, that dose will not be modified.

7.7. Continued Access to Study Drug After the End of the Study

If eligible, participants may be enrolled in a separate long-term 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.

For participants at sites where the long-term extension study is not available, there is no further intervention after the completion of this study and the Investigator will ensure that the participants transition to the appropriate standard of care.

7.8. Treatment of Overdose

In this study, the maximum daily dose of CRN04894 is 160 mg.

In the event of a confirmed or suspected overdose, the Investigator should:

- Contact the Medical Monitor immediately, providing the dose of CRN04894 ingested and the time of administration.
- Closely monitor the participant for any AEs/SAEs (including symptoms and signs of adrenal insufficiency) and laboratory abnormalities (for at least 7 days).
- If possible, obtain a plasma sample for PK analysis within 1 day of the date of the suspected overdose of study drug if requested by the Medical Monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdose.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

Adrenal insufficiency is a possible consequence of overdose with CRN04894. If there is a biochemical or clinical suspicion of adrenal insufficiency it should be treated following the local standard of care (including increase in glucocorticoid dose), without delay. See [Table 4](#) for the signs and symptoms of adrenal insufficiency.

7.9. Prior and Concomitant Therapy

Concomitant therapy is considered any therapy—including vaccines, medications (prescription and over the counter), and nonmedications (procedures, vitamins, herbal/dietary supplements, and/or alternative medicinal products [eg, essential oils])—other than study drug that is administered at any time during the study (ie, from consent until EOS or early termination [ET]).

All prior therapies (medication and nonmedication) received within 60 days prior to consent are to be recorded in the same manner as concomitant therapy.

If a new therapy should become necessary for any reason during the course of the study, the participant is required to inform the Investigator immediately.

Any prior and/or concomitant therapy (ie, medications and nonmedications) that the participant is receiving at the time of consent until EOS is to be recorded along with:

- Reason for use
- Dates of administration/procedure, including start and end dates
- Therapy/treatment information, including type (eg, prescription, over the counter), name of therapy or treatment
- Dosage information, including route of administration, dose, and frequency

All participants should agree to the following restrictions during the study:

- Refrain from starting any new prescription medication until approved by the Investigator or if required in an emergency.
- Refrain from starting or using any prohibited therapies during the study (Section 6.3).

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapies.

7.9.1. Exogenous Glucocorticoids and Adrenal Insufficiency

During the study, particularly when participants are receiving study drug, the Investigator is to assess compliance with ongoing glucocorticoid replacement and monitor for possible signs and symptoms of adrenal insufficiency (Table 4).

In the event of clinical suspicion of adrenal insufficiency based on signs and symptoms found in Table 4, glucocorticoid therapy should be immediately resumed at prescribed doses if the participant has been nonadherent or, the glucocorticoid dose increased as appropriate for concomitant illness, consistent with sick day rules/adrenal insufficiency teaching according to local practices and the instruction of the local Investigator and which may require an alternative glucocorticoid regimen (Section 12.5) Severe (hypotensive) adrenal insufficiency is defined as an acute deterioration in health status including, but not limited to, signs and symptoms (Table 4) associated with absolute hypotension (systolic blood pressure <100 mm Hg) or relative hypotension (systolic blood pressure ≥ 20 mm Hg lower than usual), with features that resolve within 1 to 2 hours after parenteral glucocorticoid (usually hydrocortisone 100 mg intravenous [IV]) administration (ie, a marked resolution of hypotension within 1 hour and improvement in clinical symptoms over a period of 2 hours) (Rushworth 2019).

The prescribed dose increase in exogenous glucocorticoids and duration of such increase is to be determined by the local Investigator based on presenting signs and symptoms. Prior to providing supplemental doses or increasing the regular dose of exogenous glucocorticoid therapy, if possible, blood should be collected for measurement of urea, creatinine, sodium, potassium, glucose, and any scheduled hormone measurements.

- For participants diagnosed with mild to moderate adrenal insufficiency during the study, study drug dosing may continue, under careful supervision, if 1 of the following scenarios occur:
 - Participant is adherent with glucocorticoid replacement and asymptomatic, or

- Any symptoms or signs related to mild to moderate adrenal insufficiency responded promptly to an increased dose of glucocorticoid treatment as determined by the Investigator.
- Participants receiving supraphysiologic glucocorticoid therapy due to severe (hypotensive) adrenal insufficiency are to discontinue study drug until clinical resolution and at least 5 half-lives (~5 days) have elapsed, and the participant has resumed the prestudy glucocorticoid regimen. If in the Investigator's judgment, the benefit versus risk balance weighs in favor of resuming study drug, SRC approval would be required.

Table 4: Signs and Symptoms of Adrenal Insufficiency

Cortisol Deficiency	Aldosterone Deficiency
Fatigue, anorexia, nausea, vomiting, abdominal pain, muscle or joint pain, weakness, lethargy, fever, confusion, coma. Laboratory findings: hyponatremia, hypoglycemia, inappropriately low serum cortisol levels, anemia, hypercalcemia	Orthostatic hypotension defined as: decrease in systolic blood pressure ≥ 20 mm Hg and/or a decrease in diastolic blood pressure ≥ 10 mm Hg upon standing for 2 to 5 minutes compared to supine blood pressure. If the participant is unable to stand, blood pressure and pulse may be taken sitting up with legs dependent. Laboratory findings: hyperkalemia, low aldosterone, hyponatremia, elevated renin
Hypotensive Adrenal Insufficiency	
Acute deterioration in health status including, but not limited to, the above signs and symptoms associated with absolute hypotension (systolic blood pressure < 100 mm Hg) or relative hypotension (systolic blood pressure ≥ 20 mm Hg lower than usual), with features that resolve within 1 to 2 hours after parenteral glucocorticoid administration (ie, a marked resolution of hypotension within 1 hour and improvement in clinical symptoms over a period of 2 hours) (Rushworth 2019).	

8. DISCONTINUATION OF STUDY DRUG AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

8.1. Discontinuation of Study Drug

All participants will be informed that they have the right to withdraw from study drug dosing at any time, for any reason, without prejudice, and without having to justify their reasons or decisions. Participants who stop study drug administration early may remain in the study so they may receive all scheduled safety monitoring procedures. Temporary discontinuation of study drug with rechallenge may be considered as appropriate (see Section 8.1.4). Permanent discontinuation from CRN04894 will require discontinuation from the study, and EOS Visit and procedures should be completed as indicated by the study protocol.

Reasons for the Investigator to permanently discontinue the participant from study drug and from the study are found in Section 8.1.1.

The Investigator is to record the reason for discontinuation and provide or arrange for appropriate follow-up for such a participant.

8.1.1. Criteria for Permanent Study Drug Discontinuation and Discontinuation from Study

Reasons for the Investigator to discontinue the participant from further study participation include but are not limited to:

1. Occurrence of AEs for which study treatment, protocol-specified noninvestigational product, and/or study participation discontinuation is desired by the participant or considered necessary by the Investigator or the Medical Monitor.
2. Positive pregnancy test
3. Indication of clinically significant cardiac symptoms or findings, including but not limited to:
 - a. Based on the average of triplicate ECGs, QTcF >500 msec (or QTcF >530 msec in participants with a bundle branch block) repeated on a second set of ECGs at least 2 hours apart and confirmed by the Investigator.
 - b. An increase in QTcF >60 msec from Baseline with an absolute QTcF <500 msec (confirmed by the Investigator) based on the average of triplicate ECGs.
 - c. Any ventricular tachyarrhythmia associated with symptoms of hemodynamic response
 - d. Sustained ventricular tachycardia (lasting >30 seconds) irrespective of symptoms
 - e. Torsades de pointes
 - f. Cardiac arrest
 - g. Cardiac pause >5 seconds observed on ECG
 - h. Type II second degree block or third-degree atrioventricular block
 - i. New occurrence of clinically significant, symptomatic bradycardia
 - j. Initiation of a concomitant medication during the study which prolongs the QT interval and is associated with Torsades de pointes (<https://crediblemeds.org/>)

- k. Any supraventricular tachyarrhythmia associated with symptoms of hemodynamic response
4. Other clinically significant drug-related abnormalities
5. SRC decision based on the occurrence of severe (hypotensive) adrenal insufficiency
6. Liver function stopping criteria (see Section 8.1.2)
7. Investigator's decision (ie, if in the Investigator's opinion it is not in the best medical interest for the participant to continue participation in the study for reasons other than AEs such as behavioral, compliance or administrative reasons)
8. A need for prohibited concomitant therapy (as listed in Section 6.3.3). Any exposure to a prohibited concomitant medication should be discussed promptly with the Medical Monitor
9. Any other protocol deviation that may result in a significant risk to the participant's safety or protocol deviations that will interfere with assessment of the efficacy of this study, including participant's noncompliance with the study procedures/study protocol.
10. Inability to fulfill study requirements and procedures
11. Death

Participant Early Study Discontinuation In case of early discontinuation of study participation, study drug will be discontinued, and an early termination EOS Visit (refer to the [Schedule of Activities](#) [SOA]) should be completed, particularly to ensure collection of AE follow-up data (if applicable) and to collect samples for laboratory evaluations. The Investigator is to record the reason for the study discontinuation and provide or arrange for appropriate follow-up for such a participant. In addition, the Investigator is to report the participant's withdrawal to the responsible Medical Monitor as soon as possible.

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent. If the participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

8.1.2. Liver Chemistry Stopping Criteria

Closely monitoring abnormalities of liver tests and discontinuation for evidence of liver injury will be performed according to the following process ([FDA 2009](#)):

- Detection of liver test abnormalities

All participants will have a serum chemistry panel as per the SOAs. Confirmation of detected liver test abnormalities is required for any participant with 1 or more of the following:

- ALT or AST $>3 \times \text{ULN}$ (for participants with ALT and AST $<\text{ULN}$ 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 $<\text{ULN}$ at Baseline);

- TB $>2\times$ ULN and $>2\times$ Baseline (for participants with TB $>$ ULN at Baseline);
- Alkaline phosphatase (ALP) $>3\times$ ULN (for participants with ALP $<$ ULN at Baseline);
- ALP $>3\times$ ULN and $>2\times$ Baseline (for participants with ALP $>$ ULN at Baseline).
- Confirmation of detected liver test abnormalities.

If any of the above-listed liver test abnormalities are detected, they should be followed by repeat testing within 48 to 72 hours (of ALT, AST, ALP, and TB) to confirm the abnormalities and to determine if they are increasing or decreasing. There also should be an inquiry made about symptoms.

If the above-listed liver test abnormalities (and/or related symptoms) persist or worsen, it is appropriate to initiate close observation to determine whether the abnormalities are improving or worsening over time. (See Close observation recommendations below.) If close monitoring is not possible, the drug should be discontinued.

- Close observation of any participant with detected liver test abnormalities.

Close observation includes:

- Repeating ALT, AST, ALP, and TB tests 2 to 3 times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the study drug has been discontinued and the participant is asymptomatic;
- Obtaining a more detailed history of symptoms and prior or concurrent diseases;
- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets;
- Ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; nonalcoholic steatohepatitis; hypoxic/ischemic hepatopathy; and biliary tract disease;
- Obtaining a history of exposure to environmental chemical agents;
- Obtaining additional tests to evaluate liver function, as appropriate (eg, international normalized ratio);
- Considering gastroenterology or hepatology consultations.

Permanent discontinuation of study drug for abnormal liver tests is required when a participant meets 1 of the conditions outlined below:

- ALT or AST $>8\times$ ULN;
- ALT or AST $>5\times$ ULN for more than 2 weeks;
- ALT or AST $>3\times$ ULN and TB $>2\times$ ULN or international normalized ratio (INR) >1.5 ;
- ALT or AST $>3\times$ ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ($>5\%$).

8.1.3. Temporary Discontinuation

Temporary study drug discontinuation of study drug of up to 10 days due to toleration (including adrenal insufficiency) may be allowed.

8.1.4. Rechallenge

If in the Investigator's judgment, the benefit versus risk balance weighs in favor of resuming study drug after a temporary study drug interruption, the Medical Monitor should be consulted.

Participants receiving supraphysiologic glucocorticoid therapy due to severe (hypotensive) adrenal insufficiency are to discontinue study drug until clinical resolution and at least 5 half-lives (~5 days) have elapsed. If in Investigator's judgment, the benefit versus risk balance weighs in favor of resuming study drug at a lower dose, SRC approval would be required.

8.2. Lost to Follow-up

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study drug. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

8.3. Criteria for Study Termination

The Sponsor reserves the right to discontinue the study at any time for any reason. Such reasons include but are not limited to the following:

- Inefficacy of the study medication
- Results from ongoing safety monitoring
- Unacceptable changes in the benefit-risk profile of the study medication
- Other medical or ethical reasons
- Regulatory Authorities/Institutional Review Boards/Independent Ethics Committees (IRBs/IECs) also have the right to terminate the study for any reason. In the event the study is terminated, the Institutional Review Boards/Independent Ethics Committees (IRBs/IECs) and Competent Authorities will be notified of the relevant decision.

9. STUDY ASSESSMENTS AND PROCEDURES

- The [Schedule of Activities](#) is the primary source for conduct of study assessments and procedures (activities).
- Section [12.2](#) provides all clinical laboratory analytes that will be assessed in this study. Refer to the Laboratory Manual for specimen collection details and instructions.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study drug.
- Section [6.3](#) provides lifestyle considerations.
- The timing (time of day and order) of activities should be performed as specified.
- The following screening tests may be repeated once if a result, in the opinion of the Investigator, is due to a transient factor and not an accurate representation of the normal state of the participant: any vital sign, ECG, clinical laboratory parameter(s), and drug screens.
- If practical, measurements also can be repeated if clinically significant (including out of range measurements) or machine/equipment error(s) occur, at the Investigator's discretion.
- Blood samples collected in this study may be stored for a maximum of 2 years (unless otherwise specified [eg, future biomarker analyses] or according to local regulations) after the study is completed at a facility selected by the Sponsor to enable further analysis of protocol-specified assessment.

9.1. Administrative and General/Baseline Procedures

Refer to the [Schedule of Activities](#) for Baseline procedures.

9.2. Efficacy Assessments

Planned time points for all efficacy assessments are provided in the [Schedule of Activities](#).

9.2.1. Magnetic Resonance Imaging

Adrenal MRI should be performed locally at visits specified in the Schedule of Activities. Tomography is not permitted as a replacement for MRI. Image acquisition standards will be provided and must be followed to allow proper evaluation of adrenal volume. All MRI assessments will be assessed by the Investigator for any findings that require immediate medical attention and will also be read by an MRI central radiologist. The clinical significance of any MRI findings will be determined by the Investigator, including after the central reading result is available. However, only MRI results provided by the local report will be recorded in the eCRF. Management of participants prior to and during the MRI should follow standard local procedures.

9.2.2. Ultrasound

██████████ will be performed according to the study site procedures for the evaluation at visits specified in the Schedule of Activities (Section 2.3). An ultrasound is required for all male participants. The results will be recorded. All ultrasound assessments will be assessed by the Investigator for any findings that require immediate medical attention and will also be read by an ultrasound central radiologist. The clinical significance of any ultrasound findings will be determined by the Investigator, including after the central reading result is available. However, only ultrasound results provided by the local report will be recorded in the eCRF. Management of participants prior to and during the ultrasound should follow standard local procedures.

9.2.3. Circadian Rhythm Assessment

For Cohorts 1-3, at specified visits, participants will be admitted to a metabolic unit for 24-hour Circadian Rhythm Assessments. 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 study treatment (between Day 12 to Day 17, and Day 70 to Day 86). Blood will be drawn for measurement of PK (Visits of Day 12 to Day 17 and Day 70 to Day 86 only), ACTH, A4, 17-OHP, ██████████ 11-DOC, ██████████ 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, ██████████, and testosterone except at 02:00 (to allow the participant to sleep). In addition, blood will be drawn for testosterone, ██████████ once at 06:00.

9.2.4. PD Biomarker Draws

For Visits 2-7 (Visits 2-8 for Cohort 4): Prior to receiving the morning GC replacement dose, (and CRN04894 dose if applicable for Cohort 4), 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 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 ICF is signed. For Screening Visit 2 (Week -2): Blood draw should be done prior to receiving the morning GC dose. Participants in Cohorts 1-3 who are included in the circadian assessments will not have PD biomarkers or PK samples redrawn on Visits 3, 4, or 6 if the circadian assessment and the visit fall on the same day.

9.3. Immunogenicity Assessments

CRN04894 is small, synthetic, nonpeptide molecule, and therefore, not likely to be immunogenic. Immunogenicity assessments will not be conducted in this study.

9.4. Safety Assessments

Safety endpoints and parameters are provided in Section 4. The following subsections summarize the safety assessments/procedures. Refer to the [Schedule of Activities](#) for specifics.

9.4.1. Physical Examinations

Perform a full physical examination and measure body weight and waist circumference at the time points specified in the SOA. Height and body mass index (BMI) are to be measured once, at Screening. Examination is to include assessment of head (external), eyes, ears, nose, and throat, lungs, cardiovascular system, abdomen, musculoskeletal system, skin, lymph nodes, central nervous system (CNS), and, where appropriate, other body systems.

A symptom-directed physical examination due to an AE or other available safety data may be conducted as an unscheduled assessment.

9.4.2. Vital Signs

Measure vital signs (resting and standing blood pressure, resting respiratory rate, and body temperature) as per standard practice at the time points specified in the [Schedule of Activities](#).

Standard blood pressure should be measured in the supine position after resting for 5 minutes. Measure standing blood pressure and standing pulse rate after the participant has been supine for 5 minutes followed by standing for 2 to 5 minutes.

9.4.3. Electrocardiograms

Collect ECGs at the time points specified in the [Schedule of Activities](#). The ECG assessment is to be a standard 12-lead ECG performed in triplicate (1 to 3 minutes apart) after the participant has rested quietly in the supine position for at least 10 minutes without significant stimulation (noise, television, etc.). Additional ECGs outside of the planned assessments are to be collected, per protocol, if clinically indicated (eg, participants with palpitations, lightheadedness).

The ECG parameters that are to be assessed include a summary of findings as well as measurement of the pulse rate, time interval between Q and T wave (QT), corrected QT by the Fridericia formula (QTcF), and time interval between P and R waves (PR), and time interval of the QRS complex (QRS duration) based on the ECG machine readings.

All ECG assessments will be initially assessed by the Investigator for any findings that require immediate medical attention and will also be read by an ECG central reader. The clinical significance of any ECG findings will be determined by the Investigator, including after the central reading result is available. Only the Investigator's assessment will be recorded in the eCRF. Any potentially significant outlier values should be confirmed by the central ECG reader. Any ECG measurement determined to be clinically significant (occurring after signing the ICF) will be noted as an AE on the appropriate eCRF page(s). Such abnormalities will be monitored until the end of the study or until resolution if considered related to the study drug.

9.4.4. Clinical Safety Laboratory Tests

Refer to Section 12.2 for the list of clinical laboratory tests to be performed and to the [Schedule of Activities](#) for the timing and frequency.

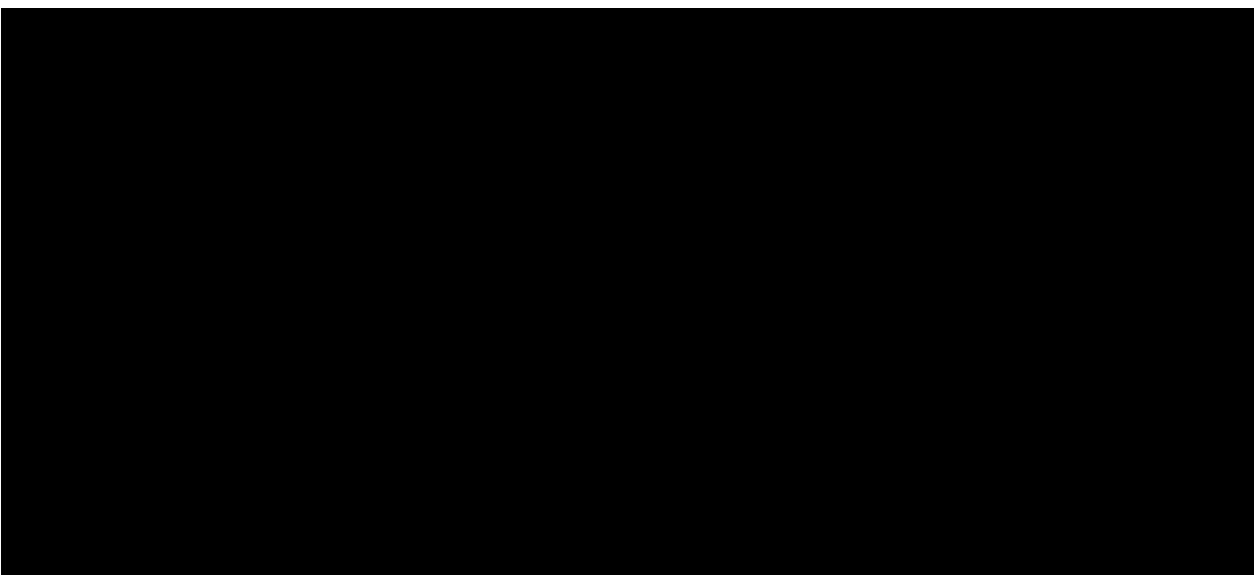
- Safety laboratory tests are to be performed by the central laboratory. Reference ranges will be per the central laboratory. Laboratory assessments are to be conducted in accordance with the Laboratory Manual and the [Schedule of Activities](#).
- The Investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as AEs. The laboratory reports must be filed with the source documents. Section [12.3.1](#) defines clinical laboratory AEs and Section [12.3.8](#) outlines recording procedures.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.
 - If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified.

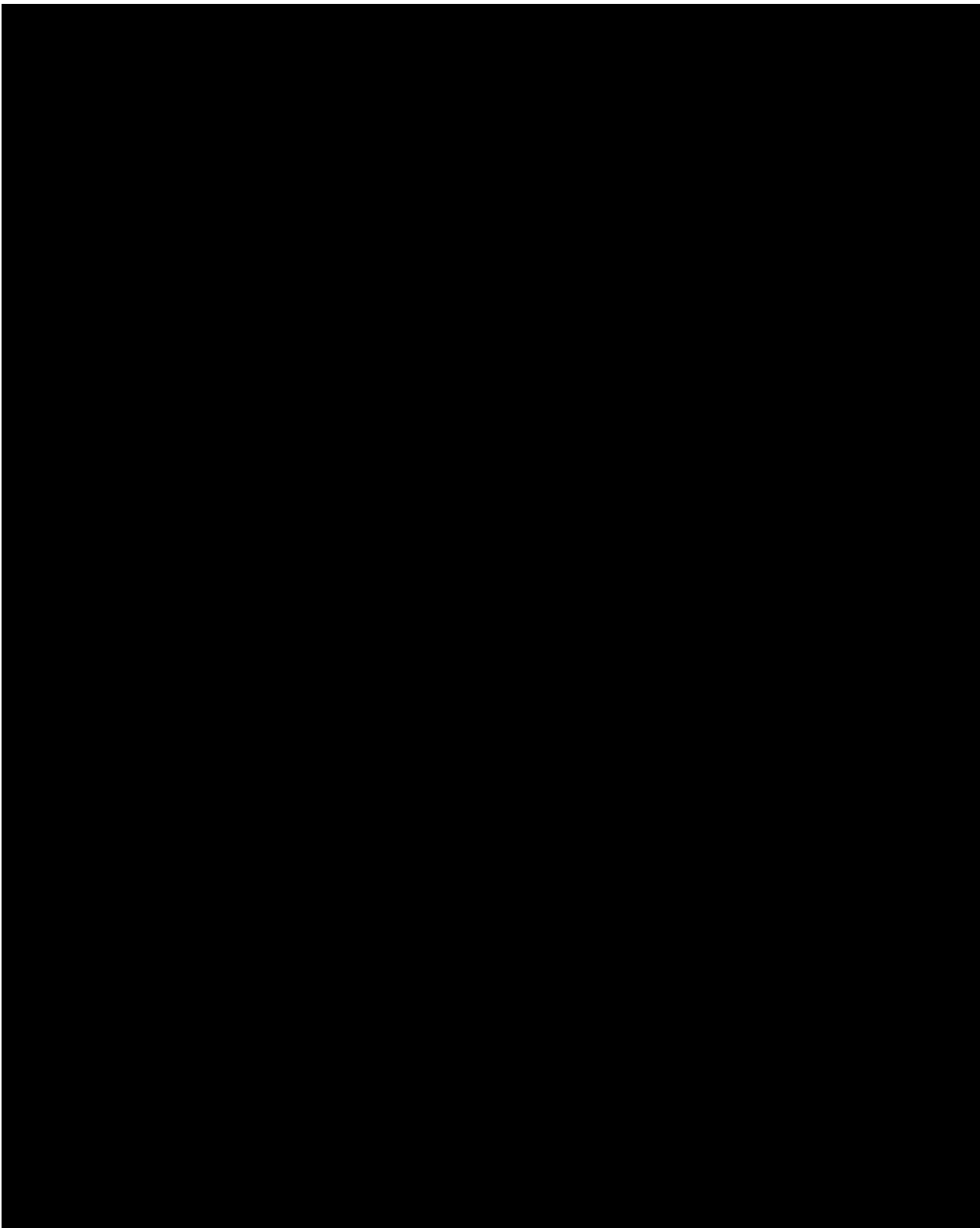
9.4.5. Pregnancy Testing

Refer to Section [6.1](#) Inclusion Criteria for a list of laboratory pregnancy testing entry criteria.

- Pregnancy testing (urine or serum as required by local regulations) should be conducted as per the [Schedule of Activities](#).
- Pregnancy testing (urine or serum as required by local regulations) should be conducted at the end of relevant systemic exposure plus an additional 14 days and correspond with the time frame for female participant contraception in Section [6.1](#), Inclusion Criteria.

Additional serum or urine pregnancy tests may be performed, as determined necessary by the Investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.





9.5. Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of AEs and SAEs can be found in Section [12.3](#).

- An AE is the development of an untoward medical condition or the deterioration of a preexisting medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product and occurring after the moment of signing the ICF until the final follow-up contact.
- An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) during a clinical study, even if no study drug has been administered.
- TEAEs are AEs occurring or worsening after administration of study drug.

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up on all AEs or SAEs whether or not considered related to the study drug or study procedures, or that caused the participant to discontinue the CRN04894. This includes events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section [12.3.7](#).

9.5.1. Time Period and Frequency for Collecting AE and SAE Information

- All AEs and SAEs will be collected starting from the signing of the ICF until 4 weeks after the last dose of study drug. When an AE/SAE occurs, it is the responsibility of the Investigator to collect and review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator is to then record all relevant AE/SAE information in the eCRF and report all SAEs on the paper SAE Report Form.

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours of first awareness, as indicated in Section [12.3.9](#). The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the Investigator considers the event to be reasonably related to the study drug or study participation, the Investigator must promptly notify the Sponsor.

9.5.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

9.5.3. Follow-up of AEs and SAEs

- After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AEs of special interest

(as defined in Section 9.5.8) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 8.2). Further information on follow-up procedures is provided in Section 12.3.

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If the participant dies during participation in the study or during a recognized follow-up period, the Investigator is to provide the Sponsor or designee with a copy of any postmortem findings including histopathology, to the extent practical.

9.5.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities for the safety of participants and the safety of a study drug under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local Regulatory Authority and other regulatory agencies about the safety of a study drug under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the Regulatory Authority, Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), and Investigators.
- An Investigator who receives an Investigator Safety Report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB/package insert or other documents and will notify the IRB/IEC, if appropriate according to local requirements.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to Investigators, as necessary.

9.5.5. Pregnancy

- Details of all pregnancies in female participants and female partners of male participants must be collected after the participant signs the ICF and until time period aligning with the postintervention contraception determined in Section 6.1.
- Any pregnancy that occurs in a study participant or partner of a male participant (after obtaining the necessary signed informed consent from the female partner) during the course of the study as defined above must be reported by the Investigator to Crinetics Pharmacovigilance (PV) Department by completing and emailing the initial Pregnancy Exposure Form within 24 hours of the Investigator or site study staff first becoming aware of the pregnancy to [REDACTED].
- Every effort should be made to gather information regarding the participant or pregnant female partner and neonate, and/or pregnancy outcome. It is the

responsibility of the Investigator to obtain this information within 30 calendar days after the initial notification of the pregnancy exposure and approximately 30 calendar days postpartum. The Investigator must forward the information to the Crinetics PV department by submitting a follow-up Pregnancy Exposure Form within 24 hours of the Investigator or site study staff first becoming aware of the follow-up information to [REDACTED].

- Any pregnancy complication or elective termination of a pregnancy for medical reasons must be reported as an SAE by submitting an SAE Report Form within 24 hours of the Investigator or site study staff first becoming aware of the outcome to [REDACTED].
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) must be reported as an SAE by submitting an SAE Report Form within 24 hours of the Investigator or site study staff first becoming aware of the outcome to [REDACTED].
- Any poststudy pregnancy-related SAE considered reasonably related to the study drug by the Investigator must be reported as an SAE by submitting an SAE Report Form within 24 hours of the Investigator or site study staff first becoming aware of the outcome to [REDACTED]. While the Investigator is not obligated to actively seek this information in a former study participants/pregnant female partner, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study drug or be withdrawn from the study.

9.5.6. Cardiovascular and Death Events

Not applicable.

9.5.7. Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

Not applicable.

9.5.8. 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, the following event is considered to be an AESI.

- Adrenal insufficiency (see Section [7.9.1](#))

9.6. Pharmacokinetics

During the treatment period, blood samples will be collected for the measurement of CRN04894 concentration in plasma and whole blood (using Mitra volumetric absorptive microsampling [VAMS]) as specified in the [Schedule of Activities](#). Instructions for the collection and handling of biological samples will be provided by the Sponsor in the Laboratory Manual. The actual date and time (24-hour clock time) of collection of each sample will be recorded. The actual date and time of last dose of study drug prior to each sample collection will also be recorded. Participants

in Cohorts 1-3 who are 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.

For Cohort 4, the CRN04894 dose and morning GC dose (if applicable) will be held and administered in clinic. At Visits 4 and 8 (Week 2 and Week 12), PK sampling will occur at predose, 1, 2, 4, and 6 hours (± 20 minutes) post dose, and a Mitra VAMS PK sample will be collected by the study participant at home approximately 12 to 18 hours post dose. Fasting status will be collected.

At Visit 6 (Week 8), PK sampling will occur at predose and 1 hour (± 20 minutes) post dose. Fasting status will be collected.

CRN04894 concentrations in plasma and whole blood will be listed and summarized by cohort and study day at each scheduled collection time point with descriptive statistics.

9.7. Pharmacodynamics

A pharmacodynamic biomarker panel (17-OHP, ACTH [plasma], testosterone, A4, [REDACTED], 11-DOC, [REDACTED], [REDACTED], aldosterone, and renin) will be measured as timepoints specified in the [Schedule of Activities](#). 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.

9.8. 24-hour Circadian Rhythm Assessments

At selected sites with 24-hour blood sampling capabilities, participants in Cohorts 1-3 will be invited to participate in 3 inpatient circadian assessments. These assessments will take place between Day -7 to Day 1, between Day 12 to Day 17, and again 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, 22:00 (predose), 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.

9.9. Genetics

Mutations in the CYP21A2 gene cause varying degrees of loss of 21-hydroxylase activity, resulting in different phenotypes. Genotyping data collected from this study may be pooled with data from other CRN04894 studies for analysis.

10. STATISTICAL CONSIDERATIONS

A full description of the analysis details will be provided in the statistical analysis plan (SAP). The SAP will be finalized before database lock, for the final analysis.

10.1. Statistical Hypothesis

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

10.1.1. Multiplicity Adjustment

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

10.2. Analysis Sets

The Full Analysis Set includes all participants who received at least one dose of CRN04894. The Full Analysis Set will be used for all demographics, disease characteristics, safety, and efficacy summaries.

10.3. Statistical Analyses

The study SAP will be finalized before database lock, and it will include a more technical and detailed description of the statistical analyses described in this section. This section provides a summary of the planned statistical analyses.

10.3.1. General Considerations

Descriptive statistics, including number of nonmissing observations, arithmetic mean, standard deviation, median, first and third quartiles, minimum, and maximum will be used to summarize continuous endpoints. The number of participants and percentages in each level will be used to summarize categorical endpoints. Unless specified otherwise, missing or unreported categorical results will be included in the summary and the number of participants in the Full Analysis Set will be used as denominator.

10.3.2. Safety Analysis

Safety endpoints include study drug exposure, AEs, clinical laboratories, vital signs, and 12-lead ECGs. Unless specified otherwise safety endpoints will be summarized by cohort and overall.

10.3.2.1. Drug Exposure

CRN04894 treatment exposure will be summarized by cohort. Exposure summaries will include number of doses, duration of treatment, and actual dose received.

10.3.2.2. Adverse Events

The AEs will be summarized by cohort and overall. AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 25.0 or later.

TEAEs are defined as AEs that occur or worsen at the time of or following the administration of the first dose of study drug. If the time of the AE or study drug administration is not available, then TEAEs will be those occurring on or after the first day of the administration of study drug. AEs that are not treatment-emergent will not be included in the summary but will be included in the listing.

A summary table of AEs will be presented detailing the number and percentage of participants, and number of events for the following categories:

- At least one TEAE
- At least one study drug-related TEAE
- At least one severe TEAE
- At least one serious TEAE
- At least one study drug-related serious TEAE
- At least one TEAE leading to treatment discontinuation

Treatment-related AEs are defined as those AEs with relationship to study drug as “Related.”

The incidence of TEAEs will be presented using counts, percentage, and number of events by System Organ Class (SOC) and preferred term (PT). SOC's will be sorted in descending frequency and the PTs within each SOC will be sorted in descending frequency based on the percentage of AEs for all participants. A participant who has multiple occurrences of an event associated with a particular SOC or a PT within a SOC, will only be counted once for the that SOC and/or PT. Separate summaries for each of the categories in the overall AE summary table will be created by SOC and PT.

In addition to the AE summaries by SOC and PT, the following will be presented by descending frequency of PT based on the percentage of AE for all participants

- TEAEs
- Treatment-related TEAEs
- Severe TEAEs

The following additional listings will be provided:

- Listing of SAEs
- Listing of TEAEs leading to treatment discontinuation
- Listing of Severe TEAEs
- Listing of deaths

10.3.2.3. Clinical Laboratory Tests

All continuous laboratory parameters in hematology and clinical chemistry will be summarized descriptively at each clinical visit, together with the corresponding changes from Baseline. Other continuous clinical laboratory tests will be summarized in the same way. The number and

percentage of participants outside of the normal range (normal, low, and high) will also be summarized by visit.

Time profile of mean and standard error of change from Baseline of laboratory tests of interest will be plotted.

All of the laboratory results will be listed including both scheduled and unscheduled results and results outside of the normal reference will be noted on the listing.

10.3.2.4. Vital Signs, Weight, and Waist Circumference

Vital signs include blood pressure (resting and standing), resting respiratory rate, and temperature. Vital signs, weight, and waist circumference will be summarized descriptively at each clinical visit. Time profile of mean and standard error of change from Baseline of waist circumference will be plotted.

All vital signs, weight, and waist circumference measurement will be included in the listings including both scheduled and unscheduled results.

10.3.2.5. Electrocardiogram

Standard 12-lead ECG data will be collected based on the schedule in Schedule of Activities. For all parameters (heart rate, QT, QTcF, PR intervals, and QRS) results at each visit and change from Baseline will be presented. The evaluation results will be summarized at each visit as well. The mean of the triplicates will be used for summary purposes.

All ECG measurements with the original triplicates results and evaluation results including both scheduled and unscheduled results will be listed.

10.3.3. Primary Efficacy Analysis

The primary efficacy endpoint is defined as the change from Baseline in early morning (before 11:00) serum A4 at Week 12. Analysis of Covariance (ANCOVA) will be used to analyze change from Baseline in A4. The model will include Baseline value as a covariate, and sex and dose cohort as fixed effects. Sensitivity analyses such as modeling the percent change from Baseline, inclusion of additional Baseline characteristics in the ANCOVA model, and nonparametric test might be carried out, and the details will be specified in the SAP. The change from Baseline at each postbaseline visit will be presented graphically with the box plots. The descriptive statistics will be presented by cohort and overall for A4 at each visit and corresponding change from Baseline.

10.3.4. Exploratory Analyses

Exploratory endpoints are specified in Section 4. For any continuous endpoint such as change from Baseline, by visit ANCOVA model with Baseline value as a covariate, sex and dose cohort as fixed effects will be used when applicable descriptive statistics will also be presented. For any categorical variables such as responder endpoints, the number of participants and corresponding percentage as well as exact binomial 95% confidence intervals will be presented.

10.4. 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 the efficacy and safety endpoints are planned to support regulatory interactions and decision-making.

10.5. Sample Size Determination

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 for Cohort 1 and/or Cohort 2. Cohort 4 will enroll an additional 6-12 participants.

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12. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

12.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

12.1.1. Regulatory and Ethical Considerations

- This clinical study will be conducted in accordance with the protocol and with the following:
 - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
 - Applicable ICH GCP guidelines
 - Applicable laws and regulations
- The protocol, ICF, IB, and other relevant documents including participant-facing documents (eg, advertisements, diary, PRO, etc.) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the clinical study is initiated.
- Any amendments and/or substantial modifications to the protocol will require IRB/IEC approval before implementation of changes made to the clinical study design, except for changes necessary to eliminate an immediate hazard to clinical study participants.
- Protocols and any substantial amendments and/or substantial modifications to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to clinical study participants.
- The Investigator will be responsible for the following:
 - Providing written summaries of the status of the clinical study to the IRB/IEC in accordance with the requirements, policies, and procedures established by the IRB/IEC
 - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
 - Providing oversight of the conduct of the clinical study at the site and adherence to requirements of ICH guidelines, the IRB/IEC, 21 CFR, European Directive 2001/20/EC for clinical trials, European Regulation 536/2014 for clinical trials, European Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations
 - Promptly report any suspected serious breaches to the Sponsor through the contact information provided by the Sponsor.

Declaration of Helsinki and amendments can be accessed via the website of the World Medical Association at <https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/>.

Conduct of the study must be approved by an appropriately constituted IRB or IEC. Approval is required for the Clinical Study Protocol, IB, Protocol Amendments, ICFs, and participant information sheet.

Amendments to the Clinical Study Protocol that entail corrections of typographical errors, clarifications of confusing wording, changes in study personnel, and minor modifications that have no impact on the safety of participants or the conduct of the study will be classified as administrative amendments and will be submitted to the IRB/IEC and regulatory authorities for information only. The Sponsor (or designee) will ensure that acknowledgment is received and filed. Amendments that are classified as substantial amendments must be submitted to the appropriate regulatory authorities and the IRBs/IECs for approval. The Sponsor (or designee) will comply with any local or national requirements that differ from the above (eg, a requirement to submit any amendment regardless of classification for review and approval).

Should protocol deviations that affect participant safety occur, the Sponsor must be informed as soon as possible. Important protocol deviations will be included in the Clinical Study Report (CSR). Reporting of protocol deviations to IRBs/IECs will be performed in accordance with applicable Regulatory Authority mandates and IRB/IEC policies.

All participants must meet all eligibility criteria in order to participate in the study. Protocol waivers for eligibility will not be granted by the Sponsor under any circumstances. If it is discovered that the participant did not meet all eligibility criteria during the course of a participant's post enrollment participation in the study, the participant will be discontinued.

12.1.2. Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial interest information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

12.1.3. Informed Consent Process

- The Investigator or his/her authorized designee will explain the nature of the clinical study, including the risks and benefits, to the participant or their legally authorized representative and answer all questions regarding the clinical study. The participant should receive information in a language that is easily understood.
- For each study participant, written informed consent will be obtained prior to any protocol-related procedures. An approved, up-to-date version of ICF must be signed and dated personally by the participant or, where the participant is not able to give informed consent, his or her legally designated representative and by the Investigator and/or the study team member designated by the Investigator to conduct the informed consent procedure. A signed and dated copy of the ICF will be given to the participant.

- As part of this procedure, the Investigator or one of their associates must explain orally and in writing the nature, duration, and purpose of the study, and the action of the drug in such a manner that the participant is aware of the potential risks, inconveniences, or adverse effects that may occur. The participant should be informed that they may withdraw from the study at any time, and the participant will receive all information that is required by local regulations and ICH guidelines. The participant must provide free and willing consent to enroll in the study. The Sponsor does not consider persons who are housed in an institution under a court or official order capable of providing free and willing consent. The Investigator will provide the Sponsor or its representative with a copy of the IRB/IEC approved ICF prior to the start of the study.
- A separate ICF form will be signed for participation in the Circadian Rhythm Assessments.
- If the applicable local regulations allow use of samples for future research or use of data for future research, the participant will be informed of the description and objectives of the future uses in the ICF. Investigator/site personnel will obtain participant consent for future use of specimen and/or data.

12.1.4. Recruitment Strategy

- Participating sites (clinical centers) will be selected based on their experience treating patients with CAH and their existing patient population. Sites will identify potential participants from their existing patient database and may call or inform the participants of the clinical study.

12.1.5. Data Protection in the European Economic Area

- The Sponsor, as Data Controller, will ensure that all processing activities involving personal data performed in the scope of this Study are compliant with the requirements set by EU General Data Protection Regulation (GDPR 2016/679), its subsequent amendments and any additional national laws on Data Protection, recommendations, and guidelines as applicable.
- To maintain participant privacy, data capture tools, study drug accountability records, study reports, and communications will identify participants by their unique identifier (assigned participant number) generated and assigned by the electronic data capture (EDC) system. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant will be informed both verbally and in written form (ICF) that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who may be required to give consent for their data to be used as described in the ICF, including use of their data that may require a separate consent. The participant will also be informed that his/her medical records may be examined by Clinical Quality

Assurance auditors, Monitors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

- To comply with the applicable rules on the protection of personal data, specifically regarding the implementation of the organizational and technical arrangements aiming to avoid unauthorized access, disclosure, dissemination, alteration or loss of information and processed personal data, the Sponsor has implemented and maintains the following measures:
 - restriction and monitoring of physical access to the offices and information processing facilities to employees, personnel and approved visitors;
 - ensuring appropriate and restricted user access relevant to the function and type of activity performed in relation to the clinical study;
 - implementing the pseudonymization and encryption of personal data, as appropriate;
 - implementing the ability to ensure the ongoing confidentiality, integrity, availability and resilience of processing systems and services;
 - implementing network, application, and database security by means of firewalls and antivirus/anti-malware; ensuring detection of malware purposed for unauthorized deletion, blocking, copying of information, disabling security measures and response to such attacks;
 - means to restore the availability and access to personal information in a timely manner in the event of a physical or technical incident;
 - logging of security events/incidents in information systems;
 - implementing procedures that cover reporting, analysis, monitoring and resolution of security incidents;
 - ensuring that information systems, computers and software involved in the performance of the services provided in the study are backed up;
 - a process for regularly testing, assessing and evaluating the effectiveness of technical and organizational measures for ensuring the security of the processing;
 - implementing procedures to capture within a reasonable time any personal data breaches;
 - implementing procedures and practices for the destruction of paper documents containing personal data;
 - implementing business continuity procedures ensuring continued provision of services through operational interruption.
- All locations, personnel and information systems that are used to perform services for the study will be covered.

- The Sponsor will ensure the technical and organizational security measures described above are regularly reviewed and updated considering any evolution of technological developments.
- The Sponsor may apply additional specific statutory requirements, where applicable in national laws, and will implement the necessary security measures even if they are not expressly listed above.
- In addition to the already mentioned technical and organizational measures, the Sponsor by means of internal measures and imposed standard contractual clauses to the selected contractors, service providers, vendors, or sub-contractors (collectively, “Representatives”) will ensure the confidentiality of records and personal data of participants.
- With exception of activities in the scope of onsite monitoring, the name of the patient will neither be asked for, nor recorded by Sponsor. An identification number will be allocated to each patient registered in the study. This number will identify the patient and will be included on all case report forms and corresponding material and data associated with the patient.
- Monitors acting on behalf of Sponsor will have access to fully identifiable information only in the scope of the onsite monitoring visits, and only for mandatory source data verification, including ICH GCP obligations, applicable to the conduct of the Study. Staff involved in the performance of this task are bound by any additional stricter confidentiality clauses imposed upon them, as compared to other staff members.
- The Sponsor has implemented a functional process for reporting of any data breach occurring at Crinetics’ or its Representatives’ facilities and premises. Investigators must promptly report to the Sponsor's Data Protection Officer (DPO) any suspected data breaches relevant to personal study-related data the Sponsor holds about the participants. If there is a suspected breach related to data that the Sponsor holds, the Sponsor’s DPO will be responsible for investigating suspected data breaches and notifying authorities, where appropriate. In case of the occurrence of any data breach, the Sponsor will immediately apply relevant measures to mitigate the risks to data subjects as appropriate in relation to the specific context of the data breach, considering its source, underlying intentions, possibilities of recovery etc. Any data breach presenting risks to the rights and freedoms of data subjects will be reported to the relevant supervisory data protection authority within 72 hours of the Sponsor becoming aware of the data breach. In addition, in case of a high-risk data breach, subjects will be informed by the Sponsor.

Investigators must promptly report to the Sponsor's DPO any participant’s request to know what personal study-related data the Sponsor holds about the participant.

12.1.6. Safety Review Committee

An SRC composed of Crinetics physicians, 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, PK, 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 [REDACTED] 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. Please refer to the SRC charter for more details.

12.1.6.1. 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 to 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 complete 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.

12.1.7. Dissemination of Clinical Study Data

Where required by applicable regulatory requirements, an Investigator Signatory will be identified for the approval of the CSR. The Investigator is to be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results.

Where required by applicable regulatory requirements, the Sponsor will also provide all Investigators with the full summary of the study results. The Investigator is encouraged to share the summary results with the study participants, as appropriate.

Study information from this protocol may be posted on the US National Institutes of Health's website www.ClinicalTrials.gov and other publicly-accessible websites where required and/or permitted. Tabular results of this study may be posted on said websites. In addition, results may also be published in peer-reviewed publications, to ensure the scientific integrity and credibility of publication activities performed by or on behalf of the company.

12.1.8. Data Quality Assurance

The study will be conducted according to GCP as outlined by ICH topic E6. The CRO maintains a quality assurance system with written Standard Operating Procedures (SOPs) to ensure that clinical studies are conducted, and data are generated, documented, and reported in compliance with the Clinical Study Protocol, GCP, and applicable regulatory requirements.

The Sponsor or its designee will perform the quality assurance and quality control activities of this study. However, responsibility for the accuracy, completeness, and reliability of the study data presented to the Sponsor lies with the Investigator generating the data.

The Sponsor will arrange audits as part of the implementation of quality assurance to ensure that the study is being conducted in compliance with the Clinical Study Protocol, SOPs, GCP, and all applicable regulatory requirements. Audits will be independent of and separate from the routine monitoring and quality control functions. Procedures will be performed at the study sites and during data management to assure that safety and efficacy data are adequate and well-documented. Study records and source documents must be preserved for at least 25 years after the completion or discontinuation of/withdrawal from the study or 2 years after the last approval of a marketing application in an ICH region or as per local requirements, whichever is the longer time period.

The Investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of participant health information. The Investigator shall ensure that study participants authorize the use and disclosure of protected health information in accordance with EU GDPR Regulation (EU) 2016/679 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data and in a form satisfactory to the Sponsor.

- All participant data relating to the study will be recorded on printed or electronic case report forms (CRFs) unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided to Investigators.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections, and provide direct access to source documents.
- Quality tolerance limits (QTLs) will be predefined in the Study Project Plan to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the CSR.
- The monitoring plan will contain details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or onsite monitoring).
- The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, CROs).

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years after the completion of the study or discontinuation/withdrawal from the study or longer, if required by applicable local and national regulations or institutional policies retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

12.1.9. Source Documents

The study will be monitored to ensure that it is conducted and documented properly according to the Clinical Study Protocol, GCP, and all applicable regulatory requirements.

Before the study begins, at a site initiation visit or at an Investigator's meeting, a Sponsor representative will review the protocol and the eCRF with the Investigators and their staff.

During the study, onsite monitoring visits will be made at appropriate times. Site monitors will visit the site regularly to check the completeness of participant records, the accuracy of entries on the eCRF, the adherence to the Clinical Study Protocol and to GCP, the progress of enrollment, the completeness of the Investigator Site File, and to ensure that study drug is stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the site monitor during these visits.

Source documents, which will be filed at the Investigator's site, provide evidence for the existence of the participant and substantiate the integrity of the data collected.

The Investigator must give the site monitor access to all relevant source documents to confirm their consistency with the eCRF entries. Full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables will be checked. Additional checks of the consistency of the source data with the eCRFs will be performed according to the study specific monitoring plan. No information in source documents about the identity of the participants will be disclosed.

12.1.10. Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site activated and will be the study start date.

Study/Site Termination

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected, any open data queries have been closed, and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

For study termination:

- Discontinuation of further study drug development

For site termination:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator
- Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should ensure appropriate participant therapy and/or follow-up.

12.1.11. Publication Policy

Both the use of data and the publication policy are detailed within the clinical trial agreement. Intellectual property rights (and related matters) of the Investigator and others performing the clinical study will be subject to the terms of a clinical trial agreement between the Institution and the Sponsor and/or their designee. With respect to such rights, the Sponsor or its designee will solely own all rights and interests in any materials, data, and intellectual property rights developed by Investigators and others performing the clinical study described in this Clinical Study Protocol, subject to the terms and conditions of the clinical trial agreement and any applicable laws. To facilitate such ownership, Investigators will be required to assign all such inventions directly to the Sponsor as will be set forth in the clinical trial agreement or another agreement as appropriate.

12.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in [Table 5](#) will be performed by the central laboratory.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study drug administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study drug decision or response evaluation, the results must be recorded.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in [Section 6](#) of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 5: Protocol-required Laboratory Tests

Laboratory Tests	Parameters		
Hematology	Platelet count		
	HbA1C		
	Red blood cell (RBC) count/Hemoglobin /Hematocrit		
	RBC indices:	MCV MCH %Reticulocytes	
	White blood cell (WBC) count with differential:	Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Hematology (coagulation)	PT/INR	PTT	
Clinical chemistry ^a	BUN Potassium Creatinine (and eGFR) Sodium Calcium Glucose (fasting) Fasting lipid panel	AST/SGOT ALT/SGPT Alkaline phosphatase ^b Total and direct bilirubin Total protein Uric acid Chloride	Phosphorus Magnesium Albumin Indirect bilirubin Amylase Lipase Bicarbonate Fructosamine ^c
Hormones	Free T4 TSH [REDACTED]/FSH	SHBG [REDACTED]	Aldosterone [REDACTED]

Laboratory Tests	Parameters		
PD biomarkers (See Section 9.2.4)	17-OHP ACTH (plasma) Testosterone A4 11-DOC		
PK	PK parameters		
21-hydroxylase gene mutation screening	Gene mutation analysis		
Circadian rhythm assessments (blood and saliva) collected every 4 hours for 24 hours (see Section 9.2.3)	PK ACTH (plasma) A4 17-OHP	11-DOC	Drawn once at 06:00: Testosterone
Routine urinalysis	pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase Microscopic examination (if blood or protein is abnormal)		
Pregnancy testing	Highly-sensitive serum or urine hCG pregnancy test (as needed for women of childbearing potential) ^d FSH (as specified in Section 6.1 in women of nonchildbearing potential only)		
Toxicology	Serum or urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, and opiates) ^e		
Serology	HIV antibody, HBsAg and hepatitis C virus antibody		

[REDACTED]; 11-DOC=11-Deoxycorticosterone; [REDACTED]
 [REDACTED]; 17-OHP=17-hydroxyprogesterone; A4=androstenedione; ACTH=adrenocorticotrophic hormone; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; [REDACTED]; ECG=electrocardiogram; EOS=end of study; FSH=follicle-stimulating hormone; HbA1C=hemoglobin A1C; HBsAg=hepatitis B surface antigen; hCG=human chorionic gonadotropin; HIV=human immunodeficiency virus; INR=international normalized ratio; LH=luteinizing hormone; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; PK=pharmacokinetic; PT=prothrombin time; PTT=partial thromboplastin time; RBC=red blood cell; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; SHBG=sex hormone binding globulin; T4=thyroxine; TSH=thyroid-stimulating hormone; WOCBP=women of child bearing potential.

^a Details of liver chemistry stopping criteria and required actions and follow-up are given in Section 8.1.2. Must be reported to the Sponsor in an expedited manner.

^b If alkaline phosphatase is elevated, consider fractionating

^c Fructosamine will be tested only if HbA1c is not evaluable as noted in Exclusion Criteria #8 and will be conducted at the site's local laboratory.

^d Serum pregnancy test to be conducted by central lab at Screening and urine pregnancy test at all other time points. These tests should be conducted locally unless otherwise specified by local regulations or in the judgment of the Investigator.

^e Alcohol screen will only be conducted at the discretion of the Investigator and will be conducted at the site's local laboratory.

12.3. Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of participants and is mandated by regulatory agencies worldwide. All clinical studies conducted by Crinetics will be in accordance with SOPs that have been established to conform to regulatory requirements worldwide to ensure appropriate reporting of safety information.

All AEs and SAEs are collected from the time of signing the informed consent up to 4 weeks after the last dose of investigational product. Participants should be informed that they do not have to wait for a scheduled visit to report AEs. At any time up to 4 weeks from the last dose of study treatment, the Investigator may report any SAE that he/she believes is possibly related to study treatment.

Where possible, a diagnosis rather than a list of symptoms should be recorded. All AEs should be captured on the appropriate AE pages in the source documents and the eCRF. The Investigator will assess the relationship of all AEs to the study drug. For information on the safety profile obtained to date for CRN04894, refer to the IB.

12.3.1. Definition of Adverse Event

An AE is any untoward medical occurrence in a clinical investigational participant administered a pharmaceutical product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. This includes any newly occurring event or previous condition that has increased in severity or frequency since the administration of study drug.

Study assessments including laboratory tests, ECGs, physical examinations, and vital signs should be performed and those deemed a clinically significant worsening from Baseline will be documented as an AE. When possible, a clinical diagnosis for the study assessment should be provided rather than the abnormal test result alone (eg, urinary tract infection, anemia). In the absence of a diagnosis, the abnormal study assessment itself should be listed as the AE (eg, bacteria in urine or decreased hemoglobin).

Investigators will be requested to evaluate abnormal study assessments for clinical significance.

This would include:

- Worsening from Baseline (change in nature, severity or frequency) of conditions present at Baseline
- Concomitant signs or symptoms related to the abnormal study assessment
- Intercurrent illnesses
- Drug interactions
- Events related to or possibly related to concomitant medications
- Further diagnostic testing or medical/surgical intervention is required

- Abnormal laboratory values (this includes significant shifts from Baseline within the range of normal that the Investigator considers to be clinically significant)
- An abnormal laboratory value will not be assessed as an AE unless it requires a therapeutic intervention or is considered by the Investigator to be clinically significant
- Clinically significant abnormalities in physical exam, vital signs or weight
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concomitant medication. Overdose in the absence of clinical sequelae will not be reported as an AE/SAE unless it is an intentional overdose.

Determination of clinical significance must be made by the Investigator. Events that do not meet the definition of an AE or SAE include:

- Planned hospital admissions or surgical procedures that are elective or for a condition that existed before the participant signed the ICF are not considered an AE unless the condition deteriorates in an unexpected manner during the study (eg, surgery had to be performed earlier than planned).
- Anticipated day-to-day fluctuations of preexisting disease(s), condition(s), and signs or symptoms present or detected prior to the start of the study that are not more severe than expected for the participant's condition.
- Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

12.3.2. Definition of Serious Adverse Event

An SAE is defined (21CFR 312.32) as any adverse experience that, in the view of the Investigator or Sponsor, results in any of the following criteria:

- Death
- Is immediately Life-threatening:
 - The term “life-threatening” in the definition of “serious” refers to an event/reaction in which the participant was at risk of death at the time of the event/reaction. It does not refer to an event/reaction which hypothetically might have caused death had it occurred in a more severe form
- Requires hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability or incapacity
 - Defined as a substantial disruption in a person's ability to conduct normal life functions

- Results in a congenital anomaly or birth defect
 - A congenital anomaly or birth defect that occurs in the offspring of a participant exposed to the study drug
- Important medical events that may not result in death, are life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in participant hospitalization, or the development of drug dependency or drug abuse.

In cases of events meeting serious criteria due to hospitalization, the onset date is the date of admission into the hospital and the stop date is the date the participant was discharged. Note that a SAE can meet more than 1 serious criterion (ie, medically important event) and therefore, event onset date and event stop date may not be the same as hospitalization dates, based on the Investigator's assessment of the event(s).

12.3.3. Intensity of Event

For both serious and nonserious AEs, the Investigator must determine the intensity of the event to study drug administration. Intensity for each AE will be defined according to the following criteria:

- **Mild** - Events require minimal or no treatment and do not interfere with the participant's daily activities. The participant may have awareness of signs or symptoms but are easily tolerated.
- **Moderate** - Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning. Discomfort is enough to cause interference with normal daily activities.
- **Severe** - Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious." Inability to perform normal daily activities.

If the intensity of an AE changes within a day, the maximum intensity should be recorded. If the intensity changes over a longer period of time, the changes should be recorded as separate events (having separate onset and stop dates for each intensity).

12.3.4. Relationship to Study Drug

For both serious and nonserious AEs, the Investigator must determine the relationship of the event to study drug administration. Investigators should use their knowledge of the participant, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an AE/SAE is considered to be related to study drug, indicating on the eCRF or SAE form that an AE/SAE is either **related** or **not related**. The following guidance should be taken into consideration when determining the relationship of an AE/SAE to study drug:

- Temporal relationship of event onset to initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (where applicable)
- Known association of the event with study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the participant or environment, or use of concomitant medications known to be associated with the event
- Presence of treatment-unrelated factors that are known to be associated with the occurrence of the event
- Whether there is a reasonable alternative explanation for the event

12.3.5. Study Drug Action Taken

The Investigator will determine the action taken with study drug as a result of the occurrence of an AE or SAE and will be classified according to the categories shown in the table below:

Classification	Definition
Not Applicable	The event occurred prior to administration of first dose of study drug, or the event occurred after the last dose of study drug
Dose Not Changed	Study drug dose or frequency not changed in response to the AE
Dose Reduced	Study drug dose or frequency lowered in response to the AE
Drug Interrupted	Study drug administration interrupted in response to the AE
Drug Withdrawn	Study drug administration permanently discontinued in response to the AE

12.3.6. Adverse Event Outcome

For both serious and nonserious AEs, the Investigator must determine the outcome of the event. Event outcome for each AE will be defined according to the following:

- Recovered/Resolved
- Recovered/Resolved with Sequelae (specify the residual effects/sequelae)
- Recovering/Resolving/Ongoing
- Not recovered/Not resolved/Ongoing

- Death
- To be used for any SAE which was the direct cause of death
- Unknown
 - Provide outcome once it becomes available

12.3.7. Procedures for Recording and Reporting Adverse Events and Serious Adverse Events

All AEs/SAEs will be collected from the time the participant signs the ICF up to 4 weeks after the last dose of study drug and entered into the electronic clinical database and source documents.

All AEs/SAEs spontaneously reported by the participant and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures must be recorded in the source document and on the appropriate page of the eCRF.

12.3.8. Adverse Event Reporting

All AEs including local and systemic reactions or clinically relevant deterioration in laboratory assessments not meeting the criteria for SAE will be captured on the appropriate electronic case report form (eCRF) and in the source documents. Information to be collected includes event description, time of onset, severity assessment, seriousness assessment, action taken, treatment administered, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while participating in the study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as Baseline history and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

12.3.9. Serious Adverse Event Reporting

Any AE meeting serious criterion which occurs up to 4 weeks after administration of the last dose of study, must be reported to Crinetics Pharmacovigilance (PV) Department (hereafter referred to as Crinetics) within 24 hours of the first awareness. All SAEs and deaths must be reported on EDC and the Crinetics SAE Report Form whether or not considered causally related to the study drug and email to [REDACTED]. All SAEs will be followed until satisfactory resolution or until the site Investigator deems the event to be chronic or the participant is stable. Other supporting documentation (admission summary, discharge summary, autopsy reports) of the event may be requested by the study Sponsor and should be provided as soon as possible.

12.3.10. Expedited Reporting

Safety reports will be prepared by Crinetics for SUSARs according to local regulatory requirements and Sponsor policy and will be forwarded to Investigators, as necessary. Any Investigator who receives a safety report describing an SAE or other specific safety information

from the Sponsor will file it in the Investigator Site File and will notify the IRB, if appropriate, according to local requirements.

12.3.11. Pregnancy Reports

If a participant or partner of a male participant becomes pregnant during the study or up until the Follow-up call, the Investigator must stop dosing with study drug immediately and the female participant should be withdrawn from the study. Early termination procedures should be implemented at that time.

The participant or partner of a male participant will be followed until the end of the pregnancy to determine the pregnancy outcome and the well-being of the mother and infant, and these results reported as described in Section 12.3.2.

Pregnancy itself does not constitute an AE or SAE. However, if the outcome of the pregnancy meets the criteria for classification as an SAE (ie, postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator must follow the procedures for reporting an SAE.

12.3.12. Process of Reporting Pregnancy

Any pregnancy that occurs in a study participant or partner of a male participant during the course of the study, as defined by the protocol, must be reported by the Investigator to Crinetics Pharmacovigilance Department by completing and emailing the Pregnancy Report Form within **24 hours** of the Investigator or site study staff first becoming aware of the pregnancy to [REDACTED] (see Section 9.5.5).

12.3.13. Regulatory Agency, Institutional Review Board, Ethics Committee and Site Reporting

Crinetics and/or the CRO are responsible for notifying the relevant regulatory authorities/US central IRBs/European Union central IECs of related, unexpected SAEs.

The Investigator is responsible for notifying the Sponsor, and local IRB, local IEC, or the relevant local Regulatory Authority of all SAEs that occur at his or her site as required.

12.3.14. Study Completion and Poststudy Treatment

The Investigator must provide follow-up medical care for all participants who are prematurely withdrawn from the study due to an AE or must refer them for appropriate ongoing care.

12.3.15. Lost to Follow-up

For participants whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the Investigator should show "due diligence" by documenting in the source documents steps taken to contact the participant, (eg, dates of telephone calls, registered letters, etc.). A participant should not be formally considered lost to follow-up until multiple attempts to contact the participant have been made, including at least 3 attempts to reach the participant by phone, followed by a certified letter sent to the participant's last known mailing address. A participant should not be formally considered lost to follow-up until his scheduled EOS Visit would have occurred.

12.4. Appendix 4: Contraceptive and Barrier Guidance

12.4.1. Definitions

Women of Childbearing Potential (WOCBP)

Women in the following categories are considered WOCBP (fertile):

- Following menarche
 - From the time of menarche until becoming postmenopausal unless permanently sterile (see below)

Women of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

- Premenopausal female with permanent infertility due to 1 of the following:
 - Documented hysterectomy
 - Documented bilateral salpingectomy
 - Documented bilateral oophorectomy
 - Documented bilateral tubal ligation at least 3 months prior to Screening
 - For individuals with permanent infertility due to an alternate medical cause other than the above.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
 - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
 - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements conducted 2 to 4 weeks apart are required during the Screening Period. 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 status.
 - Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

12.4.2. Contraception Guidance

CONTRACEPTIVES ^a ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods ^b That Have Low User Dependency
Implantable progestogen-only hormone contraception associated with inhibition of ovulation ^c
Intrauterine device (IUD)
Intrauterine hormone-releasing system (IUS) ^c
Bilateral tubal ligation
Azoospermic partner (vasectomized or due to a medical cause) <i>Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.</i> Note: Documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Methods ^b That Are User Dependent <i>Failure rate of <1% per year when used consistently and correctly.</i>
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation ^a oral intravaginal transdermal injectable
Progestogen-only hormone contraception associated with inhibition of ovulation ^c oral injectable
Sexual abstinence <i>Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.</i>

^a Contraceptive use by men or women also should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

^b Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

^c Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines {HMA.EU.CTFG, 2020 #51622}, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

Note: Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure from friction).

12.5. Appendix 5: Glucocorticoid Equivalencies

Properties, dosing equivalents and therapeutic indications of systemic corticosteroids, relative to hydrocortisone.

	Approximate Equivalent Dose ^a (mg)	Relative Glucocorticoid Activity	Relative Mineralocorticoid Activity	Duration of Action (h)	General Therapeutic Indications
Glucocorticoids					
<i>Short-acting</i>					
Hydrocortisone	20	1	1	8-12	Relatively high mineralocorticoid activity makes it suitable for use in adrenal insufficiency
Cortisone	25	0.8	0.8	8-12	Similar to hydrocortisone
<i>Intermediate-acting</i>					
Prednisone	5	4	0.8	12-36	High glucocorticoid activity makes it useful for long- term treatment, and as an anti-inflammatory/ immunosuppressant
Prednisolone	5	4	0.8	12-36	Similar to prednisone
Methylprednisolone	4	5	Minimal	12-36	Anti-inflammatory/ immunosuppressant
Triamcinolone	4	5	0	12-36	Anti-inflammatory/ immunosuppressant
<i>Long-acting</i>					
Dexamethasone Note: Dexamethasone is contraindicated in this study	0.75	30	Minimal	36-72	Anti-inflammatory/ immunosuppressant; used especially when water retention is undesirable given its minimal mineralocorticoid activity. Usually reserved for short-term use in severe, acute conditions given its high potency and long-duration of action
Betamethasone Note: Oral betamethasone is contraindicated in this study	0.6	30	Negligible	36-72	Similar to dexamethasone
Mineralocorticoids					
Fludrocortisone	— ^b	10-15	125-150	12-36	Used for aldosterone replacement

Source: (Liu 2013)

^a Equivalent dose shown is for oral or IV administration. Relative potency for intra-ocular or intramuscular administration may vary considerably.

^b Glucocorticoid doses which provide a mineralocorticoid effect that is approximately equivalent to 0.1 mg of fludrocortisone are: prednisone or prednisolone 50 mg, or hydrocortisone 20 mg.

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